Bayer HealthCare
Pharmaceuticals

Diem-Kieu Ngo, Pharm.D., BCPS
Program Management Officer
Advisors and Consultants Staff
FDA, CDER, OEP
HFD-21. Room 1093
5600 Fishers Lane

Rockville, MD 20857-1734

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Bayer HealthCare
Pharmaceuticals Inc.
Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Phone: 973 487-2109
Fax: 973-487-2016
Email:
Madhu.Anant@Bayer.com

RE: Peripheral and Central Nervous System Drugs (PCNS) Advisory Committee Meeting
October 23, 2008

Advisory Committee Briefing Document
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Dear Dr. Ngo

Reference is made to the PCNS Advisory Committee Meeting confirmed for October 23, 2008 and to your communications to Bayer on July 7 and September 6, 2008 that provided information on submission of the briefing document.

Bayer Health Care Pharmaceuticals is submitting its Briefing Document in preparation for the Advisory Committee Meeting to discuss the clinical development of radionuclide imaging products for the diagnosis of Alzheimer's disease.

The Briefing Document consists of one volume, the contents of which are available for public disclosure without redaction. Per your request dated July 7, 2008, this submission contains 25 electronic CDs of the briefing document in Adobe PDF and an additional 10 paper copies. The Briefing Document is also being submitted to the investigational ne drug application with the Division of Medical Imaging and Hematology Drug Products.

Should you have any questions, or require any additional information pertaining to this

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submission, please contact the undersigned via telephone at (973) 487-2109 or via telefax at (973) 487-2016.

Yours Sincerely,
Bayer HealthCare Pharmaceuticals, Inc.

Madhu Anant

Madhu Anant, M.Sc.,RAC
Global Regulatory Strategist
Global Regulatory Affairs

Advisory Committee Meeting

Briefing Document

Design of Phase 3 AD Diagnostic Imaging Studies

Bayer HealthCare Pharmaceuticals Inc.

Meeting Date and Time:

23 October 2008

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List of abbreviations

AD	Alzheimer's disease
^{11}C-PIB	C-11 labeled Pittsburgh B compound (^{11}C-6-OH-BTA-1)
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
COD	Confidence of Diagnosis
CP	Consensus Panel
CSF	Cerebrospinal Fluid
DLB	Dementia with Lewy Bodies
DSM IV-TR	Diagnostic and Statistical Manual of Mental Disorders fourth edition – Text Revised
^{18}F	Fluorine-18
FAB	Frontal Assessment Battery
FDA	U. S. Food and Drug Administration
FDG	2-[F-18] fluoro-2-deoxy-D-glucose
FIS	Fluctuation Inventory Scale
FTD	Fronto-Temporal Dementia
FTLD	Fronto-Temporal Lobar Degeneration
ICC	International Consensus Criteria
IQ	Intelligence Quotient
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental Status Examination
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
NINCDS-ADRDA	National Institute of Neurological, Communicative Disorders and Stroke – AD and Related Disorders Association
NINCDS-AIREN	National Institute of Neurological Communicative Disorders and Association Internationale Pour la Recherché et l'Enseignement en Neurosciences
NPI	Neuropsychiatric Inventory
NPV	Negative Predictive Value
PET	Positron Emission Tomography
p.i.	Post Injection
PPV	Positive Predictive Value
P-tau	Phosphor Tau

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PoM	Proof of Mechanism
SPECT	Single Photon Emission Tomography
SUVR	standardized uptake value ratio
T-tau	Total Tau
VaD	Vascular Dementia

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1. Executive Summary

Bayer HealthCare Pharmaceuticals has agreed to participate in an Advisory Committee Meeting called in by the FDA to discuss possible development programs for amyloid β imaging agents to be used as diagnostic tool in the diagnosis of Alzheimer's disease (AD).

Scientific and Clinical Background

With approximately 25 million cases worldwide - over 4 million in the US alone – dementia affects 7% of the general population over 65 years of age and 30% of those over 80 and significantly reduces life expectancy.

Definitive diagnosis of AD and other types of dementia relies on post mortem, histopathological examination of the brain. The current criteria for the pathologic diagnosis of AD require the presence of extra-cellular deposits of amyloid β peptides in the brain. Additional evidence that amyloid β peptide formation and deposition is inherently linked to AD has also come from genetic studies.

The diagnosis of AD during life requires thorough clinical and neuropsychiatric examination performed by a clinician experienced in dementia. For AD, the best established and only validated diagnostic criteria have been defined by the National Institute of Neurological, Communicative Disorders and Stroke – AD and Related Disorders Association (NINCDS-ADRDA). A meta-analysis of studies with pathological confirmation was conducted in which these criteria were applied to establish the diagnosis of AD. Here, the sensitivity and specificity values reported varied considerably demonstrating acceptable sensitivity, but only marginal specificity indicating that subjects with non AD dementia and/or non-neurodegenerative disorders are often misdiagnosed as having AD and underscores the need to develop ways of improving the specificity of the diagnosis without a loss in sensitivity. Ultimately a biomarker, or combinations thereof, may be needed to increase overall diagnostic precision.

Since the NINCDS-ADRDA criteria were first published in 1984, elucidation of the biological basis of AD has greatly advanced and distinctive and reliable biomarkers are now available that can lend objectivity to clinical findings in the diagnosis of AD. Revised criteria - still centered on a clinical core of early and significant memory impairment (e.g. dementia) - but also including abnormalities in at least one or more of these biomarkers, have been proposed and are currently being investigated. These include, but are not restricted to, cerebrospinal fluid (CSF) analyses, structural magnetic resonance imaging (MRI) and molecular neuroimaging with PET which are described in more detail within the document. Within this revised diagnostic framework the ideal role of the novel biomarkers is a complementary one and aimed at increasing, in particular, the specificity of the current clinical parameters.

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Neocortical amyloid β plaque deposition, a pathological hallmark of AD, occurs early in the disease process, possibly years before the onset of clinical symptoms. The availability of a non-invasive, imaging marker capable of detecting amyloid β in the brain to facilitate early and accurate in vivo disease detection of AD is, thus, a major medical need. Trials in humans with amyloid targeted PET tracers have shown significant differences in tracer uptake pattern in the neocortical regions in subjects with AD when compared to healthy volunteers. Here, in PET scans of subjects with AD, a higher tracer uptake has been seen in regions known to have amyloid β plaques compared to healthy volunteers, whereas in regions known to be unaffected by amyloid β deposition, tracer uptake was equivalent in AD patients and HV. Although initial results with tracers of this type are promising, as with all other novel diagnostic modalities, validity and reliability needs to be established on the basis of prospective clinical trials.

Clinical Usefulness of an early and accurate diagnosis in AD

Bayer HealthCare Pharmaceuticals primary goal is to develop a non-invasive diagnostic tool available as an visual adjunct to existing methodology to increase diagnostic precision in AD. The indication being pursued is based on the known pathological link between neocortical amyloid β plaque deposition in the brain and the manifestation of AD and is intended to facilitate introduction of the compound as a visual adjunct to existing methodology to increase diagnostic confidence in AD. The target proposed indication based on the diagnostic efficacy is:

The tracer can detect amyloid β plaque deposition in the brain and thereby, assist the physician in the diagnosis of (detection/exclusion) of Alzheimer´s disease.

In routine clinical practice, an amyloid-targeted tracer, or any diagnostic test in dementia, will not be used as a "stand alone" in establishing the final clinical diagnosis, but as an additional diagnostic tool - i.e. a biological footprint - aimed at assisting the clinician in making a more precise and objective differential diagnosis. Examples of differential diagnostic situations in which a tracer of this type can assist the clinician in establishing a more objective diagnosis are presented within the document.

The clinical usefulness is also important for patient, caregiver/family and physician as it facilitates implementation of appropriate therapy early on. Unnecessary investigations are avoided and cognitive symptoms alleviated, with a subsequent increase in quality of life, both for the patient and his/her family members. Current phase 3 development of novel therapeutic agents further underscores the importance of early and accurate diagnosis in AD. The availability of non-invasive imaging markers capable of detecting amyloid accumulation in the brain would not only assist in identifying patients who would benefit from therapy, but also to decrease sample size and follow-up time and, thus, time and cost to development. Finally, as the worldwide prevalence of AD is expected to quadruple by 2050, modest advances in therapeutic and preventative strategies (associated with early diagnosis) that can lead to even small delays in the onset of AD and progression can significantly reduce the global burden of the disease.

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Development Strategy and Indication

It is not feasible to rely on autopsy as the standard of truth. Instead of this rigorous standard, the clinical diagnosis established on the basis of an appropriate combination of clinical examination and the proper combination of validated tests including application of internationally accepted criteria can provide a very good approximation of the true disease state. For the diagnosis of AD and other dementias in clinical trials, the Consensus Panel approach is validated and the clinical diagnosis established in this manner has been shown to be robust and reproducible.

Phase 3 design:
The trial proposed is a pivotal efficacy trial (with an independently established clinical diagnosis as the standard of truth), the major purpose of which is to verify the efficacy of an amyloid targeted PET tracer to pursue the indication of "detection of pathology".

- Patients with clinically probable AD (high likelihood of having amyloid β in the brain) will serve as positive controls - contributing to sensitivity- and healthy volunteers who serve as negative controls (high likelihood of having not amyloid β in the brain, contributing to specificity).
- The primary endpoints will be the sensitivity and specificity of the independent blinded visual assessment of the amyloid-targeted PET tracer images in detecting/excluding cerebral amyloid β in patients with probable AD compared to healthy volunteers.
- The clinical diagnosis will serve as the standard of truth, based on internationally accepted, validated criteria and established after comprehensive clinical and neuropsychiatric examination by a consensus panel.
- Other dementia subtypes are planned to be included as a secondary (vs. primary) population in the proposed trial and will be analyzed in a descriptive manner only.

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2. Introduction

An early and accurate diagnosis of dementia, in particular of Alzheimer's disease, remains an unmet clinical need. Bayer HealthCare Pharmaceuticals, Inc. intends to develop a Positron Emission Tomography (PET) tracer for the detection of amyloid β plaques and, thereby, provide a visual adjunct to assist the clinician in establishing a more objective clinical diagnosis.

The Food and Drug Administration (FDA) considers "the development of a safe and effective diagnostic imaging agent for Alzheimer's disease (AD) to represent an important public health contribution" and, has therefore organized an Advisory Committee Meeting aimed at providing specific recommendations based on clinical utility towards the design of phase 3 diagnostic imaging studies in AD. Bayer HealthCare Pharmaceuticals has accepted the FDA's invitation to actively participate in the preparatory process for this Advisory Committee which includes:

1) Submitting a summary of the clinical development program

2) Providing an outline of a phase 3 clinical study protocol and,

3) Participating in a presentation to the Advisory Committee.

The present document contains key scientific and clinical background information, as well as a section devoted to the general considerations on the development of PET tracers of this type which have guided the company and have led to the proposed development concept and phase 3 study outline. The last section of the document contains a number of questions related to the design of a confirmatory phase 3 trial. A synopsis of a phase 3 clinical study protocol has been included as an appendix to this document.

3. Scientific and clinical background

With approximately 25 million cases worldwide - over 4 million in the US alone – dementia affects 7% of the general population over 65 years of age and 30% of those over 80 [McKeith et al. 2004, Ferri et al. 2005] and significantly reduces life expectancy [Larson et al. 2004]. Among the four major dementia subtypes, e.g. Alzheimer's disease (AD), Dementia with Lewy Bodies (DLB), vascular dementia (VaD) and fronto-temporal lobar dementia (FTLD), AD is the most common cause in the western world, accounting for over 65% of all cases [McKeith et al.2004]. Progressive aging of the mature population is expected to further increase the frequency of AD with a proportionate substantial increase in the cost of related medical care. In the US the frequency of AD is expected to increase to 14 million as the baby boomers expand the geriatric population [Silverman et al. 2004]. This will have considerable economic impact considering the present annual AD associated expenses in the US are nearly $70 billion and $100 billion when indirect costs such as the loss of caregiver productivity are considered [Silverman et al. 2000].

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3.1 Neuropathological and genetic features of Alzheimer's disease

Definitive diagnosis of AD and other types of dementia relies on post mortem, histopathological examination of the brain. The current criteria for the pathologic diagnosis of AD require the presence of extra-cellular deposits of amyloid β peptides, intra-neuronal neurofibrillary tangles and the predominance of neocortical neuronal degeneration [Braak et al. 1997]. Although amyloid β deposition is sometimes seen in other more rare dementias such as VaD and DLB, a major pathological differentiation in the former is the preponderance of micro- and/or macro-vascular lesions and, in latter, the predominance of nigrostriatal (vs. neocortical) neuronal degeneration caused by cytoplasmatic accumulation of -synuclein protein aggregates (Lewy Bodies) [McKeith et al. 2004, Perry et al. 1990]. amyloid β plaques have also been described in a sub-population of the healthy population over the age of 75 years [Price et al. 1999]. In contrast, in patients with fronto-temporal dementia (FTD), a subform of FTLD, amyloid β deposition is rarely seen upon histopathological examination.

Additional evidence that amyloid β plaque formation is inherently linked to AD has come from genetic studies verifying that autosomal dominant mutations which result in alterations in amyloid β formation and/or metabolism are present in subjects who develop the disease before the age of 60 years (i.e., approximately 0.01% of all cases) [Waring et al., 2008]

3.2 Diagnosis of Alzheimer's disease: current diagnostic tools

3.2.1 Clinical diagnosis

As in all neurodegenerative disorders, the diagnosis of AD during life requires thorough clinical assessment, including a detailed medical history (from patient and caregiver) and a full mental state, cognitive and physical examination performed by a clinician experienced in dementia. For AD, the best established and still recommended diagnostic criteria [Knopman et al. 2001] have been defined by the National Institute of Neurological, Communicative Disorders and Stroke – AD and Related Disorders Association (NINCDS-ADRDA) [McKhann et al. 1984]. These criteria are currently used together with the Diagnostic and Statistical Manual of Mental Disorders fourth edition – Text Revised (DSM IV-TR) criteria from the American Psychiatric Association (2000) to establish the diagnosis of AD.

According to the NINCDS ADRDA criteria "a clinical diagnosis of "probable" AD can be made if there is a typical insidious onset of dementia with progression and if there are no other systemic or brain diseases that could account for the progressive memory and other cognitive defects. Among the disorders that must be excluded are manic depressive disorder, Parkinson's disease, multi-infarct dementia and drug intoxication; less commonly encountered disorders that may cause dementia include thyroid disease, pernicious anemia, luetic brain disease and other

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chronic infections of the nervous system, subdural hematoma, occult hydrocephalus, Huntington's disease, Creutzfeldt-Jakob disease and brain tumors [McKhann et al. 1984].

A clinical diagnosis of "possible" AD can be made on the basis of verified dementia "in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia and in the presence of variations in the onset, in the presentation or in the clinical course and may be made in the presence of a second systemic or brain disorder sufficient to produce dementia if this condition is not considered to be the cause of the dementia." Finally criteria for the diagnosis of "definite" AD are the clinical criteria for AD together with histopathologic evidence (i.e. cerebral amyloid β plaque deposition) obtained from a biopsy or autopsy.

In view of these numerous differential diagnostic considerations, the diagnosis of AD remains difficult and time consuming – in particular in subjects with high age or IQ or those with concomitant depression - often taking months (or even years) to establish. Even among specialists in the field, the disease is sometimes not recognized; in particular in the early and/or mild disease or in cases of mixed pathology. A meta-analysis with pathological confirmation was conducted in which these criteria were applied to establish the diagnosis of "probable" (in 13 studies) and "possible" AD (4 of 13 studies). Here, the sensitivity and specificity values reported varied considerably (average sensitivity = 81%, range 49 to 100%; average specificity = 70%, range from 47 to 100%). The values reported by these clinical groups, however, need careful interpretation because of: a) the Class II trial nature of the majority of the studies, b) the variation in methods of analysis across studies, and c) the possible inclusion of cases with mixed pathology. In these studies, although the sensitivity was generally acceptable, the specificity was marginal to suboptimal [Knopman et al.2001]. This indicates even in specialized clinics subjects with non AD dementia and/or non-neurodegenerative disorders are often misdiagnosed as having AD and underscores the urgent need to develop ways of improving the specificity of the diagnosis without a loss in sensitivity. Ultimately a biomarker, or combinations thereof, may be needed to increase overall diagnostic precision.

3.2.2 Biomarkers, structural and functional neuroimaging methods

Since the NINCDS-ADRDA criteria were first published in 1984, elucidation of the biological basis of AD has greatly advanced allowing unprecedented understanding of the disease process in its earliest stages. Distinctive and reliable biomarkers are now available that can lend objectivity to the clinical diagnosis of AD. These include, but are not restricted to, cerebrospinal fluid (CSF) analyses, structural magnetic resonance imaging (MRI) and molecular neuroimaging with PET. As the originally proposed NINCDS-ADRDA guidelines have fallen behind this growth of scientific knowledge, revised criteria - still centered on a clinical core of early and significant memory impairment (e.g. dementia) - but also including abnormalities in at least one or more of these biomarkers, have been proposed [Dubois et al. 2007] and are currently being investigated. Within this revised diagnostic framework the ideal role of the novel biomarkers is a complementary one and aimed at increasing, in particular, the specificity of current clinical parameters.

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It should be noted that in the present document biomarkers are considered to be biological markers (i.e. features of body fluids or tissues) - that can be measured or evaluated - and that can act as indicators of normal vs. pathological biological processes. In accordance with this definition, *in vitro* biomarkers related to dementia can then be soluble amyloid β or tau protein fractions measured in cerebrospinal fluid and an imaging marker any anatomical, physiological, or molecular parameter detectable by means of a structural and/or functional imaging modality. This could be medial temporal lobe (MTL) atrophy in brain MRI, diminished brain glucose metabolism as detected by an FDG PET scan, or the presence of neocortical amyloid β plaque deposition as detected via an amyloid-targeted PET tracer.

Cerebrospinal fluid (CSF) biomarkers

The NINCDS-ADRDA guidelines recommend examination of CSF to exclude the presence of non-degenerative dementia due to inflammatory disease, vasculitis, and/or demyelination [McKhann et al. 1984]. Since these guidelines were first published in 1984, elucidation of the biological basis of AD has greatly advanced. Distinctive CSF markers, reflective of amyloid β aggregation (amyloid β_{1-42}) and hyperphosporylation of tau protein (total tau (t-tau), and phosphor tau [p-tau]) have been recognized and are now being assessed for their usefulness as AD-specific biomarkers [Dubois et al. 2007]. In AD amyloid β_{1-42} is decreased and t-tau is increased compared to healthy volunteers, amyloid β_{1-42} is normal in subjects with depression and decreased in Dementia with Lewy Bodies (DLB), Fronto-Temporal Dementia (FTD), and vascular dementia (VaD). This general lack of specificity of CSF markers across dementia subtypes can be only partially compensated by the use of a combination of markers and/or ratios, whereby sensitivities of 83 to 94% and specificities of 83% to 100% have been reported [Blennow et al. 2003]. The optimal CSF marker or combinations of markers still needs to be determined. It should also be noted that concentrations of CSF markers vary substantially across different assays, but also with the same assay when performed in different centers [Dubois et al. 2007].

Structural and functional *in vivo* neuroimaging methods

The role of **magnetic resonance imaging (MRI)** in the evaluation of dementia has been primarily to exclude non-neurodegenerative causes of cognitive dysfunction such as a tumor, multiple stroke syndrome, or normal pressure hydrocephalus. Selective atrophy of the MTL and/or MTL structures such as the hippocampus have been reported useful in distinguishing patients with AD from healthy volunteers [Scheltens et al. 2002, Wahlund et al. 2000]. MTL atrophy seems common in AD depending on severity (71% to 96%) and less frequent in the normal aging (29%). Hippocampal atrophy also occurs in other dementias, including Vascular Dementia (VaD), DLB and FTD. Non-neurodegenerative causes leading to atrophy such as bilateral MTL ischemia, hippocampal sclerosis, or focal epilepsy must also be ruled-out. In general MRI findings are helpful in the differential diagnosis of dementia only when closely coupled with those of history, physical and neuropsychiatric examination. Finally, as there is no specification of the amount of atrophy optimally diagnostic of AD [Dubois et al. 2007], a

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negative MRI finding would not lead the physician to rule out disease if other findings are indicative of AD.

MRI methods include both qualitative ratings and quantitative techniques with tissue segmentation and digital computation of volume. However, the best test or method for determination of MTL atrophy remains uncertain, as does the most effective evaluation technique, and for the latter, the specific region within the MTL for measurement. Due to rapid advances in MR technology wide spread application of standardized and validated software-based analysis techniques for across camera and/or vendor use – in particular for quantification – are not yet available.

As single photon emission tomography (SPECT) is more widely available than PET, it has received attention as an alternative to PET imaging in dementia. Bilateral temporal parietal hypoperfusion in AD patients can be detected with **[^{99}Tc] HMPAO SPECT** [Jagust et al. 2001]. However, this technique is not included in the revised guidelines [Dubois et al. 2007] as the diagnostic estimates for this modality generally fall below the requisite values 80% levels for biomarkers specified by the Reagan Biomarker Working Group [1998].

Positron emission tomography (PET) imaging **with 2-[F-18] fluoro-2-deoxy-D-glucose** Here, a reduction of glucose metabolism in the bilateral temporal parietal and posterior cingulate regions is currently the most commonly described diagnostic criterion for AD. A recent meta-analysis of nine studies reported that for discrimination between AD and healthy volunteers, pooled sensitivities and specificities were 86%, however, with a wide variation in values [Dubois et al. 2007]. When histopathological examination was used as the gold standard, the sensitivity was 88% to 95% and the specificity 62% to 74% [Silverman et al 2004]. Here again the values reported need careful interpretation because of single trial nature of the majority of the studies involved, as well of the variation in analysis methods and possible inclusion of cases with mixed pathology.

Open questions in FDG PET include: a) optimally specific brain regions, b)whether a qualitative or a quantitative approach should be taken for diagnosis and c) the degree of glucose hypo metabolism pertinent to diagnostic evaluation [Dubois et al.2007].

3.3 Diagnosis of Alzheimer´s disease: potential for PET amyloid-targeted imaging

3.3.1 Experience with [^{11}C] Pittsburgh B compound

The extracellular deposition of amyloid β plaques in the brain is a central event in the pathogenesis of AD and occurs early in the disease process. Therefore, a non-invasive, imaging marker capable of detecting amyloid β in the brain would facilitate early and accurate disease diagnosis. The most investigated PET tracer of this type is ^{11}C-6-OH-BTA-1 (also known as the [^{11}C] Pittsburgh B compound or [^{11}C] PIB) which was developed by Klunk et al. at the University of Pittsburgh. Trials in humans with this tracer have shown significant differences in retention patterns of [^{11}C]PIB in the neocortical regions of patients with AD compared to healthy

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volunteers [Klunk et al. 2004]. In patients with probable AD, there was a higher retention of the agent in regions of the brain that are generally known to be affected by amyloid β plaque deposition in AD patients when compared to healthy volunteers, whereas in regions known to be unaffected by amyloid β plaque, retention was similar in AD patients and healthy volunteers.

The relationship between PIB binding and amyloid β plaque burden post mortem has been demonstrated in human tissue ex vivo in studies verifying PIB binding to directly reflect amyloid β plaque burden in an AD brain [Klunk et al 2005]. In another recent study [Bacskai et al. 2007], one subject diagnosed with DLB underwent PET imaging with [^{11}C]PIB and revealed marked regions of specific tracer uptake. Autopsy, performed 3 months after the PET scan, confirmed amyloid plaque deposition in the brain corresponding to the observed regions of uptake. In a further study, in vivo [^{11}C]PIB images of one subject with AD were compared to post-mortem neuropathology data obtained 10 months after imaging [Ikonomovic et al 2008]. Here again, there was a strong correlation between in vivo [^{11}C]PIB retention and region-matched quantitative analysis of amyloid β plaques.

Additional findings have not only demonstrated that [^{11}C]PIB can reliably differentiate AD from FTD and healthy volunteers [Rowe et al. 2007], but indicate the tracer to be superior to FDG PET in discriminating between AD subjects and the normal elderly (sensitivity of 100% and specificity of 88% and 76% and 75%, respectively) [Ng et al 2007]. In this trial as well, the kappa value for inter-reader agreement with [^{11}C]PIB was 0.85 compared to 0.55 for FDG. The predictive value of a [^{11}C]PIB positive scan (as an indication of amyloid β plaque burden) has been indicated by the demonstration of a 60% a conversion rate in [^{11}C]PIB positive subjects with mild cognitive impairment (MCI) to probable AD over 12 months compared to no conversion within this time period in [^{11}C]PIB negative subjects [Forsberg et al., 2007].

Although these and other published findings support the efficacy of the agent not only in detecting amyloid it needs to be considered that [^{11}C]PIB is still experimental and has not yet been validated in a prospective, multicenter trial environment. Furthermore, the short radioactive half-life of Carbon-11 (^{11}C, $t_{1/2}$ = 20 min) prevents broad application of the agent and restricts its use to PET centers with an on-site cyclotron and an extensive radiochemistry infrastructure. A radiotracer with a longer half-life than [^{11}C]PIB is required for wider application in routine clinical diagnostic evaluation. The most established method is labelling with the positron- emitting radionuclide Fluorine-18 [^{18}F] which has a half-life of almost 2 hours and thus allows for commercialization.

3.3.2 F-18 labeled positron emission tomography (PET) tracers

Novel F-18 labelled, amyloid-targeted tracers that fulfil these requirements (such as BAY 94-9172 , a new [^{18}F]-labeled polyethyleneglycol stilbene derivative, Bayer Healthcare) are currently under development. BAY 94-9172 has been shown to have a high affinity and specificity for amyloid β *in vitro* and first human data with the tracer from a Proof of Mechanism (PoM) study indicate convincing diagnostic accuracy in the differentiation of patients with probable AD and healthy volunteers [Rowe et al. 2008]. The neocortical binding pattern in the

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BAY 94-9172 PET image was similar to that seen with [^{11}C]PIB and the images from subjects with AD could be easily distinguished from those of healthy volunteers by visual assessment alone. Furthermore, excellent separation of patients with probable AD and healthy volunteers (HVs) was observed when using the standardized uptake value ratio (SUVR) in regions of the brain characterized by amyloid deposition in AD patients. Similar efficacy profile has since also been demonstrated in and additional PoM study reported by [Barthel et al. 2008].

On the basis of the above, the development of an [^{18}F]-labeled, amyloid-targeted PET tracer as a visual adjunct to clinical findings in AD can be considered a current unmet medical need, as it could facilitate an earlier and more accurate diagnosis in AD with the potential benefit of a superior effective therapeutic intervention. The clinical program undertaken by Bayer is in adherence to the FDA *"Guidance for Industry. Developing Medical Imaging Drug and Biological Products."* [Parts 1, 2, and 3. Jun 2004] (FDA Guidance).

4. Clinical Usefulness of Early Diagnosis in AD

In line with FDA *Guidance for Industry*, *Developing Medical Imaging Drug and Biological Products, June 2004 (in Part 2),* a pathology claim "to detect and locate a specific disease or pathological state in at least one defined clinical setting" is being pursued for BAY 94-9172. The indication being pursued is based on the known pathological link between neocortical amyloid β plaque deposition in the brain and the manifestation of AD [Braak et al. 1997]. The target proposed indication based on the diagnostic efficacy is:

The tracer can detect amyloid β plaque deposition in the brain and thereby, assist the physician in the diagnosis of (detection/exclusion) of Alzheimer´s disease.

In terms of clinical usefulness FDA Guidance for Industry Developing Medical Imaging Drug and Biological Products, June 2004, Part 2: Clinical Indications recommends that a medical imaging agent be able to provide accurate and reliable information that, in one of a number of ways, facilitates clinical management, including

(1) helping make an accurate diagnosis,

(2) contributing to beneficial clinical outcome (e.g., by helping choose the right therapy), or

(3) providing accurate prognostic information.

Currently, the definitive diagnosis of AD relies on post mortem pathological examination of the brain. Awaiting post-mortem diagnosis is not feasible within the context of a clinical development program. Visualization of tracer uptake as an indication of the presence of amyloid β plaque deposition substantiates the presence of underlying AD and can, thereby, decrease clinical uncertainty. The product could be of considerable use to the dementia expert as an additional (functional) visual adjunct to his/her current diagnostic algorithm for AD, not only to increase the overall diagnostic accuracy, but also to facilitate a reduction in the time (and

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possibly the cost) to diagnosis. Finally, as AD is increasingly recognized as a pharmacologically treatable dementia, early diagnosis is important because advanced disease is less amenable to therapy.

4.1 Clinical usefulness for patient and caregiver

The clinical usefulness of an amyloid targeted PET tracer, or any other diagnostic test in dementia lies in its ability to help the clinician make a more accurate diagnosis earlier in the course of the disease. This is expected to have implications for patient management and prognosis and cost of care [Silverman et al. 2004]. Timely and accurate diagnosis or exclusion of AD is important as it helps the physician to implement appropriate treatment early on, such as administration of cholinesterase inhibitors to improve both cognitive and neuropsychiatric symptoms. Knowledge of underlying disease is reassuring for both patient and family members and, if time to diagnosis is decreased, unnecessary investigations can be avoided, symptoms alleviated and overall quality of life increased [McKeith et al. 2007]. The medical need for early diagnosis in AD is underscored by current development of drugs directed at altering disease pathogenesis through amyloid immunotherapy, gamma and beta secretase inhibition or modulation, alpha secretase activation or treatment with nerve growth factors [Dubois et al. 2007]. There is also a surge in the development of novel symptomatic therapies such as second generation cholinesterase inhibitors and substances targeting the nicotinic receptors (e.g., α4β2- and α-7). Thus, there is currently a clear neurobiological imperative to identify AD early in the course of the disease, before irreversible damage to brain tissue occurs, which could potentially prevent effective therapeutic intervention.

4.2 Clinical usefulness for the clinician

The early and accurate diagnosis of dementia subtype is not only being increasingly demanded by patients and their caregivers, but has also been emphasized by international expert panels on AD [Waldemar et al., 2007, Dubois et al. 2007], Dementia with Lewy Bodies (DLB) [McKeith et al. 2005] and fronto-temporal dementia [McKhann et al. 2001]. In routine clinical practice, an amyloid-targeted tracer, or any diagnostic test in dementia, will not be used as a "stand alone" in establishing the final clinical diagnosis, but as an additional diagnostic tool - i.e. a biological footprint - aimed at assisting the clinician in making a more precise and objective differential diagnosis. Furthermore, precise diagnosis of dementia type will prompt the clinician not only to adjust existing pharmacotherapy, but to assess the patient for additional specific symptoms related to the type of dementia indicated by the diagnostic work-up, but which is not generally associated with other dementia subtypes.

Many clinical situations exist in which detection or exclusion of amyloid β in the brain of a cognitively impaired individual presenting in a dementia clinic would provide the specialist with valuable information on which to establish an accurate differential diagnosis. Three of many possible examples are presented below:

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Example 1: In Fronto-Temporal Lobar Degeneration (FTLD) the diagnostic process is challenging even for experts in the field [Neary et al. 1998]. There are 3 subcategories of FTLD:

1. Fronto-temporal Dementia (FTD) with personality change or impairment of executive function (planning, attention)
2. Semantic dementia - a progressive loss of the meaning of words or recognition of objects and faces
3. Progressive non-fluent aphasia

Clinically AD can mimic any one of these 3 conditions and amyloid β pathology can be seen in a significant percentage of subjects with FTD (in cases in which loss of executive function is predominant), as well as in 50% of all subjects with progressive nonfluent aphasia. In general, AD rather than FTD is more likely if memory impairment is present early on, in particular if it begins before behavioural or language features are apparent. However, clinicians are frequently faced with patients presenting with both behavioural and/or language changes and memory impairment. FTD patients have specific treatment requirements and functional disabilities that differ from those of other forms of dementia and that require specialized, often multi-disciplinary treatment. In addition, progression of cognitive decline in FTD is generally more rapid than that seen in AD and, in contrast to AD; therapy with cholinesterinase inhibitors is usually ineffective. Thus, the results of an amyloid-targeted PET scan may provide the additional information necessary to establish the final diagnosis in this and optimize management and future planning.

Example 2: Depression is a frequent non-cognitive symptom of AD. On the other hand, cognitive impairment can be associated with severe depression (i.e. cognitive deficits in depression), making differential diagnosis difficult even for an experienced physician. Follow-up of these patients permits diagnosis in most cases, but this strategy is associated with a delayed initiation of effective treatment in those patients actually suffering from AD. Here a positive amyloid-targeted PET scan would confirm the diagnosis in the former and a negative scan would confirm the diagnosis in the latter case. The treatment and prognosis of the two conditions differs considerably.

Example 3: Up to 25% of AD patients can also develop Parkinsonism, a core symptom of DLB. However, at autopsy, such patients demonstrate amyloid β plaque deposition and an accumulation of neuro-tangles in the basal ganglia rather than the dopaminergic degeneration characteristic of synucleopathies such as DLB [Ballard et al. 2004, Ceravolo et al. 2004]. Here a negative vs. positive scan would not only have diagnostic implications, but would also be of importance for the choice of treatment strategy for non-cognitive symptoms, e.g. systemized delusions or hallucinations in other modalities due to neuroleptic sensitivity.

4.3 Economic Usefulness

Definitive health economics data for PET imaging in dementia with amyloid targeting tracers is not yet available. However, data may be extrapolated from that reported by

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[Silverman et al. 2002] for FDG PET brain imaging. Here, the use of FDG PET in evaluating subjects with early dementia has been shown to add valuable information to the clinical workup, without adding to the overall costs and with a greater number of patients being accurately diagnosed for the same level of financial expenditure. The results of this analysis were based on the assumptions that: a) current treatment of mild to moderate AD with cholinesterase inhibitors can delay decline in memory and other cognitive functions in AD patients and that b) this can lead to a subsequent reduction in the proportion of patients requiring nursing home placement over a given period of time. In this scenario FDG PET led to improved accuracy in identifying early AD, without adding to the overall costs of diagnosis and treatment.

In general one can assume that earlier decisions on treatment should lead to more focused and efficient treatment regimens that should reduce healthcare costs both on for AD subjects AND for subjects with other dementia subtypes.

4.4 Summary

- Early and accurate diagnosis of Alzheimer's disease (AD) is important for patient, caregiver/family and physician as it facilitates implementation of appropriate therapy early on.
- Unnecessary investigations are avoided and cognitive symptoms alleviated, with a subsequent increase in quality of life, both for the patient and his/her family members [McKeith et al. 2007].
- Current phase 3 development of novel therapeutic agents further underscores the importance of early and accurate diagnosis in AD. The availability of non-invasive imaging markers capable of detecting amyloid accumulation in the brain would not only assist in identifying patients who would benefit from therapy, but also to decrease sample size and follow-up time and, thus, time and cost to development.
- As the worldwide prevalence of AD is expected to quadruple by 2050, modest advances in therapeutic and preventative strategies (associated with early diagnosis) that can lead to even small delays in the onset of AD and progression can significantly reduce the global burden of the disease [Brookmeyer et al. 2008].

5. Development considerations in the diagnosis of Alzheimer's disease

5.1 Possible Indication for an amyloid imaging agent

The considerations in the FDA's *Guidance for Industry: Developing Medical Imaging Drug and Biological Products, June 2004, Part 2* (which state that a pathology detection claim for "a medical imaging agent" involves being able "to detect and locate a specific disease or

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pathological state in at least one defined clinical setting") - form a basis for the proposed target indication for an amyloid-targeted PET tracer.

In line with the above, the indication is based on the known pathological link between neocortical amyloid β plaque deposition in the brain and the manifestation of AD [Braak et al. 1997]. While amyloid β plaque deposition is sometimes seen in other dementias [McKeith et al. 2004] and even a small fraction of healthy elderly subjects [Price et al. 1999], AD is the only dementia which is always associated with amyloid β plaque deposition. The target proposed indication based on the diagnostic efficacy is:

BAY-94 9172 can detect amyloid β plaque deposition in the brain and, thereby, assists the physician in the diagnosis (detection/exclusion) of AD.

This proposed indication is supported by the clinical usefulness as discussed in section 4 and is discussed in more detail in section 6.1 of this document.

5.2 General Clinical Development

After initial verification of efficacy and safety in "first in man" trials, Bayer HealthCare Pharmaceuticals has pursued subsequent further clinical development according to the recommendations presented in the FDA's: *Guidance for Industry: Developing Medical Imaging Drug and Biological Products, Parts 1, 2, and 3, Jun 2004*.

Phase 2

In line with the FDA Guidance above, an appropriate endpoint of a phase 2 trial designed to verify the efficacy of an amyloid-targeted (i.e. pathology detecting) PET imaging agent would be one that compares tracer uptake pattern in PET scans from individuals with a high probability of amyloid β plaque deposition (i.e. AD patients) to the pattern in individuals with a low probability of plaque deposition (healthy volunteers). The AD cohort would serve to determine the sensitivity and the healthy volunteers to calculate specificity of the tracer. Additional phase 2 endpoints might be to develop optimized technical parameters, to standardize the imaging protocol, and to evaluate visual and quantitative analysis techniques. The results could then be applied to the larger subject population and scanner types encountered in phase 3 stage development and upon commercialization.

Phase 3

The overall design of a phase 3 program for an amyloid-targeted – or any other diagnostic agent in AD – in accordance with the basic principles outlined in the FDA Guidance should include, but is not limited to the following:

- The likelihood of disease or the spectrum of disease (e.g. severity or stage) is dependent on the clinical setting. The confirmatory trial should, thus, be conducted in a memory clinic

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environment (i.e. defined clinical setting) and should include patients presenting with AD and other dementia subtypes (i.e. the specific disease(s) in question).

- The co-primary endpoints of sensitivity and specificity should be determined on the basis of pre-defined thresholds. Determination of these parameters will necessitate the inclusion of subjects with probable AD as a cohort with a high probability of tracer uptake (i.e. amyloid deposition) as positive controls for sensitivity and healthy volunteers as a cohort with a low probability of tracer uptake as negative controls for specificity. As amyloid deposition has been reported for a small percentage of healthy volunteers, in the present case the obtainable specificity is expected to be lower than the sensitivity.

- The clinical diagnosis will serve as the standard of truth but – to provide a very good approximation of the true disease state - it should be established independently (on the basis of internationally established clinical criteria) by a Consensus Panel (CP) of experts after review of extensive clinical and neuropsychiatric data [McKeith at al, 2007].

- The images generated during the program should be visually assessed by 3 independent nuclear physicians (blinded readers) who should be blinded to all clinical information.

- Both the CP members and the independent blinded readers should be trained and validated.

For an amyloid-targeted PET tracer, a pivotal, multi-center, confirmatory efficacy program, should be considered for phase 3 development. The administered mass and radioactive dose and the formulation should be the same as that planned for the market. The currently proposed primary objective of the program would be to determine the diagnostic performance of the independent visual assessment of the PET scan results with the tracer in differentiating between patients with probable AD and healthy volunteers when compared to the clinical diagnosis (established by an independent consensus panel) as the standard of truth. Proposed secondary objectives would include a quantitative analysis of standardized regional tracer uptake ratios, the impact of the image findings on the on-site diagnosis, confidence of this diagnosis and the resulting subject management decisions (e.g., the clinical usefulness), and the inclusion of patients with other dementia subtypes (e.g., DLB, VaD, FTLD).

Generally speaking, for clinical development of an amyloid-targeted PET tracer (and associated limited specificity), sequential validation of efficacy needs to be established for discrimination at various time points in the course of the disease (e.g. moderate and mild disease). This includes discrimination of patients with manifest AD from normal healthy aging individuals (as a first step). Further steps might be the assessment of amyloid β in patients with mild cognitive impairment (MCI) and investigating the capability of the PET tracer to predict the deterioration of these mildly impaired patients into manifest AD and in discrimination of AD from non-AD dementia (e.g. DLB), FTD, VaD). For a clinical trial program for an agent of this type a key challenge that needs to be addressed is to what extent these questions can and need to be answered as part of an initial development program (e.g. prior to approval) or whether it is

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reasonable to assess some aspects that need to be addressed at a later time point, during the life cycle of the product for example.

6. Specific advice regarding the design of phase 3 AD diagnostic imaging studies

The Advisory Committee is aimed at providing specific advice regarding the design of phase 3 diagnostic imaging studies in AD and Bayer HealthCare is very interested in having a discussion pertaining to the following key salient features:

- Possible Target Indication for an amyloid binding diagnostic agent for AD
- Standard of Truth
- Proposed study population
- Clinical Usefulness

6.1 Target Indication

The FDA Guidance for Industry, Developing Medical Imaging Drug and Biological Products, Jun 2004, Part 2 states that for a pathology detection claim "a medical imaging agent …be able to detect and locate a specific disease or pathological state in at least one defined clinical setting." In line with the previous, for an amyloid-targeted PET tracer, the basis for a claim of this type could be the known pathological link between amyloid β plaque deposition in the brain (as the pathology in question) and manifestation of AD [Braak et al. 1997] (as the disease state). In line with this, a potential indication considered reasonable for an amyloid targeted PET tracer is listed below.

Because the presence of amyloid β plaque deposition is a prerequisite for the diagnosis of AD, this detection of pathology claim could also be combined with a "limited disease claim":

BAY-94 9172 can detect amyloid β plaque deposition in the brain and, thereby, assist the physician in the diagnosis of (detection/exclusion) of Alzheimer's disease.

In routine clinical practice, amyloid-targeted PET imaging will not be used as a "stand alone" in establishing a clinical diagnosis, but as an additional diagnostic tool aimed at assisting the clinician in establishing a more precise and objective differential diagnosis.

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6.2 Standard of Truth

6.2.1 The clinical diagnosis as the standard of truth

Definitive diagnosis of Alzheimer's disease and other types of dementia relies on post mortem, histo-pathological examination of the brain. However, in clinical development, it is not feasible to rely on autopsy as the standard of truth for dementia trials for various reasons. Instead of this rigorous standard, the clinical diagnosis established on the basis of an appropriate combination of clinical examination and the proper combination of validated tests including application of internationally accepted criteria can provide a very good approximation of the true disease state.

For the diagnosis of AD and other dementias in clinical trials, the Consensus Panel approach is validated and the clinical diagnosis established in this manner has been shown to be robust, reproducible, and renders a good approximation of the true disease state if established by experts, i.e. physicians with appropriate training and experience over a number of years [McKeith et al. 2000, Lopez et al. 2000, McKeith et al. 2007].

The validity of a consensus panel approach was also made apparent by the results of a longitudinal study designed to assess the accuracy of the clinical diagnosis in AD and reported by [Lopez et al. 2000]. On the basis of comparison with autopsy diagnosis an expert Consensus Panel was able to diagnose AD with a sensitivity of 97% and a specificity of 88% at the first visit when using the clinical criteria mentioned in section 6.2.2 and established on the basis of a composite of a detailed clinical, neuropsychiatric evaluation, which included neuropsychological assessment, lab tests and MR imaging of the brain. A similar diagnostic work up will be performed as part of our proposed phase 3 program (for psychometric testing, see section 6.2.2, for additional diagnostic measures, see section 6.2.3).

Within the frame of a phase 3 clinical program, the clinical diagnosis established by the independent Consensus Panel of experts is considered acceptable as a high quality standard of truth. The members of the Consensus Panel will be verified experts in the field of dementia and the methods and members will be validated before the phase 3 program commences.

6.2.2 Dementia criteria and psychometric tests

The Consensus Panel will establish their diagnosis on the basis of the following internationally accepted clinical criteria for categorizing dementia subtype**:** The DSM IV-TR criteria for Dementia and the NINCDS-ADRDA for AD, the International Consensus Criteria (ICC) for DLB, National Institute of Neurological Communicative Disorders and Association Internationale Pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) for VaD, and the Neary criteria for FTLD.

A comprehensive history, mental and physical examination would be undertaken from which standardized information would be provided to the consensus panel including:

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- Worksheet (using informant account) describing history and symptoms, with particular reference to mode of onset, course, progression, past medical and psychiatric history and concomitant medication

- Standardized physical examination (including neurological) examination

Psychometric tests

Validated psychometric tests suggested to assist the CP in establishing a diagnosis are listed below:

- **The Clinical Dementia Rating (CDR)** [Hughes et al. 1982]

  CDR has become the gold standard for global rating of primary degenerative dementia and is based upon the above and other similar neuropsychological tests. To complete the scale, the rater has to have a detailed knowledge of the subject. It is divided into 6 areas:

  - memory,
  - orientation,
  - judgment and problem solving,
  - community affairs,
  - home and hobbies, and
  - personal care.

  CDR incorporates the clinician's assessment of subjects' varying educational, cultural, socio-economic and other types of bias in its staging.

- **The neuropsychological test battery according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)** [Welsh et al. 1991], which includes the Mini-Mental Status Examination (MMSE) [Folstein et al. 1975]

  The CERAD assesses a wider range of cognitive functions, both distributed (attention, memory, abstraction) and localized (language, praxis, calculation, perception) than any other standardized schedule. Thus, it provides a means of detecting and objective assessment of the degree and type of episodic memory deficits present in the probable AD patients and verify their absence in healthy volunteers. The test has also been shown to be sensitive to early stage AD [Welsh et al. 1991].

  The Mini-Mental State Examination (MMSE) is the most widely used and studied screening measure of cognitive impairment. It has the advantage of brevity, ease of administration, and high test/retest and inter-rater reliability. The maximum score is 30. Scores below 24 are traditionally taken as indicative of cognitive impairment. The most sensitive items on the MMSE for AD dementia are delayed recall of 3 items and orientation.

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- **The Neuropsychiatric Inventory (NPI)** [Cummings et al. 1994]

  NPI is a semi-structured interview with the caregiver. The NPI covers 10 domains of behavioral disturbance:

  - delusions, hallucinations,
  - apathy,
  - depression,
  - night-time behaviors,
  - appetite and eating disorders,
  - dysphoria,
  - anxiety,
  - agitation/ aggression,
  - euphoria,
  - disinhibition,
  - irritability / liability and
  - aberrant motor activity.

  Each domain is rated for its severity and frequency. Results can be summarized as subscale scores, including a caregiver distress score, and an overall global score. The scale has been well validated and is now one of the most commonly used assessments in clinical trials.

- **The Fluctuation Inventory Scale (FIS)** [Walker et al. 2000]

  This is a short scale, designed for use by experienced clinicians to verify or rule out the presence of fluctuating cognition, a major symptom of Dementia with Lewy Bodies (DLB) [Walker et al. 2000]. In the proposed trial, this test assists the onsite physician in avoiding to misdiagnose a DLB patient as having probable AD. It consists of a series of screening questions, put to an informant, regarding fluctuating confusion, and impaired consciousness during the month prior to the assessment. Fluctuating confusion is rated as present if the informant is able to give a clear-cut example. This scale has been used previously as part of the diagnostic approach, and has achieved good diagnostic accuracy for DLB (sensitivity 83%, specificity 91%) against post-mortem diagnosis [McKeith et al, 2000].

- **The Geriatric Depression Scale** (abbreviated version) [Yesavage et al. 1983, Sheikh et al. 1986]

  Depression is a frequent accompanying symptom of AD and other dementias and severe, late onset depression can lead to a similar degree of cognitive impairment. The GDS was developed as a basic screening measure for depression in older adults. In the present study, the abbreviated 15 (vs. 30 question) scale will be used to assist the physician in objectifying depressive symptoms in both probable AD patients and

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HVs and in detecting/ruling out major, late onset depression as a cause for AD symptoms in the patients recruited into the study

- **The Frontal Assessment Battery (FAB)** [Dubois et al. 2000]

  The FAB is a short assessment battery for assessing frontal lobe function. The 6 FAB subtests explore both cognitive and behavioral domains under the control of the frontal lobes. Moreover each test is associated with specific areas of the frontal lobes based on neuro-physiological, electro-physiologic, and/or functional arguments: conceptualization with dorso-lateral areas, word generation with medial areas and inhibitory control with orbital or medial frontal areas. Therefore, performance of the 6 subtests

  - conceptualization,
  - mental flexibility,
  - programming,
  - sensitivity to interference,
  - inhibitory control and
  - environmental autonomy

  can facilitate both detection and determination of severity of the dysexecutive syndrome associated with Fronto-Temporal Lobar Degeneration (FTLD).

To assure adequate quality of the truth standard high quality data is essential. Therefore, prior to participation in the phase 3 trial, the onsite physicians and their teams should receive detailed instructions on the use of the pre-specified psychometric tests, as well as on the implementation of all other procedures and guidelines involved in reaching the final diagnosis.

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6.2.3 Additional diagnostic measures

Additional components of the diagnostic workup in the proposed study, aimed at increasing the quality of the truth standard, consist of special laboratory testing and structural MR imaging of the brain. These include, in addition to routine laboratory for hematology, coagulation, serum and electrolytes, special laboratory tests related to cognitive impairment:

- blood tests for thyroid function in order to exclude hypothyroidism as a potential cause of cognitive impairment
- blood tests for Vitamin B12 and folic acid in order to exclude deficiency of these vitamins since such deficiencies are also potential causes of cognitive impairment
- a non-contrast enhanced 3D volumetric T1-weighted and a T2-weighted brain MRI will be performed to enable detailed visualization of structural abnormalities

The Consensus Panel will be informed about the results of these diagnostic measures and will use them as additional information for establishing their diagnosis.

6.3 Proposed study population

6.3.1 Primary efficacy Population

The efficacy of an imaging agent by showing diagnostic performance, which is measured in terms of sensitivity and specificity of the diagnostic test, high enough to show the reliability of a new agent is outlined in the FDA Guidances listed in section 5.2 above. In the proposed clinical setting, which in Bayer´s opinion is the most appropriate, the proof of capability of the drug product, to detect amyloid β plaque deposition in the brain, without relying on autopsy, requires a well characterized population including "positive and negative controls". For a phase 3 program it would, therefore, be considered necessary to compare tracer uptake pattern in PET scans from individuals with a high probability of tracer uptake (i.e. probable AD as defined by the NINCDS ADRDA and the DSMIV-TR criteria) patients with a high likelihood of amyloid plaques in the brain = true positives) to that in individuals with a low probability of tracer uptake (cognitively normal healthy volunteers = true negatives). The former cohort serves as "positive controls" to determine sensitivity and the latter as "negative controls" to calculate specificity (primary endpoints).

It should be noted that amyloid β plaque deposition has been reported in healthy volunteers over 75 years of age [Price et al. 1999] and, in line with these findings, positive amyloid-targeted PET scans have been recently reported in healthy elderlies [Rowe et al. 2008, Mindon et al. 2008]. The relevance of the latter finding as a potential risk factor for the development of AD is currently the topic of intense clinical investigation. In an age matched collective (vs. younger healthy volunteers) false positive scan findings in older volunteers could negatively impact the specificity. Thus, it may be advantageous to include a cohort of younger healthy volunteers (e.g. < 60) as a comparative collective to determine the "true specificity" of the PET tracer.

6.3.2 Secondary efficacy population

Validated clinical criteria exist for dementia subtypes such as DLB, VaD, and FTLD and as such patients with dementia other than AD could be included in a phase 3 trial. However, in AD, DLB and VaD mixed pathology is frequent. In both DLB and VaD, a major fraction of patients also demonstrate AD pathology including the frequent and irregular occurrence of amyloid β plaque deposition in the brain [McKeith et al. 2004] and in DLB and AD vascular pathology is also frequent. Furthermore, due to their heterogenous clinical presentation, patients with VaD have been excluded from the majority of large dementia trials and based on current available data, imaging studies with amyloid-targeted agents have not yet been performed in this collective population. Although knowledge on amyloid-targeted tracer uptake pattern in dementia subtypes such as DLB, VaD and FTD is scarce and most assuredly of clinical value, scan results from these patients would not contribute to the determination of the target-indication specific co-

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primary endpoints (i.e. sensitivity and specificity) for detection/exclusion of amyloid β deposition in the brain (since they might or might not have amyloid in the brain and thus have to be considered as non-assessable).

However, results from this subset of subjects are valuable for assessment of differences in tracer uptake distribution pattern across dementia subtypes as a secondary endpoint. Thus, these dementia subtypes are planned to be included as a secondary (vs. primary) population in the proposed trial (see Appendix 1: Phase 3 Clinical Protocol Outline). However, the results will be analyzed in a descriptive manner only.

It should be noted at this point that the classification of probable and possible AD is dictated by the number of NINCDS-ADRDA core symptoms present rather than by the degree of uncertainty. However, diagnostic uncertainty can exist in both subjects with "probable" and "possible" AD and the diagnosis of AD based solely on clinical criteria remains difficult and is, to some degree, uncertain even in patients with "probable AD".

For "possible" AD (according to the NINCDS-ADRDA criteria), the degree of certainty of the clinical diagnosis based on validated clinical criteria is low and, thus, for this population an appropriate truth standard does not exists. The same applies to patients in whom a diagnosis based on validated clinical criteria cannot be made. The inclusion of "possible" AD patients (or those without a definitive clinical diagnosis) into the endpoint analysis would, therefore, have a misleading effect on the primary/secondary efficacy parameters and as such subjects of this type are presently not planned to be included into the program.

After substantiation of efficacy and safety in this development program, additional clinical trials may be considered for supplemental indications, such as "Disease prediction": Clinical trial designed to address mild cognitive impairment (MCI).

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6.4 List of questions

The Advisory Committee Panel is charged with providing input/consult to the Food and Drug Administration towards the specific critical aspects of developing PET tracers for the imaging of amyloid β plaques that assist in diagnosis of Alzheimer's disease.

Would the Advisory Committee consider the following salient features (addressed above in 6.1 6.3.2) as adequate and sufficient in their recommendation to the FDA:

Proposed Indication ***6.1***	The tracer can detect amyloid beta plaque deposition in the brain and, thereby, assist the physician in the diagnosis of (detection/exclusion) of Alzheimer's disease."
Standard Of Truth ***6.2***	Clinical diagnosis established by an independent expert Consensus Panel as a reasonable standard of truth in determining the efficacy of a novel PET tracer for amyloid.
Psychometric tests ***6.2.2***	The proposed battery of tests as adequate to provide sufficient neuropsychiatric data for a diagnosis of Alzheimer's disease by the Consensus Panel.
Additional testing for Dementia ***6.2.3***	Inclusion of additional examinations as proposed is reasonable to enhance the value of clinical diagnosis and improves the standard of truth.
Primary Efficacy Population ***6.3.1***	The inclusion of only those subjects diagnosed as "Probable AD" (as diagnosed by the independent consensus panel and the image interpretations of independent blinded readers) is reasonable.
Control Subjects ***6.3.1***	Relevant number of age-matched healthy volunteers is necessary for validation of the imaging method in terms of specificity.
Secondary Efficacy Population ***6.3.2***	Dementia subtypes other than AD are included only in the assessment of secondary efficacy assessment and are excluded from the primary efficacy assessment (sensitivity and specificity).

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8. Appendix 1: Phase 3 Clinical Protocol Outline

Study Title	**An open-label, non-randomized, multi-center phase 3 study to evaluate the efficacy and safety of the PET amyloid-targeted tracer for detection/exclusion of amyloid in the brains of subjects with probable Alzheimer's disease (AD) and other forms of dementia when compared to healthy volunteers.**
Clinical study phase	Phase 3
Background	Early and accurate diagnosis of Alzheimer's disease (AD), the most frequent form of dementia, is important as it helps the physician implement appropriate therapy early on. Time to diagnosis is decreased, unnecessary investigations avoided and cognitive symptoms alleviated, with a subsequent increase in quality of life, both for the patient and his/her family members [McKeith et al. 2007]. Current phase 3 development of both symptomatic and disease modifying therapies further underscores the importance of early and accurate diagnosis in AD. The availability of imaging markers capable of detecting amyloid accumulation in the brain would not only assist the clinicians to identify patients who would benefit from therapy, but also to decrease sample size and follow-up time and, thus, time and cost to development. Definite diagnosis of AD can only be made by post-mortem examination of the brain. The current criteria for the pathologic diagnosis of AD require the presence of extra-cellular deposits of amyloid β peptides [Braak et al. 1997]. Neocortical amyloid β plaque deposition, a pathological hallmark of AD, occurs early in the disease process, possibly years before the onset of clinical symptoms. The availability of a non-invasive, imaging marker capable of detecting amyloid β in the brain to facilitate early and accurate in vivo disease detection of AD is, thus, a major medical need. Trials in humans with amyloid targeted PET tracers have shown significant differences in tracer uptake pattern in the neocortical regions in subjects with AD when compared to healthy volunteers [Klunk et al. 2004, Rowe et al. 2008]. Here, in PET scans of subjects with AD, a higher tracer uptake has been seen in regions known to have amyloid β plaques compared to healthy volunteers, whereas in regions known to be unaffected by amyloid β deposition, tracer uptake was equivalent in AD patients and HV. Although initial results with tracers of this type are promising, as with all other novel diagnostic modalities, validity and reliability needs to be established on the basis of prospective clinical trials. Awaiting post-mortem diagnosis is not feasible in the context of a

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	clinical development program. Therefore, the clinical diagnosis established by an independent consensus panel (consisting of experts in the field) is considered a good approximation of standard of truth. The best established and still recommended clinical criteria for the diagnosis of AD have been defined by the National Institute of Neurological, Communicative Disorders and Stroke – AD and Related Disorders Association (NINCDS-ADRDA) [McKhann et al. 1984]. These criteria are validated by post mortem data for probable AD [Knopman et al. 2001] and will, therefore, be used to define this population in the present study. The trial described below is a pivotal efficacy trial (with an independently established clinical diagnosis as the standard of truth), the major purpose of which is to verify the efficacy of an amyloid targeted PET tracer to pursue the indication of "detection of pathology." (FDA Guidance For Industry: Developing Medical Imaging Drugs and Biological Products: June 2004) Secondary objectives include: assessment of various quantitative analysis methods, descriptive analysis of tracer uptake pattern in dementia subtypes other than AD, and initial data on clinical utility provided by evaluation of the onsite dementia experts diagnosis with and without knowledge of PET image findings. Upon verification of efficacy in this trial, Bayer may conduct additional clinical trials in pursuit of additional indications such as: 1) "Disease prediction": Clinical trial designed to address mild cognitive impairment (MCI) "2) Disease progression/therapy monitoring": Clinical trial designed to evaluate the therapeutic effects of novel agents

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Study objective(s)	**Primary Objective** To determine the diagnostic efficacy (i.e., sensitivity and specificity) of the independent visual assessment of the amyloid-targeted PET images in differentiating between subjects with probable Alzheimer's disease (AD) and healthy volunteers as determined by the clinical diagnosis as the standard of truth. • This diagnosis will be established by an independent consensus panel (CP) of experts in dementia, be based on internationally accepted diagnostic criteria and be made after comprehensive review of all available clinical, neuropsychiatric and other relevant data. The consensus diagnosis will be made without knowledge of the PET scan findings. • The PET images will be visually assessed by three independent experts in neuroimaging for the regional presence or absence of tracer uptake (which will be assumed to correlate to the presence or absence of amyloid β deposition). The readers will be blinded to all clinical findings, including the CP diagnosis. The readers will assess the blinded, randomized images consecutively and independent of one another. • For efficacy analysis, the presence of tracer uptake in a subject judged by the CP as having AD (positive control) will be a match for sensitivity and the absence of tracer uptake in a subject verified by the CP as being a healthy volunteer (negative control) will be a match for specificity. Due to the necessity of having a highly characterized collective, the primary efficacy analysis is based on probable AD patients and healthy volunteers only. Subjects not classified as probable AD patients or healthy volunteers are not included in the primary efficacy analysis. Data obtained from these subjects will only contribute descriptively to the overall body of evidence. **Secondary objectives** To determine the accuracy, positive predictive value (PPV) and negative predictive value (NPV) of the visual assessment of the PET image when compared to the CP clinical diagnosis (i.e. probable AD / healthy volunteer) as the standard of truth. To determine sensitivity, specificity, PPV and NPV of both Volume of Interest (VOI) and voxel-based quantitative image analysis in detecting/excluding cerebral amyloid when compared to the CP clinical

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	diagnosis as the standard of truth. To descriptively analyze the distribution of amyloid "positive" vs. "negative" images obtained in subjects with Dementia with Lewy Bodies (DLB), fronto-temporal lobe dementia [FTLD]) using the CP differential clinical diagnosis. To assess the on-site dementia expert's ability to establish a diagnosis before and after the PET scan the respective diagnostic confidence thereof, and the impact of scan findings on management decisions. To confirm the safety profile of a single dose of the imaging tracer in patients with dementia and healthy volunteers.
Route of administration	Intravenous injection
Duration of treatment	Single administration of a PET diagnostic agent
Indication	The tracer can detect amyloid β plaque deposition in the brain and, thereby, assist the physician in the diagnosos (detecting/excluding) of AD.

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Suggested main criteria for Inclusion and Exclusion	**Inclusion criteria:** • The subject is a man or woman and is between 55 to 90 years of age, whereby females must be without childbearing potential (confirmed by either: age ≥ 60; or history of surgical sterilization or of hysterectomy, or last spontaneous bleeding at least 2 years prior to the study start). • The subject presents with positive assessment for dementia in accordance with DSM-IV criteria and fulfils at least one of the following: - for probable AD the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA), - for DLB the International Consensus Criteria (ICC) , - for possible VaD the National Institute of Neurological Disorders and Stroke and Association Internationale Pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) - for FTD the Nearly criteria • The subject has a Mini Mental State Examination (MMSE) score of ≥ 20. • The Clinical Dementia Rating (CDR) for healthy volunteers is zero and from 0.5 to 1.5 in individuals with dementia. • The subject and the subject's caregiver or informant has given a written, informed consent. • The subject is able to provide informed consent, understand the information provided on the purpose and conduct of the trial and exhibits adequate visual, auditory and communication capabilities to enable compliance with study procedures. This includes performing the psychometric testing and being able to lie down flat in the scanner

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	Exclusion Criteria*:* • Cerebral structural vascular abnormalities indicative of major cerebral vascular disease (e.g. multi-stroke disease) have been confirmed by MR imaging and/or probable vascular dementia (VaD) has been verified by the NINDS-AIREN. • The subject is diagnosed with persistent severe depression. • The subject is diagnosed with normal pressure hydrocephalus.
Study Design	This is a phase 3, open-label; multi-center, non-randomized single dose study to determine the diagnostic efficacy (i.e. sensitivity and specificity) of the visual assessment of the amyloid-targeted PET imaging. Each subject will be required to visit the study centre during the screening phase, on the tracer imaging day (baseline), and for one follow-up visit. At the screening visit, each subject and the caregiver will be asked to provide written informed consent. During the screening phase the medical, neurological and surgical history, clinical assessments and a neuropsychiatric evaluation will be performed on all eligible subjects. Subjects will be allowed to leave the centre after all evaluations have been completed. An MRI of the brain must be performed. During the tracer imaging day, all subjects will receive a single IV injection of drug product and scanning will be performed xx minutes post-injection (phi.). Each subject will be asked to return to the site for a follow-up visit to assess safety (xx to xx hours after drug product administration).

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Methodology	The lack of cognitive impairment in healthy volunteers and the presence of dementia in AD and other dementia subjects will be verified on the basis of comprehensive clinical, laboratory, MRI and neuropsychiatric examination (including extensive psychometric testing). The standard of truth diagnosis will be established by an international CP of experts in the field of dementia. The CP will be trained and validated before the first CP session. After administration of drug product, images will be generated with state of the art PET (or PET/CT) scanners. Images will be visually assessed for the presence or absence of tracer uptake by the onsite nuclear physicians. The PET scans will be visually analyzed as part of an independent, blinded read performed by three nuclear physicians and experts in the field of neuroimaging. The blinded readers will be trained and validated before the first image analysis session. The onsite nuclear physicians and their teams will be instructed on proper PET image acquisition, processing and data transfer. To ensure optimal quality of the clinical and neuropsychiatric data to be reviewed by the independent CP; as well as standardization thereof across sites, the onsite dementia experts and their teams will be trained in all study-specific procedures. This will also ensure the overall quality of the onsite diagnosis (secondary endpoint). Quality assurance of all clinical, neuropsychiatric and image data will be performed on an ongoing basis.
Type of control	The results of the independent assessment of the PET images will be compared to the CP clinical diagnosis as the standard of truth. The diagnostic performance of the imaging agent will not be compared to that of another imaging modality.

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Plan for Statistical Methods and Planned Primary Efficacy Analysis	**Primary Variables** The co-primary efficacy variables of the study will be the sensitivity and specificity of the visual assessment of the tracer images in correctly differentiating between subjects with AD and healthy volunteers (based on the presence or absence of tracer uptake) when compared to the clinical diagnosis (determined by the independent CP) as the standard of truth. The primary efficacy population consists only of subjects with probable AD and healthy volunteers. Subjects who present with subtypes of dementia (DLB and FTLD) are excluded from the analysis of primary efficacy. This exclusion is based on the known frequent and irregular occurrence of amyloid β plaque deposition in the brains of these subjects which prevents the results from contributing to determination of sensitivity and specificity (the co-primary efficacy endpoints). However, results from this subset of subjects are valuable for assessment of differences in tracer uptake distribution pattern across dementia subtypes as a secondary endpoint. Descriptive statistics will be provided for the analysis of secondary efficacy. A hypothesis is specified for both co-primary efficacy variables. For sensitivity the null hypothesis is given as $H_{0,\ sens}$: $p \leq p_{\ sensitivity}$, the parameter p representing sensitivity. For specificity the null hypothesis is given as $H_{0,\ spec}$: $p \leq p_{specificity}$, the parameter p representing specificity. The α-level will be 0.05 (two-sided). The study is considered successful, when both null-hypotheses can be rejected. The sample size in both groups; subjects with probable AD and the healthy volunteers has been calculated such that the probability to reject one single hypothesis is 90%. The two sided 95% confidence intervals will be calculated for both the sensitivity and specificity based on the assessments of the joint blinded readers, yielding the result for the co-primary efficacy variables using normal approximation.

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McKeith I, O'Brien J, Walker Z, Tatsch K, Booijj J, Darcourt J, et al. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in Dementia with Lewy Bodies: a phase III, multi-centre study. Lancet Neurol 2007;6:305-313.

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OBSERVATION

Molecular Imaging With Pittsburgh Compound B Confirmed at Autopsy

A Case Report

Brian J. Bacskai, PhD; Matthew P. Frosch, MD, PhD; Stefanie H. Freeman, MD; Scott B. Raymond, BS; Jean C. Augustinack, PhD; Keith A. Johnson, MD; Michael C. Irizarry, MD; William E. Klunk, MD, PhD; Chester A. Mathis, PhD; Steven T. DeKosky, MD; Steven M. Greenberg, MD, PhD; Bradley T. Hyman, MD, PhD; John H. Growdon, MD

Objective: To determine the correspondence between uptake of Pittsburgh Compound B (PiB) in life and measures of β-amyloid (Aβ) in postmortem tissue analysis.

Patient: A 76-year-old man with a clinical diagnosis of dementia with Lewy bodies underwent fluorodeoxyglucose ^{18}F and PiB positron emission tomographic brain scans. Imaging revealed marked region specific binding of PiB and abnormal fluorodeoxyglucose uptake.

Intervention: Autopsy was performed 3 months after the PiB scan.

Results: Autopsy confirmed the clinical diagnosis; in addition, there was severe cerebral amyloid angiopathy and only moderate numbers of parenchymal Aβ plaques. Biochemical measures revealed a positive correlation between Aβ levels and regional PiB binding.

Conclusion: This report confirms that PiB detects Aβ in the living patient and demonstrates that amyloid deposited as cerebral amyloid angiopathy can be the dominant source of signal.

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Author Affiliations: MassGeneral Institute for Neurodegenerative Diseases, Department of Neurology, Charlestown, Mass (Drs Bacskai, Frosch, Irizarry, Greenberg, Hyman, and Growdon and Mr Raymond); C. S. Kubik Laboratory for Neuropathology (Drs Frosch and Freeman) and Department of Radiology (Drs Augustinack and Johnson), Massachusetts General Hospital, Boston; and Departments of Psychiatry (Drs Klunk and Mathis) and Neurology (Dr DeKosky), University of Pittsburgh, Pittsburgh, Pa. Dr Irizarry is now with GlaxoSmithKline, Research Triangle Park, NC.

IMAGING BRAIN AMYLOID DURING life with Pittsburgh Compound B (PiB) shows great promise as an aid to diagnosing Alzheimer disease (AD) and monitoring anti–β-amyloid (Aβ) therapies. Pittsburgh Compound B selectively binds to Aβ deposits in transgenic mice,[1] crosses the blood-brain barrier, and results in a strong positron emission tomography (PET) signal in the cortex of human patients with AD.[2] These observations are consistent with PiB's detecting Aβ deposits in the living human brain, but this assumption has never been directly confirmed. One of the proposed criteria for establishing an AD biomarker was that the in vivo finding be verified at autopsy.[3] We now report for the first time the neuropathological findings in the brain of a man with dementia whose PET scan revealed marked PiB uptake during life.

For editorial comment see page 315

REPORT OF CASE

A 76-year-old man was evaluated for memory loss and gait disorder. Aside from a single unexplained fall roughly 4 years previously, he had been well until memory loss became apparent 2 years prior to evaluation. A neurologist diagnosed peripheral neuropathy and possible Parkinson disease and began treatment with pramipexol, which was subsequently discontinued because it was deemed ineffective. A fluorodeoxyglucose ^{18}F PET scan performed 1 month prior to evaluation revealed reduced metabolism in both temporal and parietal cortices and mild reduction in the left frontal lobe; this pattern was consistent with AD. On examination, he reported having the fixed thought that a second (fictional) daughter was living in his house. He made 6 mistakes on the Information-Concentration-Memory subscore of the Blessed Dementia Scale, which ranges from 0 to 37 mistakes, 0 to 3 mistakes being within the normal range; the Mini-Mental State Exami-

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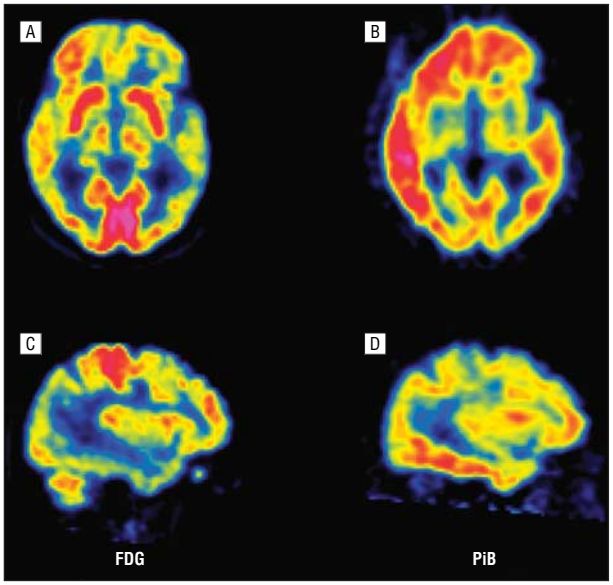

Figure 1. Positron emission tomography (PET) images from a 76-year-old patient with dementia. Fluorodeoxyglucose (FDG) and Pittsburgh Compound B (PiB) scans were performed within 3 years of each other. A and B, Positron emission tomography images from coregistered transaxial FDG (A) and PiB (B) PET images at the level of the striatum. Red areas represent higher metabolism of FDG and higher PiB retention. There is diffuse hypometabolism and PiB retention in frontal and temporal cortices. Regions with relatively normal metabolism, such as striata and medial occipital cortex, demonstrate relatively less PiB retention. Subject's left is at right. Evidence of the known subdural effusion occurring in the interval between FDG and PiB imaging is seen in the right frontal convexity of the PiB image. C and D, Coregistered left parasagittal FDG (C) and PiB (D) images at level of the insula. In this view, PiB retention is greatest in the inferior temporal gyrus, and there is relative sparing of the primary sensorimotor cortex where FDG uptake is highest.

nation score was 25 of 30. There was moderate bradykinesia, mild rigidity, and mild bilateral tremor at rest. He had stooped posture, diminished arm swing, and en bloc turning. A diagnosis of dementia with Lewy bodies was made and treatment begun. A regimen of 25 mg of carbidopa and 100 mg of levodopa 4 times daily improved motor symptoms, but memory and delusions worsened despite his receiving galantamine at 16 mg per day. Two years later, the patient was re-evaluated. A 60-minute dynamic brain PET acquisition with 15 mCi of ^{11}C-PiB was performed and showed marked uptake in association neocortical regions (**Figure 1**). Areas affected included the posterior cingulate, precuneus, posterior parietal, middle and inferior temporal, insular, and lateral and orbital frontal cortices. Formal cognitive testing performed after the PiB scan revealed global cognitive and functional impairments: the Mini-Mental State Examination score was 25 and the Clinical Dementia Rating was 1.0 against a background of above-average intelligence (American version of the National Adult Reading Test, Estimated Intelligence Quotient = 116). He died of complications following surgical evacuation of a traumatic subdural hematoma 3 months after the PiB scan, and an autopsy was performed.

RESULTS

The brain weighed 1420 g in the fresh state. There was no significant cortical atrophy evident. Moderate depigmentation of the substantia nigra and locus ceruleus was evident grossly. Microscopic examination confirmed the diagnosis of dementia with Lewy bodies, Braak stage IV.[4] There were plentiful Lewy bodies in the substantia nigra with marked neuronal loss; there were Lewy bodies in the entorhinal region as well as in cingulate and temporal neocortices. Neuropathological findings characteristic of AD were also present with moderate numbers of neurofibrillary tangles in temporal and parietal cortices as well as in limbic regions, including the amygdala and basal forebrain; rare tangles were seen in the occipital cortex. The stage of AD based on the frequency and distribution of the tangles was Braak and Braak IV.[5] There were several forms of Aβ pathology: severe bilateral cerebral amyloid angiopathy, moderate diffuse plaques, and rare cored plaques (**Figure 2**A). Diffuse plaques were frequent in the visual cortex but infrequent elsewhere; occasional cored plaques were seen in the parietal and occipital regions and were rare in other brain regions. Postmortem staining with 1μM of PiB and fluorescent detection revealed prominent PiB staining of cerebral amyloid angiopathy and dense cored plaques but not diffuse amyloid (Figure 2B). The overall frequency of plaques was low and met criteria from the Consortium to Establish a Registry for Alzheimer's Disease for "possible AD."[6] Taking the tangles into consideration along with the plaques, the findings were consistent with an "intermediate likelihood of dementia due to AD," based on criteria from the National Institute on Aging–Reagan Institute,[7] consistent with coexistent Lewy body disease. We measured soluble and insoluble Aβ40 and Aβ42 in frontal, parietal, and cingulate regions (**Table**) and compared these with measures of PiB binding in the homogenates and with measures of PiB binding obtained with PET (distribution volume ratios).[8] Together, the biochemical and histological data demonstrate that positive PET imaging of PiB in life reflects the presence of amyloid pathology. The proportion of Aβ40 to total Aβ is greater than that expected in AD,[9] supporting the strong contribution of vascular amyloid (Aβ40) to cortical amyloid load in this case.

COMMENT

To our knowledge, this study is the first pathological examination of a human brain from a patient who had a positive PiB scan during life. The autopsy confirmed the expectation that the PiB signal in life corresponds to Aβ deposits seen pathologically and measured biochemically after death. The brain contained relatively few mature cored plaques and had a restricted distribution of diffuse plaques that were present only in moderate numbers. Thus, based on criteria from the Consortium to Establish a Registry for Alzheimer's Disease, the diagnosis of AD would be "possible" but not "probable" and certainly not "definite." The most impressive finding was the severe cerebral amyloid angiopathy, which raises the notion that the PiB uptake in this case reflected Aβ in cerebral vessels more than Aβ in the brain parenchyma. Whether this observation is the rule or the exception must await additional clinical-pathological correlative

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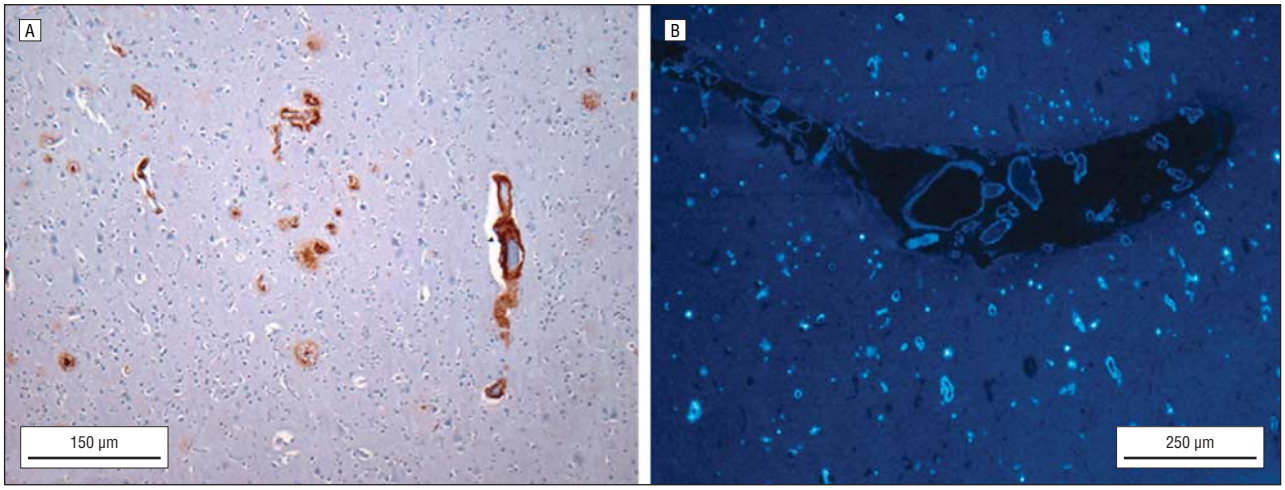

Figure 2. Examination of the brain tissue reveals various forms of amyloid pathology. β-amyloid (Aβ) immunohistochemistry using antihuman Aβ antibody 6F/3D (Dako Corp, Carpinteria, Calif) of the postmortem brain tissue from temporal lobe, showing numerous diffuse plaques, rare cored plaques, and amyloid angiopathy (A). Ex vivo imaging of brain tissue from the same case using Pittsburgh Compound B as the ligand detected with fluorescence demonstrates staining of cored plaques and abundant amyloid angiopathy (B).

Table. Comparison of Biochemical Analysis of Aβ With Quantitative PET in Affected Brain Regions

Region	DVR From PET Scan*	Soluble Aβ40, fmol/g	Soluble Aβ42, fmol/g	Insoluble Aβ40, pmol/g	Insoluble Aβ42, pmol/g	PiB Binding, pmol/g†
Frontal	1.311	6938	14 618	906	4685	444
Parietal	1.299	6788	9554	882	3703	325
Cingulate	1.504	4342	9884	881	3884	556

Abbreviations: Aβ, β-amyloid; DVR, distribution volume ratio; PET, positron emission tomography; PiB, Pittsburgh Compound B.

*Distribution volume ratio values were calculated from regions of interest within each brain region as described in Logan et al.[8] Enzyme-linked immunosorbent assays were performed on homogenates of brain tissue from these regions using capture and detection antibodies from Takeda Pharmaceutical (Osaka, Japan) as previously described.[9] Soluble fractions were extracted in Tris buffer, and insoluble fractions were extracted with formic acid. Parallel brain homogenates were analyzed with [H^3]PiB (1nM) for binding and normalized by wet tissue weight, as previously described.[10]

†Binding of 1nM [^{3}H]PiB to tissue homogenates (picomole per gram wet weight). This does not represent saturating conditions.

studies. It should be mentioned that PiB does not bind to Lewy bodies or neurofibrillary tangles at the tracer doses used for PET imaging, and even if it did, the scarcity of these intracellular pathologies would contribute negligible signal, especially compared with that from Aβ deposits.

Pittsburgh Compound B uptake appears sensitive to the presence of Aβ, but the specificity of a positive PiB scan is still under study. Uptake of PiB is a hallmark of AD and distinguishes most cases from normal controls.[2,11] Subsequent research, however, indicates that up to 15% of apparently normal people have substantial cortical PiB binding.[12] Brain amyloid accumulation is commonly seen in some elderly people at autopsy[13] and whether these deposits are harbingers of dementia is under intense investigation. Most individuals with a diagnosis of mild cognitive impairment have positive PiB scans whereas some do not, and the proportion of PiB-positive subjects with mild cognitive impairment is similar to the proportion that ultimately develop AD.[14] Our report substantiates the view that PiB uptake is a sensitive method to detect Aβ in the brain but points out the fact that clinical conditions other than probable or definite AD may harbor PiB-detectable amyloid deposits—thus broadening the range of clinically defined syndromes in which a PiB scan may be positive. Based on these findings, we would expect PiB retention to be a feature not only of AD, but also of (1) a normal elderly patient with amyloid deposition at risk for AD, (2) mild cognitive impairment, (3) cerebral amyloid angiopathy, and (4) dementia with Lewy bodies with amyloid pathology. It may be best not to equate amyloid deposition to clinical diagnosis from the outset but to think of PiB retention more fundamentally as a method to detect and quantify brain β-amyloidosis.[14] It is clear that some individuals with a clinical diagnosis of AD will not have a positive PiB scan,[2] but it is not known whether these are true negatives or false negatives. That is to say, it is not yet known if someone who meets neuropathological criteria for AD can have a negative PiB scan.

As shown by the case in this report, it is also clear that several different dementia-associated pathologies (eg, Lewy bodies and threads, neurofibrillary tangles, infarcts, etc) can coexist even within a single brain. However, the clinical diagnosis, or even the pathological diagnosis based on consensus criteria, does not directly predict the presence or absence of Aβ deposition in these mixed states. The importance of amyloid imaging is as an objective measure of Aβ pathology. In many cases, this will be a diagnostic aid but will likely be of great value

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in evaluating therapies aimed at reduction of Aβ pathology. In summary, this report describes a correspondence of amyloid pathology at autopsy with a positive PiB scan in life but demonstrates that amyloid deposited as cerebral amyloid angiopathy is the dominant source of signal.

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Correspondence: Brian J. Bacskai, PhD, MassGeneral Institute for Neurodegenerative Diseases, Department of Neurology, Massachusetts General Hospital, 114 16th St, Charlestown, MA 02129 (bbacskai@partners.org).
Author Contributions: *Study concept and design:* Bacskai, DeKosky, Hyman, and Growdon. *Acquisition of data:* Bacskai, Frosch, Freeman, Raymond, Augustinack, Johnson, Irizarry, Hyman, and Growdon. *Analysis and interpretation of data:* Bacskai, Frosch, Raymond, Irizarry, Klunk, Mathis, DeKosky, Greenberg, Hyman, and Growdon. *Drafting of the manuscript:* Bacskai, Frosch, Freeman, Klunk, and Mathis. *Critical revision of the manuscript for important intellectual content*: Frosch, Raymond, Augustinack, Johnson, Irizarry, Klunk, Mathis, DeKosky, Greenberg, Hyman, and Growdon. *Statistical analysis:* Irizarry. *Obtained funding:* Bacskai, Frosch, and Johnson. *Administrative, technical, and material support:* Frosch, Freeman, Raymond, Augustinack, Johnson, Irizarry, DeKosky, and Hyman. *Study supervision:* Bacskai, Frosch, Klunk, Mathis, Hyman, and Growdon.
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Psychiatric Morbidity in Dementia With Lewy Bodies: A Prospective Clinical and Neuropathological Comparative Study With Alzheimer's Disease

Clive Ballard, M.R.C.Psych., M.D., Clive Holmes, M.R.C.Psych., Ian McKeith, F.R.C.Psych., M.D., David Neill, M.R.C.Psych., Ph.D., John O'Brien, M.R.C.Psych., D.M., Nigel Cairns, Ph.D., Peter Lantos, M.D., F.R.C.Path., Elaine Perry, Ph.D., Paul Ince, M.D., and Robert Perry, M.D.

Objective: The literature reports considerable variation in the rates of psychiatric morbidity for patients with dementia with Lewy bodies. The authors intended to clarify the frequency of psychiatric morbidity in dementia with Lewy bodies and how it differs from probable Alzheimer's disease. **Method:** The study incorporated two groups—a clinical case register cohort (98 with dementia with Lewy bodies; 92 with Alzheimer's disease) and 80 (40 with dementia with Lewy bodies; 40 with Alzheimer's disease) prospectively studied, neuropathologically confirmed cases. Diagnoses were made by using the McKeith et al. consensus criteria for dementia with Lewy bodies and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for Alzheimer's disease. Neuropathological diagnoses were made by using the consensus criteria for dementia with Lewy bodies and the Mirra et al. protocol for Alzheimer's disease. **Results:** The occurrence of psychiatric symptoms was reported over 1 month. Hallucinations, depression, delusions, and delusional misidentification were all significantly higher for patients with dementia with Lewy bodies. The differences in frequency between dementia with Lewy bodies and Alzheimer's disease for auditory and visual hallucinations were especially pronounced for patients with mild cognitive impairment. The presence of psychiatric symptoms at presentation was a better discriminator between dementia with Lewy bodies and Alzheimer's disease than occurrence over the course of dementia. **Conclusions:** Delusional misidentification and hallucinations in the early stages of dementia may improve differentiation between patients with dementia with Lewy bodies and those with Alzheimer's disease and have important treatment implications.

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Lewy bodies are intraneuronal eosinophilic inclusion bodies that are seen in the brainstem and cortex of patients with Parkinson's disease and some patients with dementia. Studies (1–6) have suggested that dementia with Lewy bodies accounts for 10% to 25% of dementia cases in clinical populations. An international meeting developed operationalized clinical diagnostic criteria 7). Key features include persistent or recurrent visual hallucinations, parkinsonism, and fluctuating confusion associated with disturbances of consciousness.

All studies have found visual hallucinations to occur significantly more frequently in dementia with Lewy bodies than in Alzheimer's disease, although rates have varied greatly, from 25% to 83%, even when smaller studies are excluded from consideration (table 1) (4–6, 8–15). Delusions are common in patients with dementia with Lewy bodies, with rates varying from 13% to 75%. Some groups have found delusions to have a significantly higher frequency in dementia with Lewy bodies than in Alzheimer's disease (table 1) (4–6, 8–15). Auditory hallucinations have received less atten-

Received May 28, 1998; revisions received Sept. 22 and Nov. 6, 1998; accepted Dec. 15, 1998. From the Medical Research Council Neurochemical Pathology Unit, Newcastle General Hospital; the Institute of Psychiatry, London; and the University of Newcastle Upon Tyne, U.K. Address reprint requests to Dr. Ballard, Medical Research Council Neurochemical Pathology Unit, Newcastle General Hospital, Westgate Road, Newcastle Upon Tyne, NE4 6BE U.K.; m.p.walker@ncl.ac.uk (e-mail).

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TABLE 1. Literature Review of Psychiatric Morbidity in Studies of Dementia With Lewy Bodies Symptoms

Study	Year	Number of Patients		Type of Clinical Diagnosis	Neuro-pathological Diagnosis	Subjects With Hallucinations (%)					
						Visual		Auditory		Combined	
		Lewy Bodies	Alz-heimer			Lewy Bodies	Alz-heimer	Lewy Bodies	Alz-heimer	Lewy Bodies	Alz-heimer
Byrne et al. (8)	1989	15	0	—	Yes	—	—	—	—	—	—
McKeith et al. (9)	1992	21	37	—	Yes						
Point frequency						33	8	14	3	—	—
Course of illness						48	16	19	3	—	—
Ballard et al. (4)	1993	16	44	Operational-ized	No	25	0	—	—	—	—
Shergill et al. (5)	1994	30	80	Operational-ized criteria applied to case notes	No	—	—	—	—	67	25
Ballard et al. (6)	1995	12	88	Operational-ized	No	83	25	—	—	—	—
Weiner et al. (10)	1996	24	58	—	Yes	—	—	—	—	64	21
Klakta et al. (11)	1996	28	58	—	Yes	—	—	—	—	61	35
McKeith et al. (12)	1994	20	21	Retrospective	Yes	80	19	45	0	—	—
Galasko et al. (13)	1996	26	26	—	Yes	32	11	—	—	—	—
Ala et al. (14)	1997	39	60	—	Yes	—	—	—	—	23	3
Ballard et al. (15)[a]	1996	56	0	—	Yes	16	0	11	0	—	—

[a] Small pathological series.

tion, although they were described as more common in dementia with Lewy bodies than in Alzheimer's disease by McKeith et al. (9–12). Rates have varied from 11% to 45% (table 1) (4–6, 8–15). Delusional misidentification has not been studied in postmortem series, although two clinical studies found these symptoms to be common in patients with dementia with Lewy bodies (6, 16).

The rate reported for depression has varied from 14% to 50% in patients with dementia with Lewy bodies. Using a broad clinical definition, Klakta et al. (11) reported depression in 50% of patients with dementia with Lewy bodies. McKeith et al. (9) reported depressive symptoms in 33% of patients with dementia with Lewy bodies, although only 14% met the criteria for major depression, whereas Ballard et al. in a clinical study (6) found that 33% of patients with dementia with Lewy bodies had DSM-III-R major depression. Depressive symptoms are common in patients with dementia with Lewy bodies, although the proportion of patients with major depression requires clarification (table 1) (4–6, 8–15).

The rates of many important psychiatric symptoms have not been accurately determined for patients with dementia with Lewy bodies. Equally important, it is unclear whether some of these symptoms are more common in patients with dementia with Lewy bodies than in Alzheimer's disease patients and whether they change with increasing severity. The variability of previous reports is probably accounted for by the small study group sizes, the retrospective design of many studies, the different assessment methods for psychiatric symptoms, the variable time courses of symptom ascertainment, and the biases introduced by clinical selection criteria.

The current study focused on the two largest dementia with Lewy bodies cohorts reported so far. Our aims were to examine the frequency of psychiatric symptoms among patients with dementia with Lewy bodies and to evaluate the differences in symptom profile between patients with dementia with Lewy bodies and those with Alzheimer's disease.

METHOD

Clinical Cohort

The first cohort was based on patients from the Newcastle dementia case register (337 clinically assessed dementia patients, including 98 with dementia with Lewy bodies and 92 with probable Alzheimer's disease), incorporating consecutively referred patients with mild or moderate dementia seen by psychiatric services with defined geographical catchment areas who have an informant in regular contact. After a full explanation, written consent was obtained from the patients, with written assent from their nearest relatives. Following death, the next of kin was approached and given a full explanation regarding the aims of the related postmortem study, and written consent was obtained. The study was approved by human subjects ethical committees in both Newcastle and London. Patients from the register who met operationalized clinical criteria for a consensus diagnosis of dementia with Lewy bodies (7) (applied by three experienced clinicians in consensus [C.B., I.M., J.O.]) were compared with patients from the same cohort who met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (17) for probable Alzheimer's disease. Data from the first 50 patients from within this series for whom there was a postmortem examination showed a positive predictive value of 0.92 for a diagnosis of dementia with Lewy bodies against postmortem diagnosis (18). The corresponding figure for the positive predictive value of a clinical diagnosis of probable Alzheimer's disease against neuropathological diagnosis was 0.80.

The assessment included a standardized psychiatric history (history and etiology schedule [19]) and an assessment of cognitive func-

Subjects With Delusions (%)		Subjects With Delusional Misidentification (%)		Subjects With Overall Psychosis		Subjects With Depression (%)		Subjects With Anxiety (%)		
Lewy Bodies	Alzheimer	Lewy Bodies	Alzheimer	Lewy Bodies	Alzheimer	Lewy Bodies	Alzheimer	Lewy Bodies	Alzheimer	Psychiatric Diagnosis
—	—	—	—	33	0	20	0	—	—	Case note review
48	8	—	—	—	—	14	0	—	—	Case note review
57	11	—	—	—	—	14	5	—	—	Case note review
44	38	—	—	—	—	44	16	—	—	Operationalized 1-month rates
67	25	—	—	—	—	—	—	—	—	Case note review; time frame not specified
75	47	50	27	—	—	33	17	—	—	Operationalized 1-month rates
43	10	—	—	—	—	46	16	—	—	Clinical rating point frequency
57	53	—	—	—	—	50	14	—	—	Standardized, retrospectively, over illness course
80	19	—	—	—	—	—	—	—	—	Case note review over illness course
43	29	—	—	—	—	16	16	—	—	Operationalized over illness course
—	—	—	—	—	—	18	7	—	—	Case note review; presenting symptoms
13	0	—	—	—	—	14	0	—	—	Case note review over illness course

tion using the cognitive section of the Cambridge Assessment for Mental Disorders of the Elderly (20), a widely used and validated cognitive assessment instrument, scored out of a possible 107 points. A standardized physical examination incorporated the Unified Parkinson's Disease Rating Scale (21). An assessment of psychosis used the Columbia University Scale for Psychopathology in Alzheimer's Disease (22), and an evaluation of depression was undertaken by using the Cornell Scale for Depression in Dementia (23). All scales to assess psychiatric morbidity measured the occurrence over 1 month. A computerized tomography scan or magnetic resonance imaging scan and full dementia blood screen were also performed.

The diagnosis of depression was made by using DSM-III-R criteria, ignoring the caveat regarding exclusion if there is evidence of organic causation. Definitions regarding the presence and classification of psychotic features were taken from the criteria of Burns et al. (24). Delusional misidentification included the Capgras delusion and delusional misidentification of television images and mirror images.

Neuropathological Cohort

This cohort's patients were recruited from two centers (80 prospectively assessed patients with dementia: 40 patients with dementia with Lewy bodies, 40 patients with Alzheimer's disease)—the Institute for the Health of the Elderly in Newcastle (28 patients with dementia with Lewy bodies, 12 patients with Alzheimer's disease) and the Institute of Psychiatry in London (12 patients with dementia with Lewy bodies, 28 patients with Alzheimer's disease). Both centers have a case register of dementia sufferers from defined geographical areas. The Newcastle case register has been described previously. In London, the case register included subjects with dementia known to hospital and social services. All cases of patients with neuropathologically confirmed dementia with Lewy bodies from both centers were included in the current report, together with an equal number of age- or gender-matched patients with neuropathologically confirmed cases of Alzheimer's disease. At the point of entry into the study, written consent was obtained from the patients, with assent from the next of kin, after a full explanation was given. A separate written consent was obtained from the next of kin after death to permit postmorten examination.

The assessment measures at the Newcastle center are described in the previous section. In London, a standardized psychiatric history was taken by using the Cambridge Assessment for Mental Disorders of the Elderly (20). Both the history and etiology schedule and the Cambridge Assessment for Mental Disorders of the Elderly schedules contain detailed information regarding patient history, medication use, mental state, history of psychiatric symptoms, and fluctuation and disturbances of consciousness. The Mini-Mental State examination (25) (derived from the cognitive section of the Cambridge Assessment for Mental Disorders of the Elderly in Newcastle) was used for cognitive assessment, and the Cornell Scale for Depression in Dementia (23) was used for assessing depression. The Cornell scale was augmented by additional DSM-III-R items pertaining to the duration of the mood disturbance and its effect on social functioning. Psychotic symptoms were evaluated in London by using the Manchester and Oxford Universities Scale for the Psychopathological Assessment of Dementia (26) (all of the Columbia University Scale for Psychopathology in Alzheimer's Disease items are contained within the Manchester and Oxford Universities Scale for the Psychopathological Assessment of Dementia). All standardized assessments reported the occurrence of psychiatric symptoms over 1 month. A physical examination was performed that included assessment of parkinsonism with the Webster scale (27) and staging through use of the Hoehn and Yahr system (28), with a rating of 1 or more taken as evidence of significant parkinsonism. This detailed operationalized assessment was repeated at annual intervals until the patient's death.

Psychiatric symptoms were diagnosed by using the same procedures outlined in the clinical section. The symptoms at presentation were recorded from the baseline assessment. Information regarding symptoms over the course of the illness was obtained by combining information from the psychiatric history, the baseline assessment, and subsequent annual assessments.

The neuropathological diagnosis of Alzheimer's disease was made by using quantitative techniques to determine plaque and tangle densities (6) and according to the criteria of the Consortium to Establish a Registry for Alzheimer's Disease (29). The quantitative assessment of Lewy body density followed the consensus protocol (7), using ubiquitin and Tau2, Alz50, and AT8 antibodies to detect and distinguish cortical Lewy bodies. The neuropathological diagnosis of dementia with Lewy bodies was made according to the international consensus criteria (7).

The number of patients with dementia with Lewy bodies and those with Alzheimer's disease experiencing symptoms of interest at presentation were compared by using the chi-square test. The same method was used to compare the rates of symptoms over the course of the illness. The rates of symptoms were described for patients

TABLE 2. Demographic Characteristics of Patients With Dementia With Lewy Bodies and Patients With Alzheimer's Disease

Characteristic	Clinical Cohort (N=190)						Neuropathological Cohort (N=80)					
	Patients With Dementia With Lewy Bodies (N=98)		Patients With Alzheimer's Disease (N=92)		Analysis		Patients With Dementia With Lewy Bodies (N=40)		Patients With Alzheimer's Disease (N=40)		Analysis	
	N	*%*	*N*	*%*	χ^2 *(df=1)*	*p*	*N*	*%*	*N*	*%*	χ^2 *(df=1)*	*p*
Female gender	49	50	65	71	7.7	<0.006[a]	20	50	20	50	—[b]	—
	Mean	*SD*	*Mean*	*SD*	z[c]	*p*	*Mean*	*SD*	*Mean*	*SD*	z[c]	*p*
Age (years)	78.6	7.8	82.1	6.3	4.9	<0.001[a]	79.5	5.4	80.2	4.1	—[b]	—
Score on cognitive section of the Cambridge Examination for Mental Disorders of the Elderly (out of 107)	46.2	26.2	49.1	24.4	0.9	0.39	—	—	—	—	—	—
Score on Mini-Mental State examination (out of 30)	—	—	—	—	—	—	13.2	17.9	9.2	7.3	1.6	0.16
Duration of illness at presentation (years)	2.6	1.9	3.1	2.3	1.4	0.17	3.6	2.4	4.2	1.5	2.4	0.02[a]
Duration of illness to death (years)							4.3	2.3	5.6	1.8	2.7	0.008[a]

[a] Statistically significant. [b] Matched. [c] Mann-Whitney U test.

with mild (Mini-Mental State examination score of 20 or more), moderate (Mini-Mental State examination score=10–20), and severe (Mini-Mental State examination score less than 10) cognitive impairment. Overall scores on the Mini-Mental State examination and scores on the cognitive section of the Cambridge Assessment of Mental Disorders of the Elderly were compared between patients with dementia with Lewy bodies and Alzheimer's disease patients by using the Mann-Whitney U test. All statistics were obtained by using the Statistical Package for the Social Sciences (30).

RESULTS

The clinical case register cohort included 337 patients with dementia, 329 of whom met the criteria for dementia with Lewy bodies (N=98), Alzheimer's disease (92 probable, 74 possible), or vascular dementia (N=65). Only the patients with probable dementia with Lewy bodies or probable Alzheimer's disease were considered in the present study. The neuropathological series included 40 patients with dementia with Lewy bodies who were compared with 40 Alzheimer's disease patients matched by age and gender. Their demographic characteristics are described in table 2. The patients with dementia with Lewy bodies in the clinical cohort were more likely to be male and were significantly younger. The patients in the neuropathological cohort were matched for these variables, but the Alzheimer's disease patients were significantly more cognitively impaired and had a longer illness duration (table 2).

At presentation, visual and auditory hallucinations, delusions, delusional misidentification, and depression were significantly more common in patients with dementia with Lewy bodies, in both the clinical and neuropathological cohorts. The rates of individual symptoms are shown in table 3 and are similar in the two study groups, apart from the lower frequency of depression in the clinically diagnosed patients. Most psychiatric symptoms had rates exceeding 30% in patients with dementia with Lewy bodies from the clinical cohort, with visual hallucinations occurring in more than 70% of the patients. The two dementias showed the biggest differences regarding visual and auditory hallucinations and delusional misidentification.

The differences in the frequency of psychiatric symptoms between patients with dementia with Lewy bodies and those with Alzheimer's disease were less dramatic when observed over the course of the dementia, especially for delusions. That was also true for visual hallucinations, which occurred in more than 30% of Alzheimer's disease patients over the course of the illness (table 4).

Table 5 shows the rates of key psychiatric symptoms in clinically diagnosed patients with mild, moderate, and severe dementia defined by Mini-Mental State examination cutoff scores. Most important, both auditory (0%) and visual (5%) hallucinations were extremely uncommon among Alzheimer's disease patients scoring over 20 on the Mini-Mental State examination. Among patients with Mini-Mental State examination scores over 20, all patients with auditory hallucinations and 93% of patients with visual hallucinations had a diagnosis of probable dementia with Lewy bodies.

DISCUSSION

The strength of the current study is the combination of prospective clinical assessment with neuropathological confirmation of diagnoses in two independent

TABLE 3. Psychiatric Symptoms at Presentation in Patients With Dementia With Lewy Bodies and Patients With Alzheimer's Disease

Symptom	Clinical Cohort (N=190)						Neuropathological Cohort (N=80)					
	Patients With Dementia With Lewy Bodies (N=98)		Patients With Alzheimer's Disease (N=92)		Analysis		Patients With Dementia With Lewy Bodies (N=40)		Patients With Alzheimer's Disease (N=40)		Analysis	
	N	%	N	%	χ^2 (df=1)	p	N	%	N	%	χ^2 (df=1)	p
Hallucinations												
Visual	71	72	15	16	60.4	<0.001[a]	26	65	10	25	12.9	<0.001[a]
Auditory	37	38	5	5	28.8	<0.001[a]	14	35	4	10	7.2	0.007[a]
Delusions	56	57	28	30	14.5	<0.001[a]	24	60	12	30	7.3	0.007[a]
Delusional misidentification	49	50	18	20	19.3	<0.001[a]	15	38	2	5	14.1	<0.001[a]
Major depression	19	19	7	8	5.6	0.02[a]	13	32.5	5	12.5	4.6	0.03[a]
Anxiety	40	41	30	33	1.4	0.24	15	38	10	25	1.5	0.23

[a] Statistically significant.

but compatible cohorts with dementia with Lewy bodies.

The study confirms the high frequency of visual hallucinations (clinical cohort, 72%; neuropathological cohort, 65%), auditory hallucinations (clinical cohort, 38%; neuropathological cohort, 35%), delusions (clinical cohort, 57%; neuropathological cohort, 60%), and depression (clinical cohort, 19%; neuropathological cohort, 32.5%) at presentation to clinical services in patients with dementia with Lewy bodies. The rates are similar between the clinical and neuropathological cohorts for most symptoms except depression. The last discrepancy is not surprising given the higher mortality rates of depressed dementia patients (31).

Visual and auditory hallucinations, delusions, and depression all occurred at significantly higher rates in patients with dementia with Lewy bodies than in Alzheimer's disease patients. The presence of visual or auditory hallucinations in patients with Mini-Mental State examination scores greater than 20 was even more suggestive of dementia with Lewy bodies, which may have important implications for early diagnosis. Patients with hallucinations early in the course of their dementia are also a key group for intervention studies aiming to reduce the severity, persistence, and distress of these symptoms as well as preventing the expedited institutionalization that often ensues.

When symptom rates across the course of the dementia were calculated, the magnitude of difference between dementia with Lewy bodies and Alzheimer's disease patients diminished. This is supported by previous work, where the differences in frequency of psychiatric symptoms for dementia with Lewy bodies and Alzheimer's disease patients are more substantial in studies evaluating point or 1-month rates (table 1). Although a good psychiatric history is important and will more accurately identify a particular symptom over the course of an illness, it is suggested that the differential diagnosis of dementia with Lewy bodies can be made more accurately by focusing on symptoms over the month before presentation. This is particularly true for delusions, reflecting the tendency of Alzheimer's disease patients to experience brief delusional episodes (32).

TABLE 4. Psychiatric Symptoms at Any Stage of Dementia in a Neuropathological Cohort of Patients With Dementia With Lewy Bodies and Patients With Alzheimer's Disease

Symptom	Patients With Dementia With Lewy Bodies (N=40)		Patients With Alzheimer's Disease (N=40)		Analysis (df=1)	
	N	%	N	%	χ^2	p
Hallucinations						
Visual	29	73	15	37.5	9.9	0.002[a]
Auditory	18	45	5	12.5	10.3	0.001[a]
Depression	19	47.5	7	17.5	8.2	0.004[a]
Delusions	28	70	27	67.5	0.1	0.81
Delusional misidentification	16	40	4	10	9.6	0.002[a]

[a] Statistically significant.

Alzheimer's disease patients in the clinical cohort were older and more likely to be female, whereas Alzheimer's disease patients in the neuropathological cohort had more severe cognitive impairment and a longer duration of illness. Each of these factors may have elevated the relative frequency of some psychiatric symptoms, although the confounding effects would operate in the opposite direction from the current findings. Because patients from the clinical cohort met the clinical diagnostic criteria for dementia with Lewy bodies, it is possible that the reported rates of visual hallucinations may have been elevated by selection biases. However, the magnitude of difference was similar in the neuropathologically diagnosed patients.

Both cohorts reported in the current study showed significantly higher rates of depression with dementia with Lewy bodies than with Alzheimer's disease. Five out of six previous studies have reported higher rates of depression in patients with dementia with Lewy bodies (table 1), although many of the study groups have not been large enough to demonstrate statistically significant differences. This is consistent with the cur-

TABLE 5. Relation of Dementia Severity to Psychiatric Symptoms at Presentation in a Clinical Cohort of Patients With Dementia With Lewy Bodies and Patients With Alzheimer's Disease

	Mini-Mental State Examination Score											
	Patients With Dementia With Lewy Bodies						Patients With Alzheimer's Disease					
	<10 (N=20)		10–20 (N=53)		>20 (N=25)		<10 (N=18)		10–20 (N=52)		>20 (N=22)	
Symptom	N	%	N	%	N	%	N	%	N	%	N	%
Depression	4	20	10	19	5	20	1	6	4	8	2	9
Delusions	12	60	31	58	13	52	5	28	15	29	7	32
Hallucinations												
Visual	16	80	40	75	15	60	4	22	10	19	1	5
Auditory	6	30	21	40	10	40	0	0	5	10	0	0
Delusional misidentification	12	60	27	51	10	40	5	28	9	17	4	18

rent study, where the effect size was less substantial than for psychotic features.

Delusional misidentification and anxiety have received little previous attention. Anxiety was common in both patients with dementia with Lewy bodies and those with Alzheimer's disease. However, delusional misidentification was substantially more common in patients with dementia with Lewy bodies and may also be of diagnostic importance.

Given the high frequency of psychiatric symptoms in patients with dementia with Lewy bodies, developing safe and effective treatments is a priority but depends on understanding treatment mechanisms. Perry et al. (33) identified a strong association between visual hallucinations in patients with dementia with Lewy bodies and the severity of cholinergic depletion in the temporal cortex, a finding supported by parallel work with Alzheimer's disease, suggesting that anticholinesterase inhibitors may improve psychosis (34).

The mechanisms underlying other psychiatric symptoms have received less attention. A pilot study (35) suggested a link between the severity of parkinsonism and depression in dementia with Lewy bodies. Given the established link between depression and Parkinson's disease, the possibility that similar mechanisms are important merits further study.

For Alzheimer's disease, Förstl et al. (36) suggested that relative preservation of the parahippocampal gyrus is associated with delusions. The relative sparing of medial temporal lobe structures in patients with dementia with Lewy bodies (37) may hence predispose them to delusional phenomena. Further work needs to focus on the neurochemical correlates of preserved temporal lobe structures to inform the development of therapeutic strategies. Förstl et al. (36) suggested that delusional misidentification may be associated with more severe neuronal loss in the hippocampus.

While there is already sufficient evidence to merit trials of treatment intervention with cholinesterase inhibitors for visual hallucinations, further work is required to understand the basis of other psychiatric symptoms.

This report confirms a significantly higher frequency of psychiatric symptoms, especially psychotic features, in patients with dementia with Lewy bodies. The finding that these differences were especially pronounced in patients with mild dementia has implications for early diagnosis and treatment.

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Article

Neuropathological Substrates of Psychiatric Symptoms in Prospectively Studied Patients With Autopsy-Confirmed Dementia With Lewy Bodies

Clive G. Ballard, M.R.C.Psych., M.D.

Robin Jacoby, F.R.C.Psych., D.M.

Teodoro Del Ser, M.D.

M. Nadeem Khan, Ph.D.

David G. Munoz, M.D., F.R.C.P.(C), F.R.C.Path.

Clive Holmes, M.R.C.Psych., Ph.D.

Zsuzanna Nagy, M.D., D.Phil.

Elaine K. Perry, Ph.D.

Catherine Joachim, M.D.

Evelyn Jaros, Ph.D.

John T. O'Brien, F.R.C.Psych., D.M.

Robert H. Perry, F.R.C.Path.

Ian G. McKeith, F.R.C.Psych., M.D.

Objective: This investigation was undertaken to clarify the neuropathological substrates of key psychiatric symptoms in dementia with Lewy bodies.

Method: The authors studied 112 autopsy-confirmed cases of dementia with Lewy bodies in patients who had had annual standardized clinical evaluations until their death. The relationships of persistent psychiatric symptoms (visual hallucinations, delusions, depression) to plaques (Consortium to Establish a Registry for Alzheimer's Disease protocol), tangles (Braak staging), and Lewy bodies (consensus Lewy body staging) were evaluated. In addition, symptom frequency and persistent symptoms were compared in the patients with Lewy body dementia and 90 patients with autopsy-confirmed Alzheimer's disease studied prospectively during life.

Results: The main neuropathological correlate of persistent visual hallucinations was the presence of less severe tangle pathology, but there was no significant association between tangle pathology and persistent delusions. Lewy body staging was associated with the presence of persistent visual hallucinations and persistent delusions. All baseline psychiatric features were significantly more frequent in dementia with Lewy bodies than in Alzheimer's disease, as were persistent visual hallucinations, but patients who had dementia with Lewy bodies and severe tangle pathology had a clinical symptom profile more similar to that of Alzheimer's disease patients and were less likely to have neocortical Lewy bodies.

Conclusions: The modest proportion of patients with Lewy body dementia and more severe tangle pathology resembled Alzheimer's disease patients clinically. Unlike Alzheimer's disease, dementia with Lewy bodies showed a significant inverse association between tangle burden and psychosis.

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Dementia with Lewy bodies accounts for 15% to 25% of dementia cases (1–5). The condition is important because of the difficult clinical management issues presented by the high frequency of psychiatric symptoms (6–9) and the risk of severe neuroleptic sensitivity reactions (10). Visual hallucinations are consistently reported to be more frequent in dementia with Lewy bodies than in Alzheimer's disease, with most prospective studies indicating a frequency greater than 50%. Visual hallucinations are more persistent and appear earlier in the disease (11, 12) in Lewy body dementia than in Alzheimer's disease. Delusions are more common in dementia with Lewy bodies (frequency, 13%–75%) than in Alzheimer's disease but are not more persistent (12). The frequency of major depression is probably greater than 30% in dementia with Lewy bodies (13, 14) and has been shown in some studies to be more frequent than in Alzheimer's disease (8, 9), but it is not more likely to persist (12).

Patients who have dementia with Lewy bodies show a spectrum of pathology along the interface between Parkinson's disease and Alzheimer's disease. Seventy-five percent of patients with Lewy body dementia have many of the neuropathological features of Alzheimer's disease, including senile plaques and neurofibrillary tangles (1). Although typically the density of neocortical plaques is similar to that in Alzheimer's disease (1), the burden of tangles is less than in "pure" Alzheimer's disease (1, 13). When Lewy bodies occur in conjunction with Alzheimer pathology sufficient to meet the criteria of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) for probable or definite Alzheimer's disease (15), neocortical neurofibrillary tangles are usually rare or absent, and tangles in the entorhinal cortex and hippocampus are intermediate between those of elderly comparison subjects and Alzheimer's disease patients (1, 13). Fewer than 40% of patients with Lewy body dementia meet the criteria of Braak and Braak (16) for stage IV or higher neurofibrillary tangles and neuropil threads. The occurrence of Lewy bodies varies from restriction to the brainstem, or brainstem and limbic area, to widespread neocortical distribution (14, 17).

A number of studies have compared clinical features in Alzheimer's disease patients with and without Lewy bod-

TABLE 1. Neuropathological Rating Procedures Used at Four Sites to Assess Brain Plaques, Tangles, and Lewy Bodies in Patients With Lewy Body Dementia or Alzheimer's Disease

Method	Brain Regions (Brodmann's areas)	Stains	Feature Evaluated	Range of Values	Adjustment for Age
Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol (15)	Superior temporal (area 21/22), prefrontal (area 8/9), inferior parietal (area 40)	Bielschowsky, thioflavin S, von Braunmuhl	Neuritic plaques	Sparse, moderate, or frequent	Yes
Braak and Braak staging (16)	Transentorhinal, entorhinal, hippocampus, occipital cortex	Gallyas, Palmgren, AT8	Neurofibrillary tangles, europil threads	Stages 0–VI	
Consensus protocol for dementia with Lewy bodies (5)	Transentorhinal (area 28), anterior cingulate (area 24), superior temporal (area 21/22), prefrontal (area 8/9), inferior parietal (area 40)	Ubiquitin, alpha-synuclein	Cortical Lewy bodies	Lewy body staging (thresholds: brainstem, 0–2; limbic area, 3–6; neocortex, 7–10	
Immunohistochemical staining by avidin-biotin peroxidase complex (ABC) method	—	—	—	—	
Ubiquitin stain	—	—	—	—	
AT8 stain	—	—	—	—	
Alpha-synuclein stain	—	—	—	—	
Alz50 monoclonal antibody	—	—	—	—	
A4 monoclonal antibody	—	—	—	—	

[a] Modified according to the method of Nagy et al. (34).

ies (1, 11, 18–23), and they suggest that the presence of Lewy bodies is associated with visual hallucinations, delusions, and depression. To our knowledge, only one study has examined the persistence of psychiatric symptoms, suggesting an association with persistent visual hallucinations (11). The majority of studies have been small case series, and many have used retrospective evaluation of clinical symptoms, with some potential for inaccurate symptom ascertainment and limited statistical power. In addition, several studies have compared patients with "pure" cases of Lewy body dementia (variously defined but usually including cases not meeting the CERAD criteria for probable or definite Alzheimer's disease) to patients exhibiting significant Alzheimer's disease pathology. One of these investigations focused on neuropsychiatric symptoms assessed with standardized scales, comparing 11 patients with pure cases of Lewy body dementia to 18 patients who exhibited mixtures of Lewy body dementia and Alzheimer's disease pathology and 35 patients with pure Alzheimer's disease (13). The patients who had pure Lewy body dementia showed more hallucinations, delusions, and parkinsonism, whereas the patients with mixed cases resembled those with Alzheimer's disease. In addition, one recent study examining the association of Lewy bodies with visual hallucinations across a pathological spectrum of parkinsonism, which included 29 patients with Lewy body dementia, showed a significant association between visual hallucinations and Lewy body density in the inferior temporal cortex (24). These studies have mainly focused on Alzheimer's disease patients with or without Lewy bodies, with little emphasis on the associations of psychiatric symptoms across the full range of patients with Lewy body dementia, including those with little Alzheimer's disease pathology.

From an overview of this inconclusive literature, there is some indication that the presence of Lewy bodies in Alzheimer's disease is associated with psychosis and that there are differences in clinical presentation between pure cases of dementia with Lewy bodies and those with concurrent Alzheimer's disease pathology. The present study is based on an extensive study of prospectively studied patients who had autopsy-confirmed dementia with Lewy bodies.

Method

In total, we studied 112 patients with autopsy-confirmed dementia with Lewy bodies who had been prospectively assessed during life in one of four centers in Newcastle upon Tyne, U.K. (Newcastle Dementia Case Register, Institute for Ageing and Health); Oxford, U.K. (Oxford Project to Investigate Memory and Ageing, University of Oxford); London (Institute of Psychiatry Case Register); and London, Ont., Canada (Dementia Study Project, University of Western Ontario). At each center, consecutively assessed dementia patients who agreed to participate were enrolled. Diagnosis was made at autopsy according to the consensus criteria for a neuropathological diagnosis of dementia with Lewy bodies (5). All patients meeting these neuropathological criteria were included. An additional 90 patients with neuropathologically diagnosed Alzheimer's disease from the three U.K. centers were included as a comparison group. They comprised all prospectively studied patients from these centers with a neuropathological diagnosis of Alzheimer's disease who had a Mini-Mental State Examination (25) score higher than 0 at death (specification made to minimize differences between the two dementia groups at death, as far more of the patients with Lewy body dementia died before "end-stage" dementia). In total, autopsy tissue was collected from 445 prospectively assessed patients, 333 (75%) with Alzheimer's disease and 112 (25%) with Lewy body dementia. At each of the centers, written consent was obtained for clinical evaluation, with written assent from each patient's nearest relative after a full explanation of the study. Following death, written consent for autopsy was obtained from the next of kin in all cases. The study was approved by the human subjects research ethics committee in each of the centers.

A standardized psychiatric history (26, 27) and a standardized assessment of cognitive function (25, 28) were completed; differ-

Use of Method by Each Research Center			
Newcastle, U.K.	Oxford, U.K.	London, U.K.	London, Ont., Canada
Yes	Yes	Yes	Yes
Yes	Yes[a]	Yes	Yes
Yes	Yes	Yes	Yes
	Yes		
Yes	Yes	Yes	Yes
Yes		Yes	Yes
Yes	Yes		
Yes			Yes
		Yes	

ent centers used different instruments. To estimate cognitive performance across centers, each patient was given a percentage score (the percentage of points scored by the patient out of those available on the schedule used), with a higher percentage indicating better performance.

A full neuropsychiatric evaluation was completed at each center with validated instruments (29–31). The diagnosis of depression was made by using DSM-III-R criteria but without the organic exclusion clause when dementia was the only relevant organic condition. Definitions of the presence and classification of psychotic features were taken from the criteria of Burns et al. (32). At each center a standardized physical examination included a detailed evaluation of parkinsonism (33). Repeat evaluations were undertaken at least annually until death. Symptoms were rated as persistent if they were present for at least 6 months continuously at some stage of the dementia (either present at two or more consecutive assessments or present for 6 months according to the patient's history at the time of the initial evaluation). For the individuals who died before any follow-up assessment was completed, the determination of chronicity was made on the basis of a history of the continuous presence of the symptom for at least 6 months before the evaluation. This is the same definition of chronicity as applied in previous publications from the Newcastle group.

At each center, the neuropathological diagnosis of Alzheimer's disease was made according to the CERAD protocol (15), and the severity of plaques was determined by using the CERAD guidelines (15). The staging method of Braak and Braak (16) was used to quantify tangle pathology. The presence or absence of Lewy bodies was assessed in the brainstem and in limbic and neocortical areas as outlined in the consensus criteria for dementia with Lewy bodies (5). The staging of Lewy body pathology followed the same consensus guidelines. The neuropathological diagnosis of dementia with Lewy bodies was hence independent of the severity of Alzheimer's disease pathology, and patients with sufficient Lewy bodies in the key diagnostic areas were diagnosed as having dementia with Lewy bodies even in the presence of extensive plaque or tangle pathology. Lewy bodies were not evaluated in other areas, and so coincidental Lewy bodies in other regions, such as the amygdala, would not lead to a diagnosis of dementia with Lewy bodies.

The neuropathological methods and the staining procedures used at each center are summarized in Table 1.

An additional 90 patients with neuropathologically confirmed Alzheimer's disease from the three U.K. centers, who had been assessed prospectively during life with the same standardized procedures, were included as a comparison group. For the patients with Lewy body dementia, the Braak stages, CERAD stages, and Lewy body dementia stages were correlated in independent analyses with key symptoms by using the chi-square test. The numbers of patients with Lewy body dementia and with Alzheimer's disease who experienced the symptoms of interest at presentation and the numbers who had them persistently (≥6 months) during the course of the dementia were compared by using chi-square tests. Correlations between different pathologies were undertaken by means of Spearman's rank correlation. The Statistical Package for the Social Sciences was used for all evaluations (35).

Results

Nearly half of the patients who had dementia with Lewy bodies were female. Their mean age and duration of dementia are presented in Table 2. The median duration between the baseline assessment and death was 2 years, and the median number of clinical assessments for the patients with Lewy body dementia was three per participant, although 23 (21%) of the patients died before any follow-up evaluations were completed. There were high frequencies of visual hallucinations, delusions, and major depression among the patients with Lewy body dementia (Table 2).

Braak staging was significantly correlated with dementia duration (Table 3), but there was no association between the number of years of dementia and Lewy body staging. As anticipated, Braak and CERAD staging were significantly correlated (r_s=0.40, N=112, p<0.0001). The severity of Lewy body pathology was independent of plaques (CERAD staging: r_s=0.12, N=112, p=0.19), but there was a significantly lower proportion of patients with neocortical Lewy bodies among those with Braak stage V or VI tangle pathology (Table 4).

Within the group who had Lewy body dementia there was a significant association between lower Braak stage and higher frequency of persistent visual hallucinations (Table 5). There was no association between the CERAD staging and any of the psychiatric symptoms. Significant associations between higher Lewy body staging and both persistent delusions and persistent visual hallucinations were identified. Persistent visual hallucinations were most frequent in patients with neocortical Lewy bodies.

The characteristics of the groups with Lewy body dementia and Alzheimer's disease are shown in Table 2. Compared to those with Alzheimer's disease, the patients with Lewy body dementia had significantly higher frequencies of depression, delusions, visual hallucinations, and parkinsonism at the beginning of the study. Longitudinal data were available for 77 (86%) of the Alzheimer's disease patients, of whom 14 (18%) had persistent visual hallucinations, 24 (31%) had persistent delusions, and 14 (18%) had persistent depression. In comparison with the

TABLE 2. Demographic and Clinical Characteristics of Prospectively Followed Patients With Autopsy-Confirmed Lewy Body Dementia or Alzheimer's Disease

Characteristic	Dementia With Lewy Bodies (N=112)		Alzheimer's Disease (N=90)		Analysis		
	Mean	SD	Mean	SD	t	df	p
Age at first assessment (years)	76.2	7.6	78.3	7.6	—	—	n.s.
Age at death (years)	79.5	6.8	81.9	7.0	—	—	n.s.
Duration of dementia from onset to death (years)	7.4	4.3	9.2	7.2	—	—	n.s.
Score on cognitive test battery (%)[a]	48	28	31	24	3.4	1	0.0001
	N	%	N	%	χ^2	df	p
Female gender	55	49	60	67	6.5	1	0.01
Psychiatric symptoms at first assessment							
Depression	44	39	10	11	19.9	1	<0.0001
Delusions	62	55	25	28	16.0	1	<0.0001
Visual hallucinations	66	59	18	20	34.4	1	<0.0001
Parkinsonism	49	44	24	27	6.0	1	0.01

[a] Either the Mini-Mental State Examination (25) or the Extended Scale for Dementia (28).

TABLE 3. Relation of Demographic and Clinical Characteristics to Brain Plaques, Tangles, and Lewy Bodies in 112 Prospectively Followed Patients With Lewy Body Dementia

Neuropathological Rating	Age at First Assessment (years)		Age at Death (years)		Female Gender		Total Duration of Dementia (years)[a]		Duration of Parkinsonism (years)[b]	
	Mean	SD	Mean	SD	N	%	Mean	SD	Mean	SD
Staging of neurofibrillary tangles and neuropil threads by method of Braak and Braak (16)										
Stage 0 (N=7)	76.1	6.9	78.7	5.1	1	14	5.5	2.8	6.4	6.5
Stage I or II (N=36)	75.8	5.1	80.8	6.1	17	47	6.1	3.3	3.9	6.3
Stage III or IV (N=40)	79.4	5.9	82.1	6.4	18	45	4.2	2.0	2.2	2.3
Stage V or VI (N=29)	72.2	9.3	77.3	8.7	19	66	10.6	4.0	0.1	0.4
Staging of neuritic plaques by protocol of Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (15)										
No plaques (N=16)	74.1	5.2	78.5	5.9	8	50	8.2	3.5	3.9	5.7
Scarce plaques (N=17)	74.9	9.6	78.7	7.4	4	24	5.9	4.0	3.3	9.2
Moderate plaques (N=31)	77.1	6.7	79.5	7.0	14	45	5.8	3.6	2.9	3.4
Abundant plaques (N=48)	76.7	8.1	80.2	7.0	29	60	8.4	4.8	1.6	3.1
Staging (present/absent) of Lewy bodies by consensus protocol (5)										
Brainstem (N=19)	78.6	7.0	81.6	6.2	7	37	6.3	4.6	2.1	3.8
Limbic area (N=28)	74.0	9.1	78.5	7.9	15	54	8.6	6.0	3.6	7.3
Neocortex (N=65)	76.4	7.0	79.3	6.5	33	51	7.0	3.1	2.2	3.7

[a] Significant correlation with Braak staging (r_s=0.47, N=112, p<0.0001).
[b] Significant correlations with Braak staging (r_s=–0.34, N=112, p=0.005) and CERAD staging (r_s=–0.37, N=112, p=0.002).

patients who had Lewy body dementia, the Alzheimer's disease patients were significantly less likely to have persistent visual hallucinations (χ^2=19.4, df=1, p<0.0001) but not delusions (χ^2=0.48, df=1, p=0.49) or depression (χ^2=0.73, df=1, p=0.39). Patients with Lewy body dementia who had a higher Braak stage (V or VI) had a frequency of persistent visual hallucinations (21%) that was more similar to that of the patients with Alzheimer's disease (20%) than the frequency for patients with Lewy body dementia who had a Braak stage of 0–II (Table 2, Table 5).

Discussion

This study of patients with autopsy-confirmed Lewy body dementia elucidates the relationship of pathology to clinical features in dementia with Lewy bodies. There were two main findings. First, a low tangle count is the main correlate of persistent visual hallucinations in dementia with Lewy bodies, but the presence of neocortical Lewy bodies also increases the frequency of both visual hallucinations and delusions. Second, patients who have Lewy body dementia with Braak stage V or VI tangle pathology have a symptom profile more similar to that of Alzheimer's disease patients than do other patients with Lewy body dementia, and they also have significantly fewer neocortical Lewy bodies. This indicates that patients with Lewy body dementia with higher tangle counts and fewer neocortical Lewy bodies are a discrete subgroup with different clinical and neuropathological characteristics. This series confirms that patients with Lewy body dementia have high frequencies of visual hallucinations (59%), delusions (55%), and depression (39%), each of which was present

TABLE 4. Relation of Brain Tangles to Lewy Bodies in 112 Patients With Autopsy-Confirmed Lewy Body Dementia[a]

Staging of Lewy Bodies by Consensus Protocol (5)	Staging of Neurofibrillary Tangles and Neuropil Threads by Method of Braak and Braak (16)							
	Stage 0 (N=7)		Stage I or II (N=36)		Stage III or IV (N=40)		Stage V or VI (N=29)	
	N	%	N	%	N	%	N	%
Present in brainstem	3	43	3	8	9	23	4	14
Present in limbic area	1	14	9	25	5	13	13	45
Present in neocortex[b]	3	43	24	67	26	65	12	41

[a] Nonsignificant correlation between Lewy body and Braak staging (r_s=–0.10, N=112, p=0.29).
[b] Significant difference among Braak stages (χ^2=4.6, df=3, p=0.04)

TABLE 5. Relation of Brain Plaques, Tangles, and Lewy Bodies to Persistent Psychiatric Symptoms in 112 Prospectively Followed Patients With Autopsy-Confirmed Lewy Body Dementia[a]

Neuropathological Rating	Persistent Depression		Persistent Delusions[b]		Persistent Visual Hallucinations[c]	
	N	%	N	%	N	%
Staging of neurofibrillary tangles and neuropil threads by method of Braak and Braak (16)						
Stage 0 (N=7)	2	29	2	29	4	57
Stage I or II (N=36)	10	28	8	22	23	64
Stage III or IV (N=40)	12	30	14	35	23	58
Stage V or VI (N=29)	4	14	6	21	6	21
Staging of neuritic plaques by protocol of Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (15)						
No plaques (N=16)	5	31	4	25	8	50
Scarce plaques (N=17)	7	41	1	6	7	41
Moderate plaques (N=31)	9	29	13	42	18	58
Abundant plaques (N=48)	7	15	12	25	23	48
Staging (present/absent) of Lewy bodies by consensus protocol (5)						
Brainstem (N=19)	6	32	2	11	6	32
Limbic (N=28)	9	32	9	32	11	39
Neocortical (N=65)	13	20	24	37	39	60

[a] Symptoms were rated as persistent if they were present for at least 6 months continuously at some stage of the dementia (either present at two or more consecutive assessments or present for 6 months according to the patient's history at the time of the initial evaluation).
[b] Significant differences among Lewy body stages (χ^2=8.8, df=2, p=0.01).
[c] Significant differences among Braak stages (χ^2=13.8, df=3, p=0.003) and among Lewy body stages (χ^2=6.5, df=2, p=0.04).

significantly more frequently than in Alzheimer's disease patients, and also that visual hallucinations (present for 6 months or more in 50% of the patients with Lewy body dementia), but not other psychiatric features, are significantly more persistent.

Patients with Lewy body dementia who had Braak stage V or VI tangle pathology had a frequency of persistent visual hallucinations more similar to that of the Alzheimer's disease patients than to that of the patients with Lewy body dementia who had Braak stage 0–IV pathology. This is important for diagnosis, as a lower proportion of these patients meet operationalized clinical criteria for dementia with Lewy bodies. Taken together with the lower proportion of patients with neocortical Lewy bodies, this finding hence provides some justification for considering this group as having a "Lewy body variant of Alzheimer's disease." This concept has been described previously in relation to plaque pathology (1) but, on the basis of the present data, should be focused on patients with Lewy body dementia who have severe tangle pathology. It will be important to determine whether "Lewy body variant" patients experience severe neuroleptic sensitivity reactions and how responsive their neuropsychiatric symptoms are to cholinesterase inhibitors.

Visual hallucinations and delusions in patients with Lewy body dementia have different pathological substrates, a finding that is consistent with results from previous neurochemical studies (14), and the neuropathological associations of psychosis are different in dementia with Lewy bodies and Alzheimer's disease. In Alzheimer's disease patients there is a significant positive association between the presence of neurofibrillary tangles in the neocortex and the occurrence of psychotic symptoms, defined as either visual hallucinations or delusions (36); this relationship is the opposite of the inverse association between visual hallucinations and neurofibrillary tangle staging in the current study. This difference may be due to the fact that the patients with Lewy body dementia had more pronounced cholinergic deficits in the medial temporal lobe than did the patients with Alzheimer's disease, despite a lower tangle burden (14, 37). The different underlying bases of visual hallucinations and delusions and the different neuropathological substrates of psychotic symptoms in dementia with Lewy bodies and Alzheimer's disease are crucial for developing a meaningful classification of psychiatric syndromes in dementia patients, for designing clinical trials, and for developing rational treatment approaches. The results of treatment studies focus-

ing on psychiatric symptoms in dementia with Lewy bodies hence do not enable us to predict the responsiveness of these symptoms to the same treatments in Alzheimer's disease patients.

The presence of persistent visual hallucinations was significantly inversely associated with Braak stage. More widespread Lewy bodies were also associated with the persistence of visual hallucinations. Previous work indicates that visual hallucinations in dementia with Lewy bodies (and also Parkinson's disease) are related to the severity of cholinergic deficits (14) and probably also to the extent of cortical Lewy body pathology (11), particularly in the temporal cortex (24). The present findings are consistent with those of previous studies but also emphasize the importance of less severe tangles. Delusions were not associated with plaque or tangle staging in our study, although persistent delusions were associated with Lewy body distribution. While these findings have important implications for the classification of cases of dementia with Lewy bodies and for understanding differences in the neuropathological basis of psychiatric symptoms in Lewy body dementia and Alzheimer's disease, this is only the first step. Further work needs to evaluate in detail the pattern of associations between plaque, tangle, and Lewy body pathology in specific regions of interest. Important smaller studies have been reported; for example, Harding et al. (24) reported an association between visual hallucinations and the density of Lewy bodies in key temporal lobe regions in 29 patients with Lewy body dementia. Building on this work in large systematic studies will be important to develop a more comprehensive understanding of the neuropathological substrates of key symptoms in dementia with Lewy bodies.

Although frequent, depression in patients with Lewy body dementia was not associated with plaque, tangle, or Lewy body pathology. Consistent with this finding was the association with serotonergic measures in a previous neurochemical study (38).

Lewy bodies were less prevalent in patients with high Braak staging, consistent with earlier evidence that there may be a degree of mutual exclusion between Lewy body and tau pathology. According to Arima et al. (39), the presence of neurofibrillary tangles or tau-epitopes within neurons containing Lewy bodies is rare, although in a more recent study (40) using tau and alpha-synuclein immunohistochemistry the coexistence of neurofibrillary tangles and Lewy bodies in the same neurons in the subiculum was identified. Both of these pathological studies suggested that alpha-synuclein stimulates the accumulation of phosphorylated tau in terminal axons.

To our knowledge, this is the largest comparison of dementia with Lewy bodies and Alzheimer's disease. At each center the patients were diagnosed at autopsy but had been prospectively assessed during life with standardized clinical evaluations. We determined the correlations of initial symptoms and persistent symptoms (of 6 months' duration) over the course of the illness to neuropathological features at death. The first patients to come to autopsy in longitudinal series usually die of concurrent causes in the mild to moderate stages of the disease. As a result, the median duration between first assessment and death was only 2 years. The longitudinal design has particular advantages for the evaluation of associations with persistent psychosis.

Assessments were completed with validated staging systems, although the detailed methodological procedures differed between the individual centers. The biggest potential disadvantage is the different staining procedures used for the identification of Lewy bodies. While this may have been a problem for the detailed quantification of Lewy body density, it is unlikely to have made a substantial difference to the standard staging procedure. For example, in a comparative study, alpha-synuclein staining improved the identification of Lewy bodies by only 5% over other methods (18).

In conclusion, in patients with Lewy body dementia, the major neuropathological characteristic associated with persistent visual hallucinations is the absence of severe tangle pathology, indicating a different neuropathological basis from that previously described for psychotic symptoms in patients with Alzheimer's disease. An important implication is that treatment response is also likely to be different, and results of clinical trials cannot easily be generalized from one patient group to the other.

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Proof of mechanism study to detect cerebral β-amyloid plaques in patients with Alzheimer's disease (AD) using BAY 94-9172 and PET

Barthel, Henryk[1]; Patt, Marianne[1]; Hammerstein, Eva[2]; Becker, Georg[1]; Eggers, Birk[3]; Lindemann, Stefanie[4]; Holl, Gerhard[4]; Hegerl, Ulrich[2]; Gertz, Hermann-Josef[2]; Sabri, Osama[1]
Departments of [1]Nuclear Medicine and [2]Psychiatry, University of Leipzig, [3]Arzneimittelforschung Leipzig Ltd., [4]Bayer Schering Pharma AG, Berlin, Germany

Objectives: A broader availability of a PET technique to detect cerebral β-amyloid plaques, a histological hallmark in AD, requires radiolabels with adequate half life. BAY 94-9172 is a new [^{18}F]-labeled polyethyleneglycol stilbene derivative with high affinity to synthetic β1-42-amyloid fibrils and post-mortem human AD brain homogenates. This tracer is currently tested in a clinical proof of mechanism study with regard to its suitability to diagnose AD.

Methods: We so far included 10 AD patients (age 69±7yrs, MMSE 19±7) and 7 age-matched healthy controls ((HCs), MMSE≥28). After i.v. administration of 300MBq BAY 94-9172, the brains of all subjects were scanned on an ECAT EXACT HR+ system. 70-90 min p.i. image time-frames were scored visually by three blinded experts and analyzed voxelwise on a single-case base with a normal database constructed of the PET data of the HCs (SPM2).

Results: In visual analysis, none of the HCs but 9 of the 10 AD patients were scored positive (κ for inter-rater agreement = 0.84 - 1.00, $p \leq 0.001$). In keeping with that, SPM revealed clusters with increased tracer uptake ($p < 0.01$) mainly in frontal, parietal and posterior cingular cortex of 9 AD patients, but in none of the HCs. For all subjects, the volume of increased tracer uptake had a non-linear negative relationship with the MMSE ($r^2 = -0.69$, $p < 0.01$).

Conclusions: From these preliminary data it is concluded that BAY 94-9172-PET has a great potential to diagnose AD in the living human brain. Further efforts are currently undertaken towards full kinetic modeling of the tracer dynamics.

CSF markers for incipient Alzheimer's disease

Kaj Blennow and Harald Hampel

Early diagnosis of Alzheimer's disease (AD) is needed to initiate symptomatic treatment with acetylcholinesterase inhibitors, and will be of even greater significance if drugs aimed at slowing down the degenerative process, such as vaccination regimes and β-secretase and γ-secretase inhibitors, prove to affect AD pathology and to have clinical effect. However, there is no clinical method to determine in which patients mild cognitive impairment (MCI) will progress to AD with dementia, and in which patients MCI is benign. Hence, there is a great clinical need for biomarkers to identify incipient AD in patients with MCI. The CSF biomarkers total tau protein, phosphorylated tau protein, and the 42 amino-acid residue form of amyloid-β may, if put in the right clinical context, prove to have high enough diagnostic accuracy to meet this challenge.

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Mild cognitive impairment (MCI) is an age-related syndrome that has gained increasing attention in the research community and also in the general population. MCI is characterised by memory impairment that can be verified by objective measures adjusted for age and education in the absence of dementia.[1]

MCI is aetiologically heterogeneous, and many patients with the disorder have incipient Alzheimer's disease (AD), whereas others have a benign form of MCI. Cerebrovascular disease may also contribute to memory impairment but can be identified by the presence of cerebrovascular risk factors (eg, hypertension) and findings of vascular pathology (eg, infarcts, white-matter lesions) by use of brain-imaging techniques. The definition and pathophysiology of MCI were recently reviewed in *The Lancet Neurology*.[2]

In many cases, MCI is a transition between normal ageing and AD, with a conversion rate reaching as high as 15% a year.[2] Research efforts have been directed to find methods to identify in which patients MCI will progress to AD and in which patients it will not. In this paper, we review the potential of CSF analyses as diagnostic markers for AD, specifically their usefulness in the identification of incipient AD, and their role in the diagnosis of MCI in clinical practice. We also give suggestions for how to use CSF markers in clinical practice.

Diagnostic markers

The introduction of effective symptomatic treatment of AD with acetylcholinesterase inhibitors has highlighted the importance of early and accurate diagnosis of AD. However, the most commonly used criteria for the clinical diagnosis of AD was outlined almost 20 years ago by the National Institute of Neurological and Disorders and Stroke and the Alzheimer Disease and Related Disorders (NINCDS–ADRDA) Work Group.[3] These criteria largely depend on the exclusion of other dementias. Although the NINCDS–ADRDA criteria have been reported to have a high accuracy rate (80–90%),[4,5] studies of the diagnostic accuracy come from specialised expert research academic centres, and most data are from patients in later stages of the disease who were studied for several years before death and autopsy. The clinical diagnostic accuracy is probably lower in patients in the earlier stages of AD, especially in those with MCI, when specific symptoms other than memory disturbances are absent or indistinct.

The increasing knowledge and awareness of possible drug treatments for AD have made patients seek medical advice at an earlier stage of the disease. Many patients do not present with characteristic symptoms of moderate to severe AD, but have only mild memory disturbances without dementia. There is no clinical method to determine which patients will progress to AD with dementia, except for an extended clinical follow-up. Thus, there is a great clinical need for biomarkers to identify incipient AD in patients with MCI. This need will be much larger if new drugs to slow or stop the degenerative process (eg, vaccination regimes, β-secretase and γ-secretase inhibitors, and β-sheet breakers) prove to have a beneficial clinical effect. Such compounds are probably most effective early in the disease course, before neurodegeneration is too severe and widespread.

State and stage markers for AD

The degenerative process in AD probably starts 20–30 years before the clinical onset of the disease.[6] During this preclinical phase of AD, plaque and tangle loads increase, and at a certain threshold the first symptoms appear. There are no data to suggest that the intensity of the disease process (ie, the rate of neuronal degeneration and plaque and tangle formation) changes during the disease process. Diagnostic markers for AD can be divided into two groups: state markers and stage markers.

KB is at the Department of Clinical Neuroscience, Sahlgrenska Academy, Gothenburg University, Sweden, and HH is at the Alzheimer Memorial Center and Geriatric Psychiatry Branch, Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany.

Correspondence: Kaj Blennow, Department of Clinical Neuroscience, Section of Experimental Neuroscience, Sahlgrenska University Hospital, SE-431 80 Mölndal, Sweden.
Tel +46 31 3431791; fax +46 31 3432426;
email kaj.blennow@neuro.gu.se

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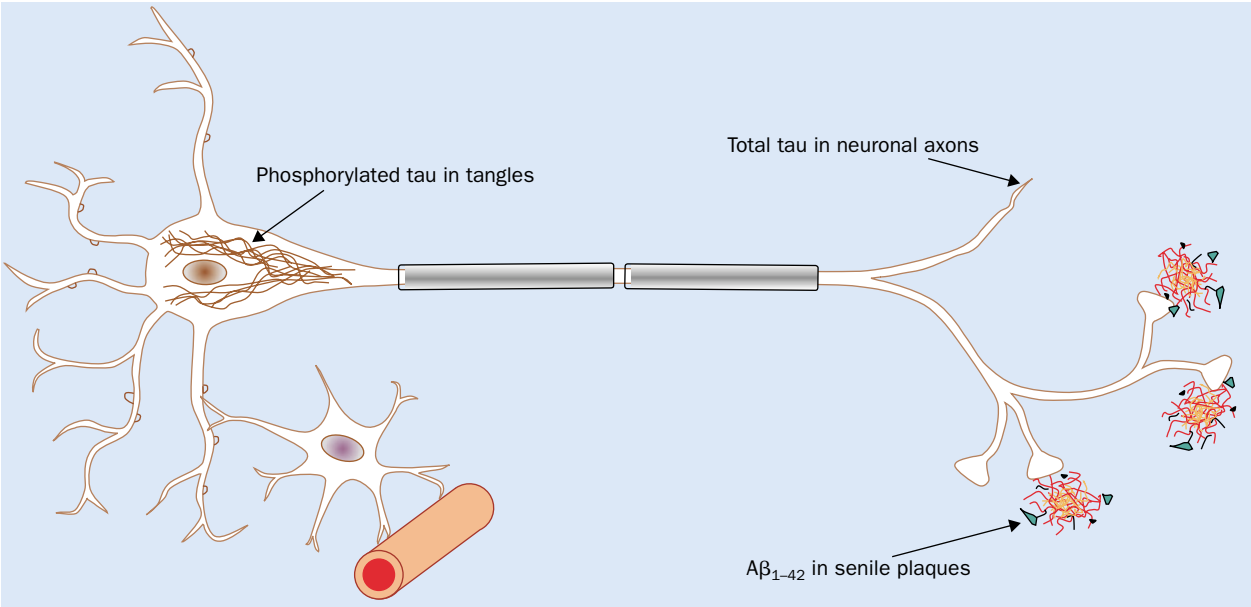

Figure 1. Schematic drawing of a neuron with an adjacent astrocyte and capillary. The central pathogenetic processes in AD and their corresponding biochemical markers are depicted. Total concentration of tau protein is a marker of neuronal and axonal degeneration, $A\beta_{1-42}$ concentration is a marker of plaque formation, and concentration of phosphorylated tau is a marker for hyperphosphorylation of tau and formation of tangles.

State markers

State markers reflect the intensity of the disease process. One example of a state marker is the total amount of tau protein. The total concentration of tau protein in the CSF probably indicates the intensity of the neuronal damage and degeneration. In acute disorders (such as ischaemic stroke) there is a transient increase in tau protein concentration in the CSF that correlates with infarct size measured by CT.[7] Furthermore, the degree of increase in tau protein concentrations in the CSF is highest in disorders with the most intense neuronal degeneration, such as Creutzfeldt-Jakob disease,[8] whereas a moderate increase is found in AD, in which the degeneration is less intense, and a normal concentration is found in patients with depression and no or limited degeneration.[9]

Stage markers

Stage markers give a measure of how far the degenerative process has proceeded. An example of a stage marker is atrophy of the hippocampus as measured with CT or MRI. Clinical rating scales (which measure the stage of the cognitive decline) are also stage markers.

Because the disease process starts several years before the onset of the first symptoms, both state and stage markers are probably positive in the early phase of AD. Indeed, patients with MCI have both high concentrations of tau protein in their CSF and hippocampal atrophy.[10] However, the increase in tau protein concentrations is larger (210–290% increase)[11–15] than the degree of hippocampal atrophy (9–15% reduction of hippocampal volume).[10] State markers, such as tau protein, probably have a larger potential than stage markers, such as hippocampal atrophy on CT or MRI, as prognostic markers to identify incipient AD in patients with MCI.

CSF markers for AD

The CSF is in direct contact with the extracellular space of the brain, and hence biochemical changes in the brain affect the CSF. Because AD pathology is restricted to the brain, CSF is an obvious source of biomarkers for AD. Biochemical markers for AD should reflect the central pathogenetic processes (ie, the neuronal degeneration, the deposition of amyloid-β peptide [Aβ] in plaques, and the hyperphosphorylation of tau with subsequent formation of tangles; figure 1). Possible biomarkers for these pathogenetic processes are the concentrations in the CSF of total tau protein, the 42 amino acid form of Aβ ($A\beta_{1-42}$), and phosphorylated tau protein.

Tau protein

Tau protein is located in the neuronal axons. There are six different isoforms and numerous phosphorylation sites of tau protein in the human brain (figure 2). The first report on tau protein concentration in the CSF as a biomarker for AD—in which ELISA with a polyclonal antibody was used—was published in 1993.[16] After this, ELISA methods based on monoclonal antibodies that detect all isoforms of tau protein, independent of their phosphorylation, have been developed (figure 2).[9,17]

The concentration of tau protein in the CSF probably reflects the intensity of neuronal degeneration in chronic neurodegenerative disorders.

$A\beta_{1-42}$

Aβ is the major component of plaques.[18] It is a proteolytic cleavage product from the amyloid precursor protein: APP is cleaved by β-secretase to release a large N-terminal derivative called β-sAPP, which is cleaved by γ-secretase to release free Aβ.

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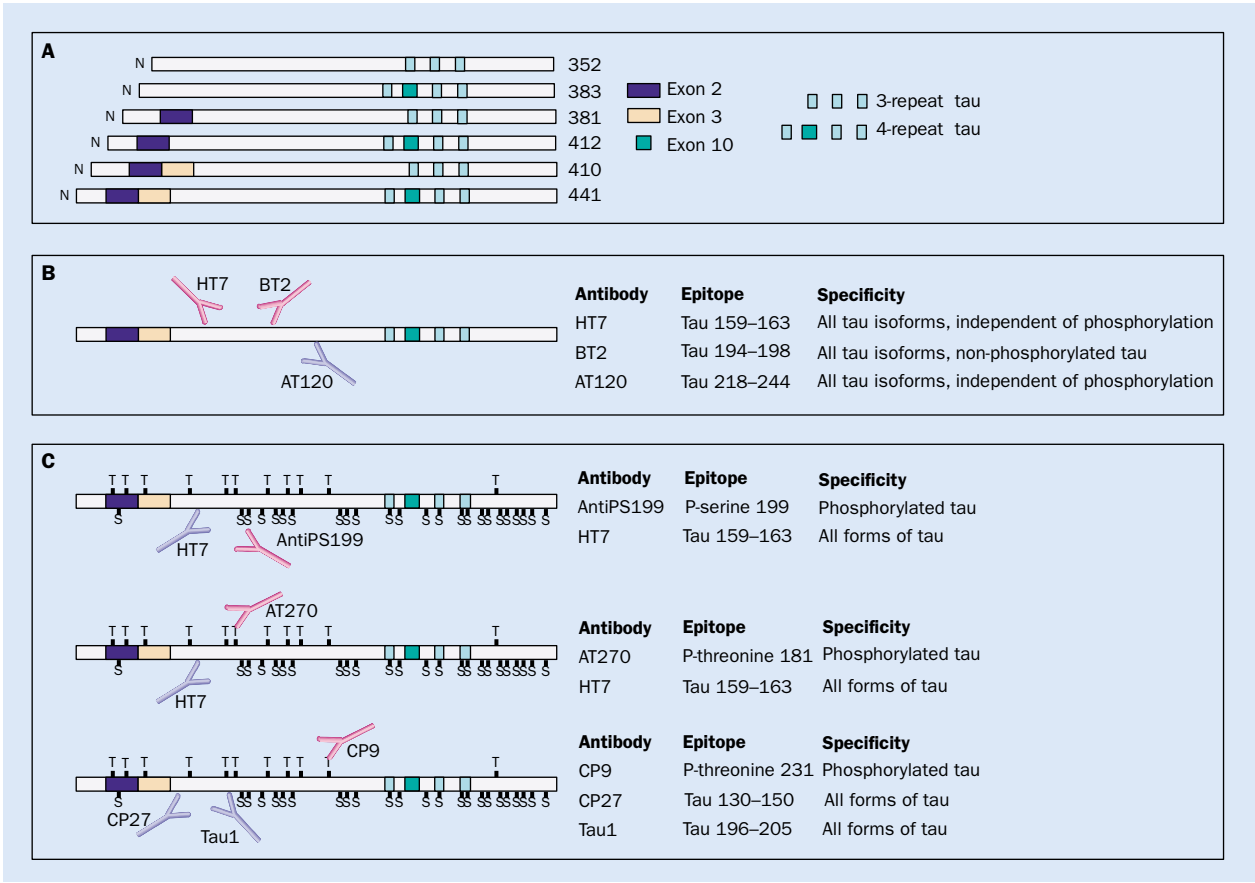

Figure 2. The six isoforms of human tau protein, with alternatively spliced exons marked (A). The smallest contains 352 amino-acid residues and three repeat (microtubule-binding) domains. The largest tau isoform has 441 residues (tau_{441}) and four repeat domains with exon 10 spliced in and two extra domains from exons 2 and 3. Schematic drawing of an ELISA for total tau (B).[9] The antibodies were selected to react with tau irrespective of phosphorylation state, and are specific for epitopes outside the alternatively spliced exons. Thus, ELISA recognises all forms of tau. Three ELISAs specific for phosphorylated tau (C). Phosphorylation sites on tau_{441}, either threonine (T) or serine (S), are marked. All ELISAs are based on the combination of an antibody that recognises all isoforms of tau irrespective of phosphorylation state together with an antibody specific to different phosphorylated amino acids. Top: ELISA specific for the serine 199 isoform of phosphorylated tau protein.[31] Middle: ELISA specific for the threonine 181 isoform.[30] Bottom: ELISA specific for P-threonine 231.[32]

The first reports on CSF Aβ as a biomarker for AD were disappointing, and results ranged form a slight decrease in AD to no change.[19–21] In these studies total Aβ in the CSF was measured. After research showed that there are two major C-terminal variants of Aβ, with either 40 ($A\beta_{1-40}$) or 42 ($A\beta_{1-42}$) amino-acid residues, and that $A\beta_{1-42}$ has the highest tendency for aggregation and is the quickest Aβ to form plaques,[22,23] ELISA methods were developed with antibodies specific for this form (figure 3).[24,25]

The decrease in concentrations of $A\beta_{1-42}$ in the CSF was first thought to be caused by a deposition of the peptide in plaques.[25] However, later studies showed a substantial decrease in CSF $A\beta_{1-42}$ in disorders without Aβ plaques, such as Creutzfeldt-Jakob disease,[26] amyotrophic lateral sclerosis,[27] and multiple system atrophy.[28] Although a recent population-based autopsy study found a strong association between low concentrations of $A\beta_{1-42}$ in the CSF and high numbers of plaques in the neocortex and hippocampus.[29] Therefore, the decrease in CSF $A\beta_{1-42}$ in AD may be due, at least in part, to deposition of Aβ in plaques.

Phosphorylated tau protein

The most recently discovered biomarker for AD is phosphorylated tau protein. Several ELISA methods have been developed for different phosphorylated epitopes of tau protein—including threonine 181 and 231,[9] threonine 181,[30] threonine 231 and serine 235,[31] serine 199,[31] threonine 231,[32] and serine 396 and 404.[33]

The concentration of phosphorylated tau protein in the CSF probably reflects the phosphorylation state of tau in the brain. In contrast to the total concentration of tau protein, there is no change in the concentration of phosphorylated tau protein after acute stroke.[34] Furthermore, despite a very pronounced increase in total tau protein concentrations in Creutzfeldt-Jakob disease, there is no increase in the concentration of the phosphorylated protein.[35] These findings suggest that the concentration of phosphorylated tau protein in the CSF is not simply a marker for neuronal damage, like total tau protein, but that it specifically reflects the phosphorylation state of tau and, thus, the formation of tangles in AD.

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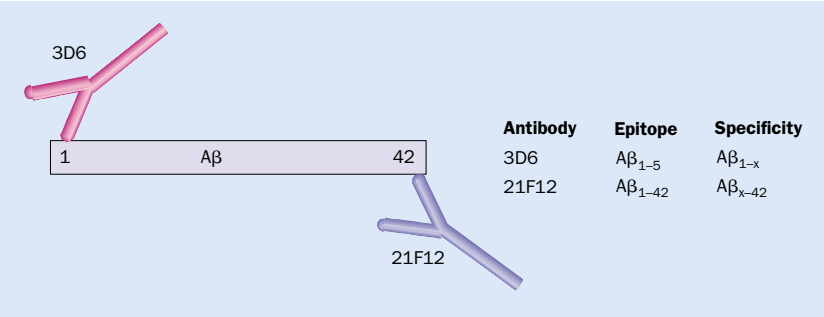

Figure 3. ELISA specific for $A\beta_{1-42}$. The ELISA does not cross-react with either of $A\beta_{1-40}$ or $A\beta_{1-43}$, or with N-terminally truncated Aβ peptides.[24]

Specificity and sensitivity of CSF markers for AD

Tau protein

An increase in the total concentration of tau protein in the CSF has been found in many studies of AD; concentrations are about three times higher in patients with AD than in control individuals. For the most commonly used method, the "Innogenetics ELISA",[9] sensitivity and specificity figures are available from 36 different studies, which include about 2500 AD patients and 1400 controls (figure 4).[9,12,24,27,30,33,36–66] The specificity of this assay is 90% and the mean sensitivity to AD is 81% (figure 4). In the five studies with the "Athena" assay,[17] the mean sensitivity was lower, with similar specificity (figure 4).[17,25,67–69]

Importantly, normal total concentrations of tau protein in the CSF are found in several important differential diagnoses—including depression, alcoholic dementia, and chronic neurological disorders, such as Parkinson's disease and progressive supranuclear palsy.[9,36,40,47,60,61]

The specificity for tau protein is not optimum, because high concentrations are also found in some other dementia disorders. In vascular dementia, a high concentration of tau protein has been found in a large percentage of patients in some studies,[9,46,61] although in other studies the concentration of tau protein was raised in only a few patients.[17,36,52] High total tau protein concentrations in clinically diagnosed vascular dementia may be caused by the presence of concomitant AD pathology, which is a common finding at autopsy.[70,71] The same explanation was also suggested in a CSF study with longitudinal MRI in patients with vascular dementia.[61] A mild to moderate increase in the total concentration of tau protein in the CSF has also been found in frontotemporal dementia in some,[9,44] but not in all,[30,52] studies.

$A\beta_{1-42}$

In patients with AD, a decrease in CSF concentration of $A\beta_{1-42}$ to about 50% of that in control individuals has been recorded. For the most commonly used method,[24,72] the "Innogenetics ELISA", sensitivity and specificity figures are available from 13 different studies, which include about 600 patients with AD and 450 control individuals (figure 5).[24,26,27,46,47,50,54,57–59,63,72,73] With specificity at 90%, the mean sensitivity of CSF $A\beta_{1-42}$ to discriminate between AD and normal ageing is 86%. In the two studies with the "Athena" assay,[25] sensitivity and specificity figures were similar (figure 5).[25,68]

There are not many data on the ability of CSF $A\beta_{1-42}$ to distinguish AD from other dementias and neurological disorders. Normal CSF $A\beta_{1-42}$ concentrations are found in psychiatric disorders such as depression and in chronic

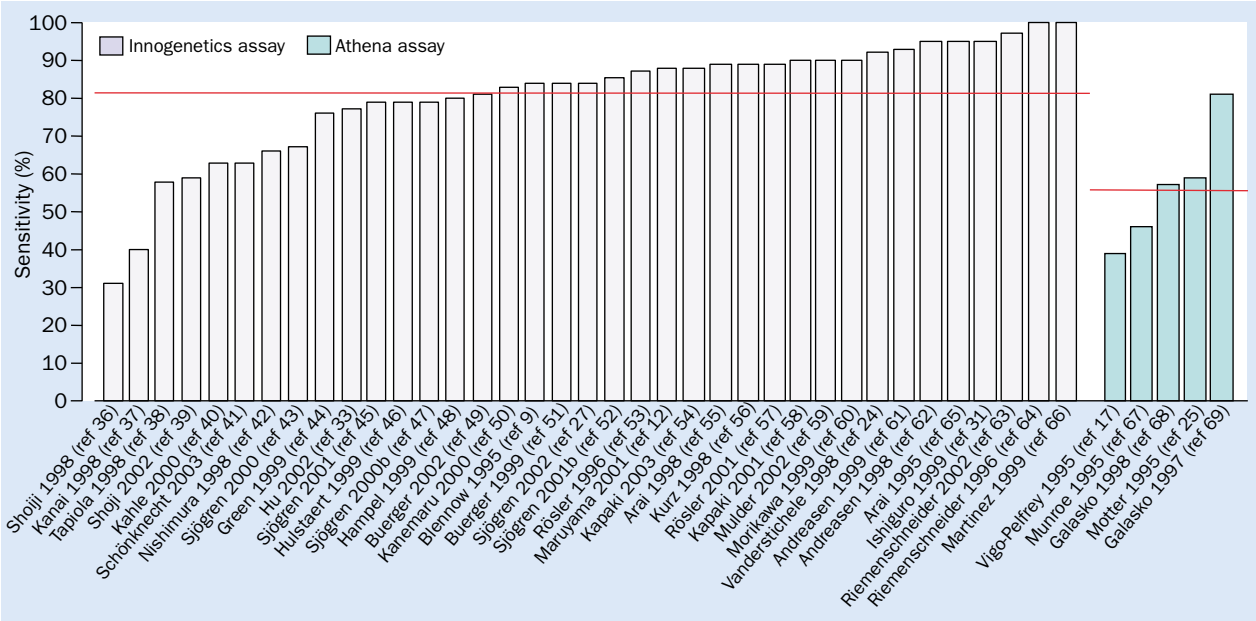

Figure 4. CSF total tau (T-tau) as a diagnostic marker for AD. Bars represent sensitivity figures for the two most commonly used ELISAs, the Innogenetics ELISA[9] and the Athena ELISA.[17] Red lines represent the mean sensitivity for AD versus controls. Reference number, first author, and year of publication are given for each study.

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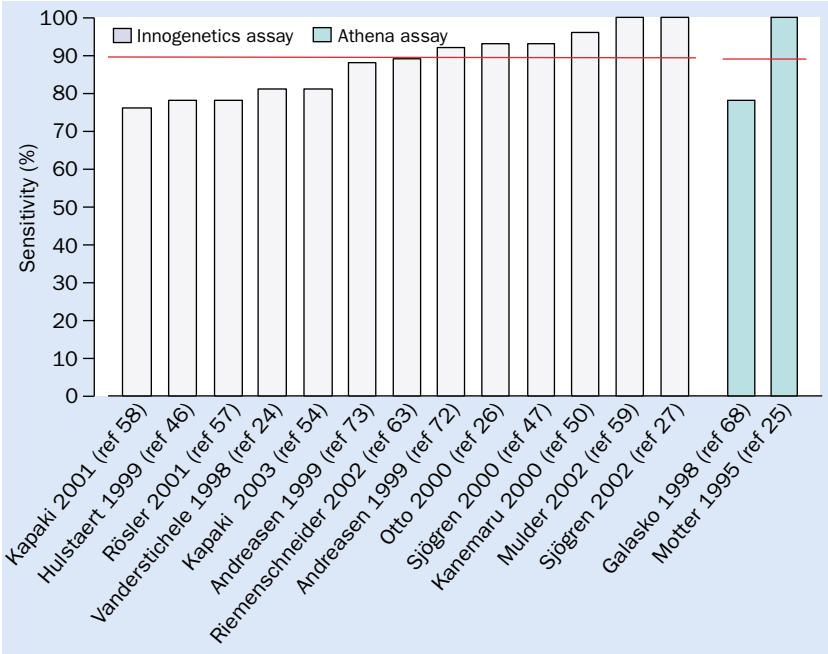

Figure 5. CSF $A\beta_{1-42}$ in the diagnosis of Alzheimer's disease. Bars represent sensitivity figures for the two most commonly used ELISAs, the Innogenetics ELISA[24,72] and the Athena ELISA.[25] Red lines represent the mean sensitivity for AD versus controls.

neurological disorders such as Parkinson's disease and progressive supranuclear palsy.[27,28,47,50] However, the specificity of CSF $A\beta_{1-42}$ for AD is not optimum, because low concentrations are also found in a proportion of cases with other dementia disorders. Moderately low concentrations are also found in Lewy-body dementia,[50,72] a disorder also characterised by senile plaques, but a mild to moderate decrease in CSF $A\beta_{1-42}$ is also found in some patients with frontotemporal and vascular dementias.[27,46,47]

Phosphorylated tau protein

Six different ELISA methods showed a high concentration of phosphorylated tau protein in the CSF of patients with AD.[9,30–33] 11 different studies of sensitivity and specificity have been published, which include about 800 patients with AD and 370 control individuals (figure 6). At a specificity of 92%, the mean sensitivity of assessment of phosphorylated tau protein to discriminate between AD and normal ageing is 80% (figure 6). Sensitivity varies widely among studies both with different and the same ELISA methods. Thus, further studies are needed to determine if there is a difference in sensitivity and specificity figures for the different phosphorylated tau protein methods. The phosphorylated-tau protein epitopes threonine 181, serine 199, and threonine 231 have similar diagnostic results, with sensitivity figures of about 85% (unpublished).

Importantly, the specificity of CSF phosphorylated tau protein for AD is higher than for total tau protein and $A\beta_{1-42}$. High concentrations of tau protein have only been shown in patients with AD, and normal concentrations have been found in patients with psychiatric disorders such as depression;[9,76] in chronic neurological disorders such as amyotrophic lateral sclerosis and Parkinson's disease,[9,27,52] and in vascular, frontotemporal, and Lewy-body dementias.[27,30,49,52,74,75] Thus, phosphorylated tau protein will increase the specificity of CSF biomarkers in the discrimination between AD and other dementias.

Use of CSF markers to identify incipient AD

Several studies have examined the performance of CSF markers in patients with AD with mild dementia (Mini-Mental State Examination[77] >23; figure 7) and high concentrations of total and phosphorylated tau protein, and low concentrations of CSF $A\beta_{1-42}$ are present, with sensitivity figures similar to those found in later stages of the disease (figure 7).

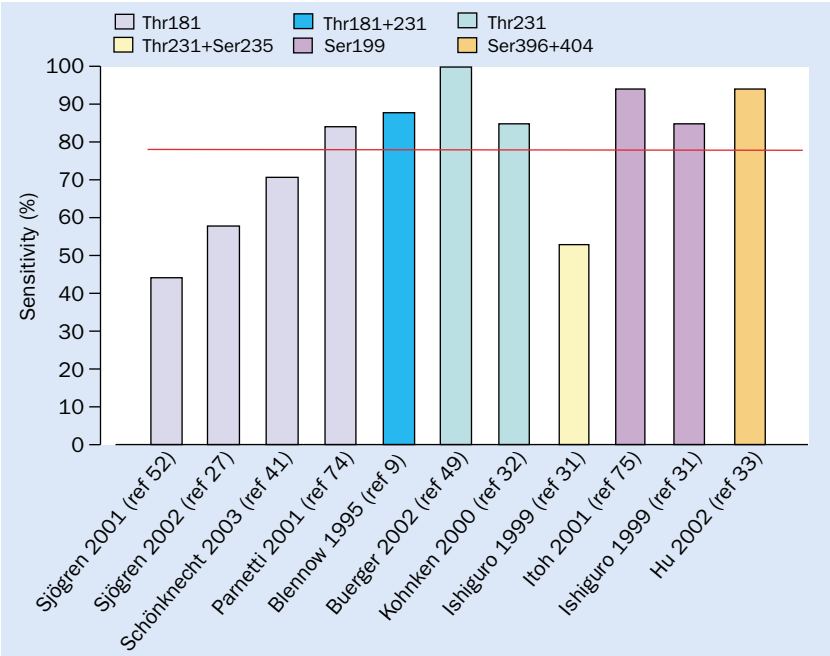

Figure 6. CSF phosphorylated tau in the diagnosis of Alzheimer's disease. Bars represent sensitivity figures for the ELISAs, including the phosphorylation epitopes threonine 181,[30] threonine 181 and 231,[9] threonine 231,[32] threonine 231 and serine 235,[31] serine 199,[31] and serine 396 and 404.[33] The red line represents the mean sensitivity for AD versus controls.

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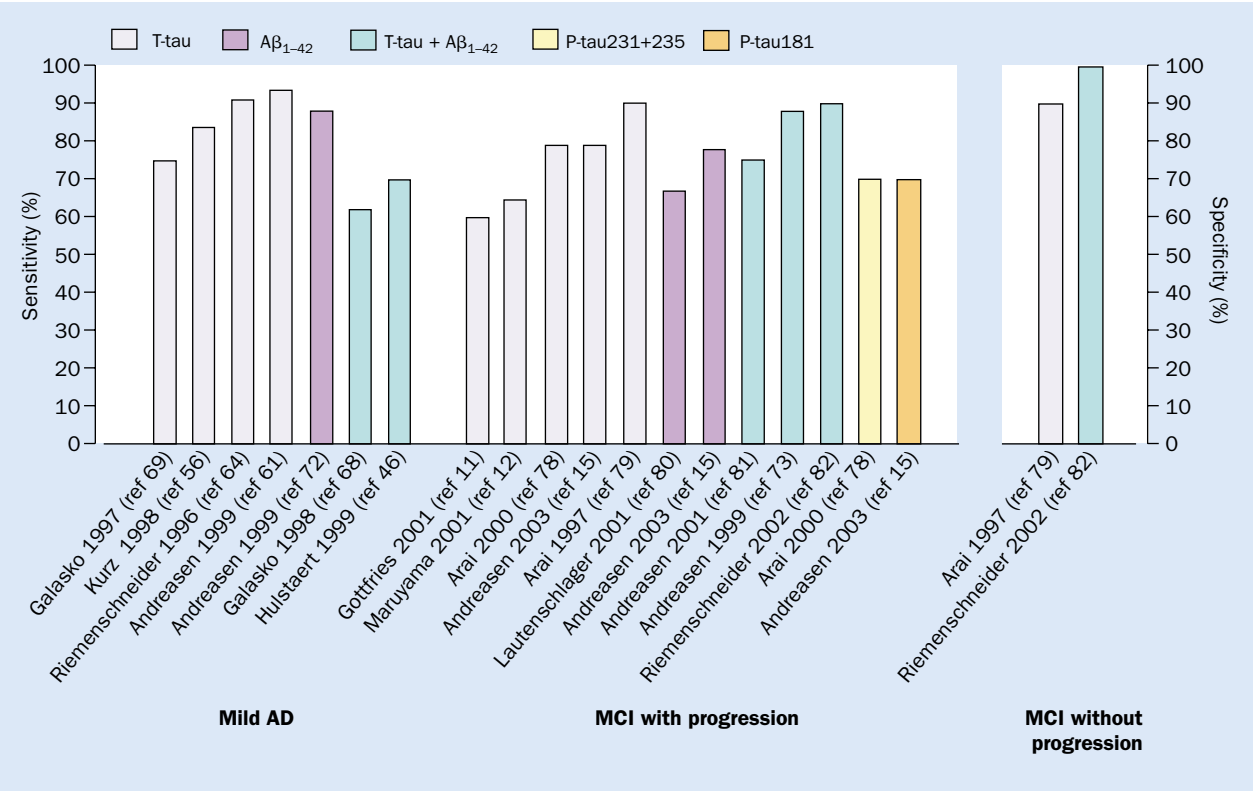

Figure 7. Sensitivity figures for CSF markers in the diagnosis of mild AD with mini-mental state examination score[77] above 23, MCI with progression to AD and specificity figures for MCI with progression to AD.

Several groups of researchers have examined patients with MCI who developed AD during a clinical follow-up period of 1–2 years. All studies have found high total and phosphorylated tau protein and low CSF concentrations of $A\beta_{1-42}$ already in this early phase of AD, with sensitivity figures similar to, or slightly lower than, those found in AD cases with dementia (figure 7).

A pitfall with the studies of CSF markers in patients with MCI is that because only around 15% of MCI cases progress to AD each year,[2] a very extensive follow-up period (>5 years) is needed to be certain that patients with MCI have stable disorder and do not develop dementia. In the first study with this approach, a high total concentration of tau protein in the CSF was found to discriminate patients with MCI that later progressed to AD from those that did not progress, with 90% sensitivity and 100% specificity.[79] Another study also found high total concentrations of tau protein and low concentrations of $A\beta_{1-42}$ in 90% of patients with MCI that later progressed to AD with dementia, compared with 10% of patients with stable MCI.[82] Similarly, a recent study also found a substantially higher concentration of phosphorylated tau protein in patients with MCI that progressed to AD than in those with stable MCI.[13] Taken together, these studies suggest that CSF markers are positive very early in the disease process in AD, and may be of clinical value to differentiate MCI cases with incipient AD—which will progress to AD—from benign MCI cases.

Limitations of CSF studies in clinically diagnosed patients

Almost all data on the diagnostic capacity of CSF markers come from studies of clinically diagnosed patients. This introduces a risk of circular evidence—ie, the diagnostic performance of CSF markers cannot be higher than the accuracy of the clinical diagnostic criteria used. Some patients who fulfil the NINCDS-ADRDA criteria[3] for AD have other disorders. Further, there is an overlap between AD and other dementias. Neuropathological studies have shown that a high proportion (40–80%) of clinically diagnosed patients with vascular dementia have notable concomitant AD pathology,[5,71] and that there is a large overlap between AD and Lewy-body dementia.[83]

Asymptomatic elderly people may have presymptomatic AD lesions in their brains;[84] therefore, extensive follow-up is needed to account for those individuals who have preclinical AD. These limitations with clinical CSF studies make it difficult to judge whether suboptimal sensitivity and specificity figures are caused by shortcomings of the CSF markers or by the patients and controls studied. Indeed, although the differences did not reach statistical significance, AD cases confirmed by autopsy showed a tendency for lower concentrations of $A\beta_{1-42}$ than clinically diagnosed cases (170 pg/mL *vs* 187 pg/mL) and a trend for higher concentrations of total tau was also found (677 pg/mL *vs* 559 pg/mL), even after exclusion of five misdiagnosed patients.[85]

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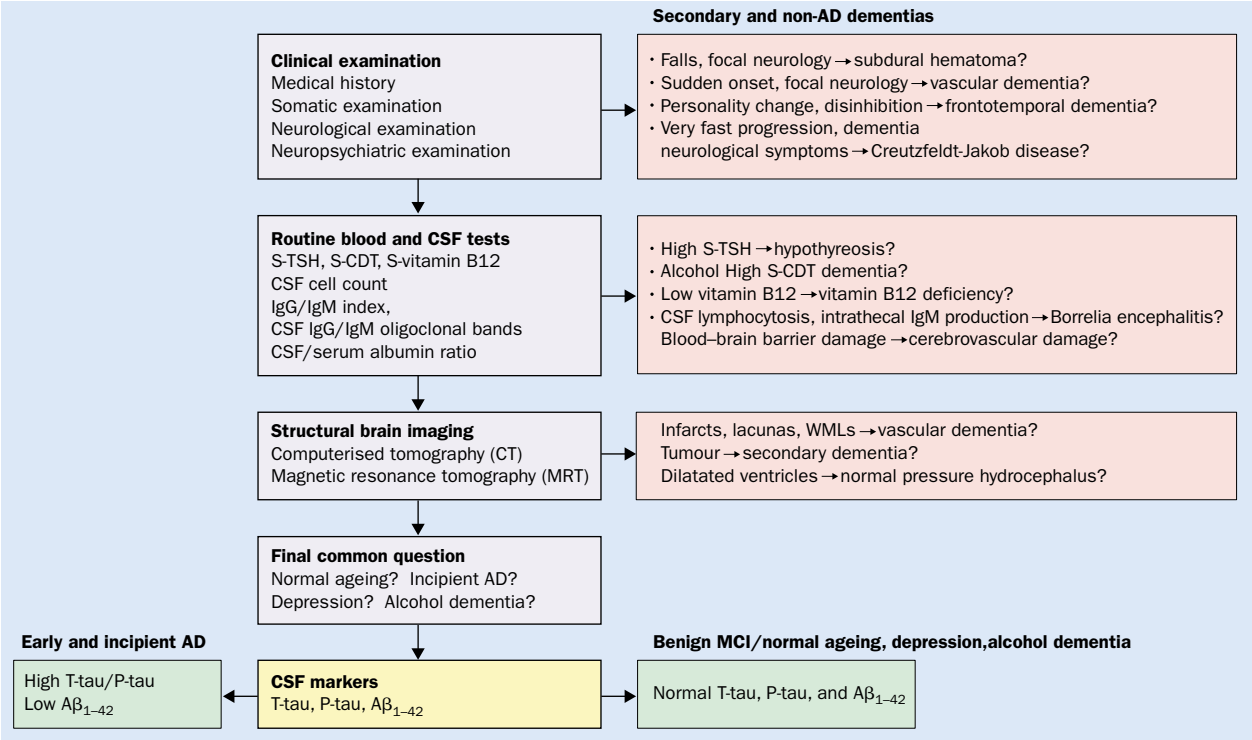

Figure 8. Flow chart for the position of CSF markers in the clinical assessment of patients with MCI and early AD. The suggested investigation is simplified and the secondary and non-AD dementias are only examples, intended to show the position of CSF markers in the clinical investigation. TSH=thyroid stimulating hormone, CDT=carbohydrate deficient transferrine.

Another limitation in the interpretation of the performance of CSF markers is the lack of standardisation of these CSF assays. Concentrations of the CSF markers have been found to vary among studies from different centres with the same ELISA method and among studies with different methods. For example, in studies with the same ELISA method,[9] there is a 354% variation (from 106 pg/mL[66] to 375 pg/mL) variation in total concentrations of tau in the CSF between the control groups.[43] Thus, future availability of external control CSF samples for standardisation of methods will be a prerequisite for direct comparisons of results from different academic centres.

CSF markers in clinical practice

Complications after lumbar puncture

Lumbar puncture is often avoided because of fear of post-lumbar-puncture headache. However, the incidence of this headache is strictly age-related and less common in individuals over 60 years of age than in younger individuals.[86] Furthermore, the incidence of post-lumbar-puncture headache is even lower (<2%) in patients admitted for assessment of cognitive symptoms, most of whom have only minimal discomfort.[81,87] Thus, a spinal tap in the geriatric populations is a safe procedure when done by a trained physician.

Analysis and confounding factors

There are several preanalytical and biological confounding factors (ie, factors that may influence the analytical outcome) that need to be accounted for before a CSF marker can be introduced in clinical routine. The only preanalytical confounding factor is that both tau protein and Aβ have a tendency to stick to the walls of test tubes made of glass and hard plastic, which results in falsely low measurements.[72] Therefore, CSF should be drained into non-absorbent test tubes made of polypropylene. The CSF sample can be sent to the laboratory either at room temperature or at 4°C, and storage for up to 3 days does not influence concentrations of these proteins. In the laboratory, all CSF samples are frozen before assay. Reproducibility of ELISA results are confirmed by use of two internal controls, stored at –80°C, on each ELISA plate. The analytical variation for these ELISA methods (10–15%) is acceptable.[72]

A biological factor that has to be taken into account is variation in CSF concentrations of biomarkers with disease progression. Large longitudinal studies on total tau protein and $A\beta_{1-42}$ show no significant change at 1–2 year follow-up.[61,72] Similarly, there is no significant change in concentrations of either total tau, $A\beta_{1-42}$, or threonine-181 phosphorylated tau in longitudinal studies of patients with MCI that progress to AD with dementia.[15,73] In contrast, in a 6 year longitudinal study, phosphorylated tau epitope threonine 231 concentration decreased linearly with time in patients with AD,[88] and a 1 year longitudinal study of MCI showed progressive increase in the concentration of this epitope in patients with MCI at follow-up.[89]

Clinical routine

Although many studies have assessed the diagnostic potential of these CSF markers, almost all have been done in research settings with selected patient samples and CSF analyses run on

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Search strategy and selection criteria

Data were identified by searches on MEDLINE and references from relevant articles. The search terms "Alzheimer", "CSF", and either "tau" or "amyloid" were used. CSF markers that have been assessed in more than ten studies, by independent research groups using different methods, were considered. Only studies that include sensitivity and specificity figures, or in which such figures could be calculated from graphs, were included. Studies were excluded if they included mixed control groups, did not report CSF proteins in concentration units (ie, mass or mole per volume CSF), or included less than ten patients with AD. Only papers published in English were reviewed.

one occasion (ie, under conditions providing figures on the optimum capability of the markers). Two studies have, however, been done in prospective patient samples, with ELISA assays run each week in clinical neurochemical routine. Also, in these studies the ability of total tau and the combination of total tau and $A\beta_{1-42}$ to differentiate AD from normal ageing, depression, and Parkinson's disease was high, with sensitivity figures similar to, or higher than, other studies.[62,81] However, the specificity against other dementias was less than optimum.

As in other areas of medicine, CSF markers for AD should not be used as isolated tests. A possible analogy is myocardial infarction, for which the clinical diagnosis is based on the combined information from the clinical examination, electrocardiogram, and biomarkers (eg, creatine kinase and troponin T). Likewise, the clinical diagnosis of AD should be based on cumulative information from the clinical examination, brain-imaging techniques (eg, single photon emission CT and MRI), and CSF biochemical markers.

Patients with cognitive disturbances are now seeking medical advice at a very early stage, in many cases when mild memory impairment is the only objective symptom. In these cases there is no clinical method to determine which patients will progress to AD and which patients will not. Biomarkers may be included in the assessment of these patients to help identify incipient AD (figure 8). After the clinical examination and standard auxiliary investigations, secondary dementias (eg, hypothyreosis and subdural haematoma) and also dementias with differing history, symptoms, and findings on brain imaging (eg, frontotemporal or vascular dementia) can be identified. A common final question is whether a patient with MCI has incipient AD or benign MCI. Other possible differential diagnoses that may be hard to differentiate from incipient AD are depression and variants thereof, and alcohol-related cognitive dysfunction. Although more studies are needed to determine the diagnostic capability of CSF markers to identify incipient and early AD, we suggest that CSF markers have a great clinical potential to help to resolve this diagnostic challenge. Early diagnosis of AD is of importance to be able to initiate symptomatic treatment with acetylcholinesterase inhibitors, and ongoing studies will tell us whether these drugs are also effective in patients with MCI or incipient AD. Furthermore, identification of incipient AD will be the basis for initiation of treatment with drugs that might slow or stop the degenerative process, such as inhibitors of β-secretase and γ-secretase.

Authors' contributions

Both authors contributed equally to this review.

Conflict of interest

We have no conflicts of interest.

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OPEN PEER COMMENTARY

Frequency of Stages of Alzheimer-Related Lesions in Different Age Categories

H. BRAAK[1] AND E. BRAAK

Department of Morphology, J. W. Goethe University, D-60590 Frankfurt, Germany

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BRAAK, H. AND E. BRAAK. *Frequency of stages of Alzheimer-related lesions in different age categories.* NEUROBIOL AGING **18**(4) 351–357, 1997.—Alzheimer's disease is a relentlessly progressing dementing disorder. Major pathological hallmarks include extracellular deposits of amyloid protein and intraneuronal neurofibrillary changes. No remissions occur in the course of the disease. Initial amyloid deposits develop in poorly myelinated areas of the basal neocortex. From there, they spread into adjoining areas and the hippocampus. Deposits eventually infiltrate all cortical areas, including densely myelinated primary fields of the neocortex (stages A–C). Intraneuronal lesions develop initially in the transentorhinal region, then spread in a predictable manner across other areas (stages I–VI). At stages I–II, neurofibrillary changes develop preferentially in the absence of amyloid deposits. A proportion of cases shows early development of amyloid deposits and/or intraneuronal changes. Advanced age is thus not a prerequisite for the evolution of the lesions. Alzheimer's disease is an age-related, not an age-dependent disease. The degree of brain destruction at stages III–IV frequently leads to the appearance of initial clinical symptoms. The stages V–VI representing fully developed Alzheimer's disease are increasingly prevalent with increasing age. The arithmetic means of the stages of both the amyloid-depositing and the neurofibrillary pathology increase with age. Age is a risk factor for Alzheimer's disease. © 1997 Elsevier Science Inc.

Alzheimer's disease Amyloid-protein Neurofibrillary change Aging

THE insidious onset of Alzheimer's disease (AD) is characterized by a subtle decline in memory functions. As time passes, changes in personality, deterioration of language functions, and eventually motor dysfunction are added to the initial symptoms. The gradual progress in the clinical picture mirrors the development of AD-related brain destruction. Major pathological hallmarks include extracellular deposits of Aβ-amyloid protein and intraneuronal neurofibrillary changes. The predictable alteration in the pattern and severity of the pathology permits the distinction of stages in amyloid-deposition (A–C) and neurofibrillary changes (I–VI) (8,10). The possible relationships among the three factors (age, amyloid-depositing, and neurofibrillary changes) have not been sufficiently explored. Goal of this study is to partially fill in these gaps in knowledge through assessment of nonselected autopsy cases using a staging procedure for AD-related lesions.

MATERIALS AND METHODS

A total of 2,661 brains obtained at autopsy was examined in this study. The brains were collected between 1986 and 1996 and were sent by three Departments of Pathology and one Department of Forensic Pathology belonging to three Universities in Germany. The material included cases from all the affiliated University clinics. It did not originate in special gerontopsychiatric institutions and does not correspond to such preselected material as might have been provided by a Department of Neuropathology. All cases received by our laboratory during this time period were examined for AD-related changes. The relatively few cases below the age of 25 and above the age of 95 were excluded from the study. The material was checked for, but did not include, cases with diseases known to be associated with the development of neurofibrillary changes but different from AD (Down's syndrome, type C of Niemann-Pick disease, subacute sclerosing panencephalitis, progressive supranuclear palsy, corticobasal degeneration). Staged cases at our disposal from prospective studies on the development of Alzheimer's disease were not included. Age distribution and the number of cases permit division into age categories encompassing a range of 5 years. The number of cases and the male or female predominance in each age category is displayed in Table 1 and Fig. 1.

Brains were fixed by immersion in a 4% aqueous formaldehyde solution. Blocks of tissue including anteromedial portions of the temporal lobe were removed at the mid-uncal level, and portions of

[1] Request for reprints should be addressed to Heiko Braak, Department of Anatomy, J. W. Goethe University Theodor Stern Kai 7, D-60590 Frankfurt, Germany.

TABLE 1

RELATIVE FREQUENCY OF FEMALES AND MALES IN THE MATERIAL EXAMINED

Age Category	Female	Male	Total Number
26–30	19 (31%)	42 (69%)	61
31–35	25 (43%)	33 (57%)	58
36–40	36 (43%)	47 (57%)	83
41–45	28 (36%)	50 (64%)	78
46–50	42 (33%)	87 (67%)	129
51–55	61 (37%)	104 (63%)	165
56–60	66 (29%)	158 (71%)	224
61–65	91 (37%)	157 (63%)	248
66–70	147 (49%)	153 (51%)	300
71–75	146 (50%)	144 (50%)	290
76–80	160 (51%)	155 (49%)	315
81–85	234 (58%)	171 (42%)	405
86–90	153 (65%)	82 (35%)	235
91–95	50 (71%)	20 (29%)	70
	1258	1403	2661

the occipital lobe were cut perpendicular to the calcarine fissure. The blocks were embedded in polyethylene glykol and cut at 100 μm. Three staining techniques were applied. The aldehyde fuchsin-Darrow red method was used for topographic orientation (7,12). Modern silver techniques taking advantage of physical development of the nucleation sites were applied: a silver-iodide technique for neurofibrillary changes and argyrophilic grains, and a silver-pyridine method for amyloid deposits and Lewy bodies (9,12,15,23). These techniques demonstrate the pathological material reliably, even if the tissue has been stored for decades in formaldehyde. The results obtained by applying the advanced silver techniques for neurofibrillary changes and amyloid deposits are nearly identical to those seen in immunostained sections for Aβ-protein and abnormally phosphorylated tau protein (9,13,23). Diagnoses of stages in the development of amyloid deposits and neurofibrillary changes were performed using published criteria and were achieved without knowledge of clinical and pathological data or age and gender of the individuals (8,10).

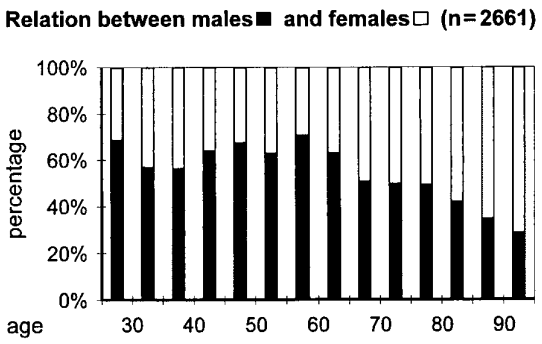

FIG. 1. Diagram showing the relative frequency of females and males in each age category. In higher age categories, the predominance of males is replaced by a gradual increase in the proportion of females.

RESULTS

The proportion of cases exhibiting no amyloid deposits or neurofibrillary changes decreases with advancing age (Figs. 2 and 3, upper row). Neither amyloid deposits nor neurofibrillary changes necessarily accompany old age. The evolution of amyloid deposits is shown in Fig. 2 and Table 2. The subpopulations devoid of neurofibrillary changes are represented by the blank areas in the columns in Fig. 2, and the dark areas indicate the subgroups expressing any degree of neurofibrillary changes. Figure 3 and Table 3 are similarly designed and display the evolution of neurofibrillary changes. Here, the blank areas stand for the subgroups devoid of amyloid deposits and the dark areas represent the subgroups exhibiting them.

Amyloid Deposits

Cortical deposits of amyloid protein appear gradually, distributed more or less symmetrically, at specific predilection sites. Initially, extensive cloud-like formations with ill-defined boundaries appear. With advance of the disease, they are replaced by sharply outlined globular plaques of variable sizes. Intensely stained plaques occur preferentially in neocortical layers III and Va. Layers containing a myelinated plexus (IV and Vb) generally show less dense precipitations. Subpial portions of layer I contain confluent plaques, and layers II and VI are frequently free of deposits. Often, band-like precipitations are seen in the outer and inner pyramidal cell layers of the hippocampal CA1 sector and in layers pre-β and pre-γ of the entorhinal region. The number of deposits increases until a certain level of density is reached. Even at maximum density, a notable amount of the gray matter remains free of deposits. An inverse relationship is observed between the degree of myelination and the density of amyloid deposition, with sparsely myelinated cortical areas and/or layers displaying a denser depositing than those rich in myelin (13).

Stages in the Evolution of the Amyloid Deposits

Three stages can be distinguished in the gradual development of cortical amyloid deposits (8,10). Typically, the initial patches are seen in the basal neocortex, most frequently in poorly myelinated temporal areas such as the perirhinal and/or ectorhinal fields (stage A, Fig. 2, second row). Some individuals develop initial deposits in young adulthood. The depositions increase in number and spread into the adjoining neocortical areas and the hippocampal formation (stage B, Fig. 2, third row). At this stage, the perforant path is decorated with deposits as it pierces the subiculum and travels through the molecular layers of CA1 and the fascia dentata. Eventually, deposits are found in all areas of the cortex, including the densely myelinated primary areas of the neocortex (stage C, Fig. 2, fourth row). The diagrams of stages A to C show a shift towards higher age-categories (Fig. 2). The prevalence of stage C cases increases with age. More and more individuals arrive at a higher stage of amyloid-depositing with advancing age. The arithmetic means of the relative frequency in the occurrence of amyloid-stages increase with age (A = 1, B = 2, C = 3; Fig. 4, upper portion of the right half).

Neurofibrillary Changes of the Alzheimer Type

Neurofibrillary tangles (NFTs), neuropil threads (NTs), and argyrophilic dystrophic neurites of neuritic plaques (NPs) are different types of the intraneuronal changes. In general, the first

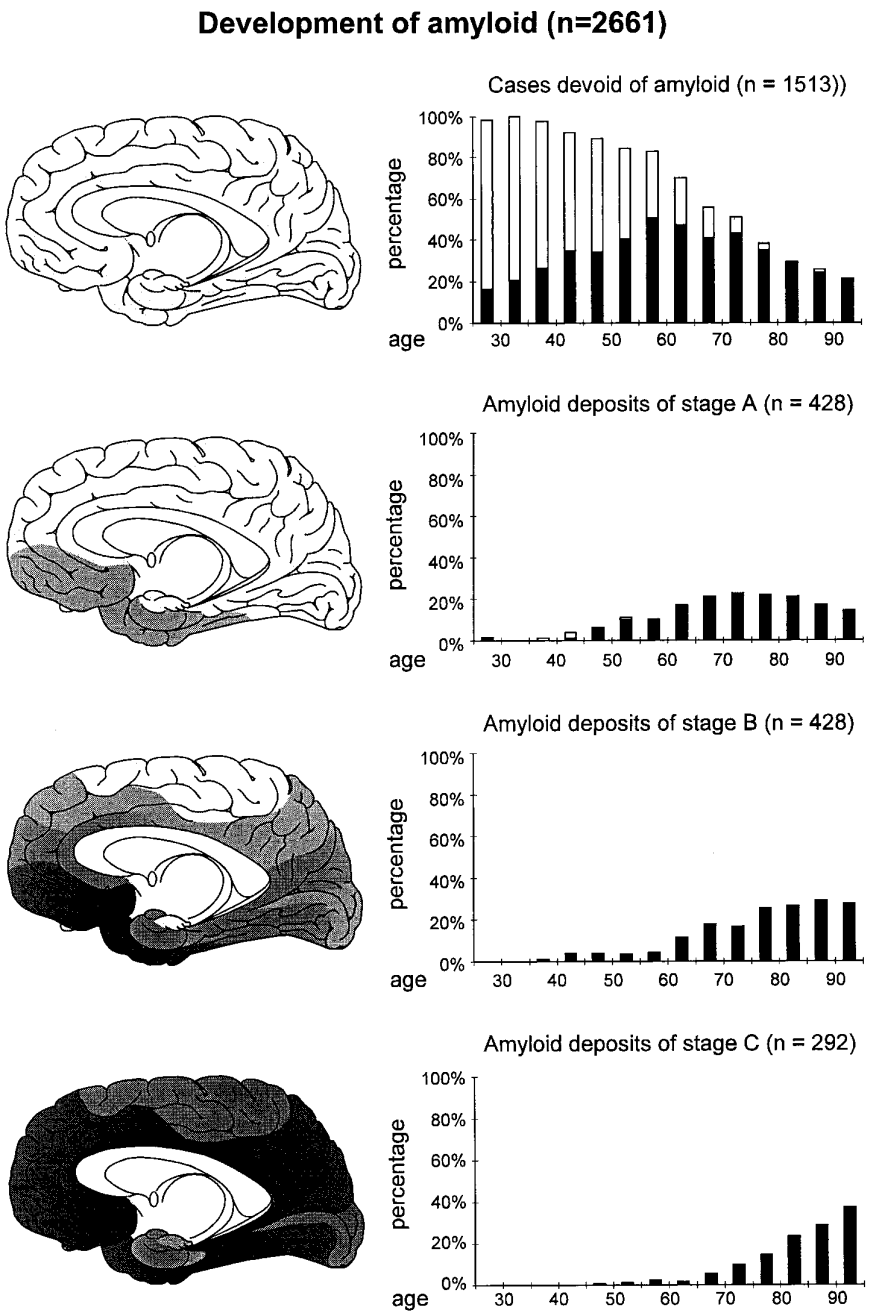

FIG. 2. Development of amyloid deposits in 2,661 nonselected autopsy cases. The first line displays the frequency of cases devoid of changes in relation to the total number of cases in the various age categories. The second, third, and fourth lines are similarly designed, and show the evolution of the AD-related changes. The dark areas of the columns refer to subgroups showing the presence of neurofibrillary changes.

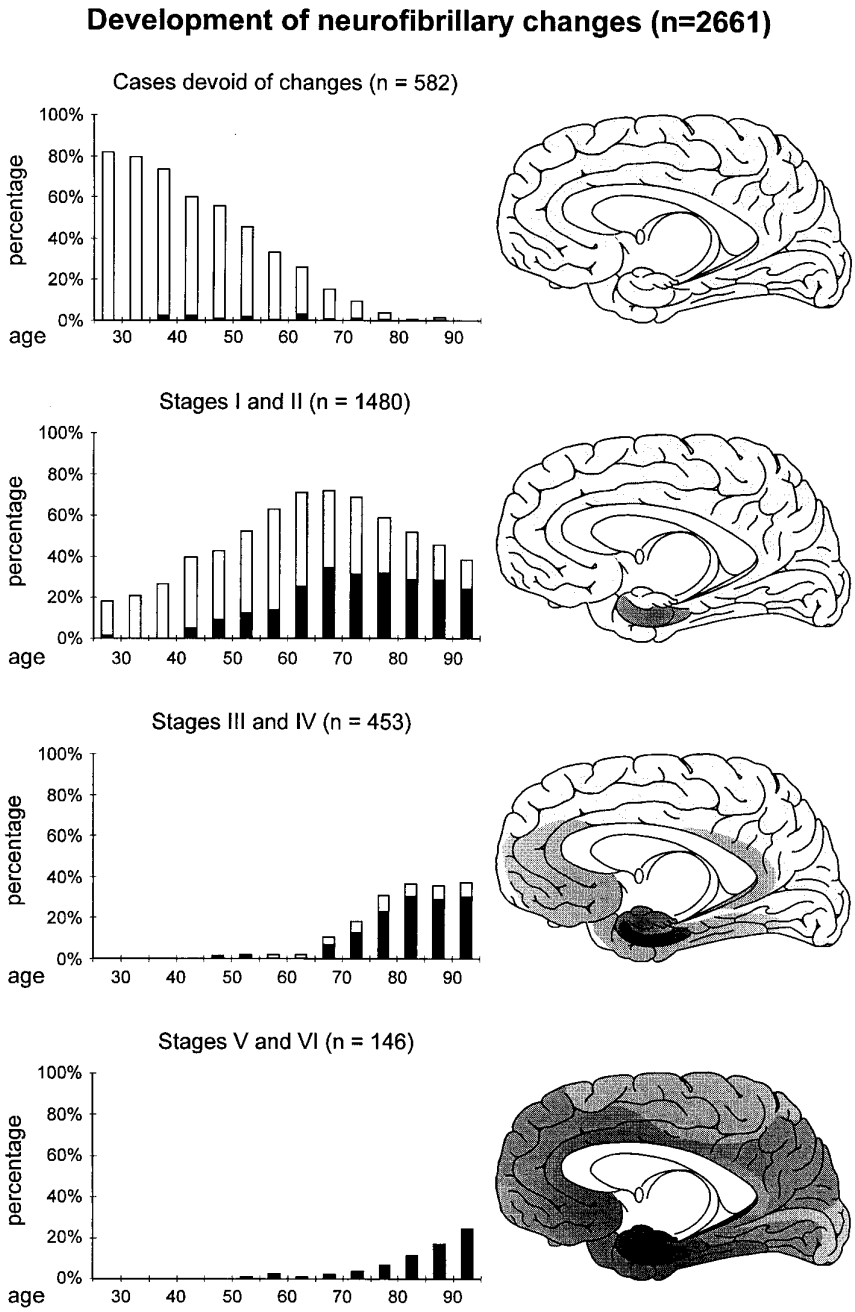

FIG. 3. Development of neurofibrillary changes in 2,661 nonselected autopsy cases. The first line displays the frequency of cases devoid of changes in relation to the total number of cases in the various age categories. The second, third, and fourth lines are similarly designed, and show the evolution of the AD-related changes. The dark areas of the columns represent the subgroups displaying amyloid deposits.

TABLE 2

NUMBER OF CASES AT AMYLOID-STAGES A–C OR DEVOID OF AMYLOID DEPOSITS IN VARIOUS AGE CATEGORIES

Age Category	No Change	Stage A	Stage B	Stage C	Total Number
26–30	60 (10)	1 (1)	0 (0)	0 (0)	61
31–35	58 (12)	0 (0)	0 (0)	0 (0)	58
36–40	81 (22)	1 (0)	1 (0)	0 (0)	83
41–45	72 (27)	3 (1)	3 (3)	0 (0)	78
46–50	115 (44)	8 (7)	5 (5)	1 (0)	129
51–55	139 (67)	18 (16)	6 (5)	2 (2)	165
56–60	186 (113)	23 (23)	10 (9)	5 (5)	224
61–65	174 (117)	42 (40)	28 (22)	4 (3)	248
66–70	167 (123)	63 (61)	53 (53)	17 (16)	300
71–75	148 (125)	65 (63)	48 (44)	29 (27)	290
76–80	120 (110)	69 (68)	80 (79)	46 (43)	315
81–85	118 (116)	85 (85)	107 (106)	95 (93)	405
86–90	60 (57)	40 (39)	68 (68)	67 (67)	235
91–95	15 (15)	10 (10)	19 (19)	26 (26)	70
	1513	428	428	292	2661

Cases displaying presence of neurofibrillary changes in brackets.

changes seen in the brain consist of NTs and NFTs; NPs develop later. The distribution of NPs is patchy and differs from that of NFTs/NTs and of amyloid precipitations. Only a few of the many neuronal types in the brain are capable of developing NTs/NFTs (8,10). Poorly myelinated areas and/or layers display a higher density of neurofibrillary changes than those rich in myelin (11). Entangled neurons eventually die. The pathological material is then converted into a less densely twisted extraneuronal "ghost" tangle (3,6). Fresh NFTs/NTs and a variable number of "ghost" tangles usually co-occur; just "ghost" tangles alone were not observed in the material examined.

TABLE 3

NUMBER OF CASES AT NFT/NT-STAGES I–VI OR DEVOID OF NEUROFIBRILLARY CHANGES IN VARIOUS AGE CATEGORIES

Age Category	No Change	Stage I/II	Stage III/IV	Stage V/VI	Total Number
26–30	50 (0)	11 (1)	0 (0)	0 (0)	61
31–35	46 (0)	12 (0)	0 (0)	0 (0)	58
36–40	61 (2)	22 (0)	0 (0)	0 (0)	83
41–45	47 (2)	31 (4)	0 (0)	0 (0)	78
46–50	72 (1)	55 (12)	2 (1)	0 (0)	129
51–55	75 (3)	86 (20)	3 (1)	1 (1)	165
56–60	74 (1)	141 (30)	4 (1)	5 (5)	224
61–65	65 (8)	176 (63)	5 (1)	2 (2)	248
66–70	46 (2)	216 (104)	32 (21)	6 (6)	300
71–75	27 (4)	200 (91)	53 (37)	10 (10)	290
76–80	12 (2)	185 (101)	97 (72)	21 (20)	315
81–85	3 (1)	210 (117)	147 (124)	45 (45)	405
86–90	4 (1)	108 (67)	84 (68)	39 (39)	235
91–95	0 (0)	27 (17)	26 (21)	17 (17)	70
	582	1480	453	146	2661

Cases displaying presence of amyloid deposits in brackets.

Stages in the Evolution of the Neurofibrillary Tangles and Neuropil Threads

The intraneuronal changes develop at specific predilection sites. From there, the changes spread in a predictable manner across the cerebral cortex. Six stages can be distinguished in the gradual development of NFTs/NTs (8,10). Specific projection cells in the transentorhinal region (temporal lobe) are the first cortical neurons to show the changes (stage I). The lesions then extend into the entorhinal region proper (stage II). These changes develop preferably in the absence of amyloid deposits (Fig. 3). A significant number of cases show early development of stage I/II pathology (Fig. 3, second row). Proceeding toward higher age categories, the relative frequency of stage I/II cases increases, reaches a culmination point, then decreases. Note in separate illustrations that the culmination point of stage I cases is reached at a younger age than that of stage II cases (Fig. 4, left half). The pathological process then proceeds into both the hippocampus and the temporal proneocortex (stage III), then reaches association areas of the adjoining neocortex (stage IV). Eventually, the lesions spread superolaterally (stage V) and extend into the primary areas of the neocortex (stage VI). This pattern bears a resemblance to the inverse sequence of cortical myelination (11). The limbic stages III/IV (Fig. 3, third row) and neocortical stages V/VI (Fig. 3, fourth row) display only an ascending portion of the age distribution. The prevalence of stage V/VI cases increases with age. The arithmetic means of the relative frequency in the occurrence of NFT/NT-stages increase with age (Fig. 4, lower portion of the right half).

Combinations between Amyloid- and NFT/NT-Stages in Three Age Ranges

Sixteen combinations are possible among cases without amyloid deposits or neurofibrillary changes, the amyloid stages A, B, C, and the NFT/NT-stages I+II, III+IV, and V+VI (Table 4). Some of these occur more frequently than others. The pattern of the prevailing combinations changes with age. A rough division into three age categories permits recognition of the major trend. The frequently encountered combination of absence of both amyloid deposits and neurofibrillary changes in the younger group decreases with age, and the combination of amyloid-stage C with NFT/NT-stages V–VI increases. In general, initial neurofibrillary changes (stages I–II) develop in the absence of amyloid deposits, while stages V–VI are associated with amyloid-stage C (Table 4).

DISCUSSION

The clinical diagnosis of AD is fraught with difficulty and definite diagnoses cannot presently be made. Both false positive and false negative diagnoses occur in a significant proportion of cases, underlining the necessity for postmortem evaluation. Epidemiological studies often focus on avoiding selection bias, yet still face the problem of inaccurate diagnoses (1,17,20,22,25,27). Postmortem assessments offer the advantage of unambiguous diagnoses, however, they unavoidably fail to be representative of a living population (21).

The slow progression in the clinical symptoms of AD reflects the gradual development of the brain changes (4,14,18,19,24). Most conventional criteria for a postmortem diagnosis permit recognition of fully developed AD, but fail to correctly distinguish the broad spectrum of cases with less severe changes. Application of the staging system takes into consideration the gradual progression of AD, provides accurate diagnoses in the initial phases, and even takes note of the brain changes preceding the appearance of clinical symptoms. The basic assumptions underlying the proce-

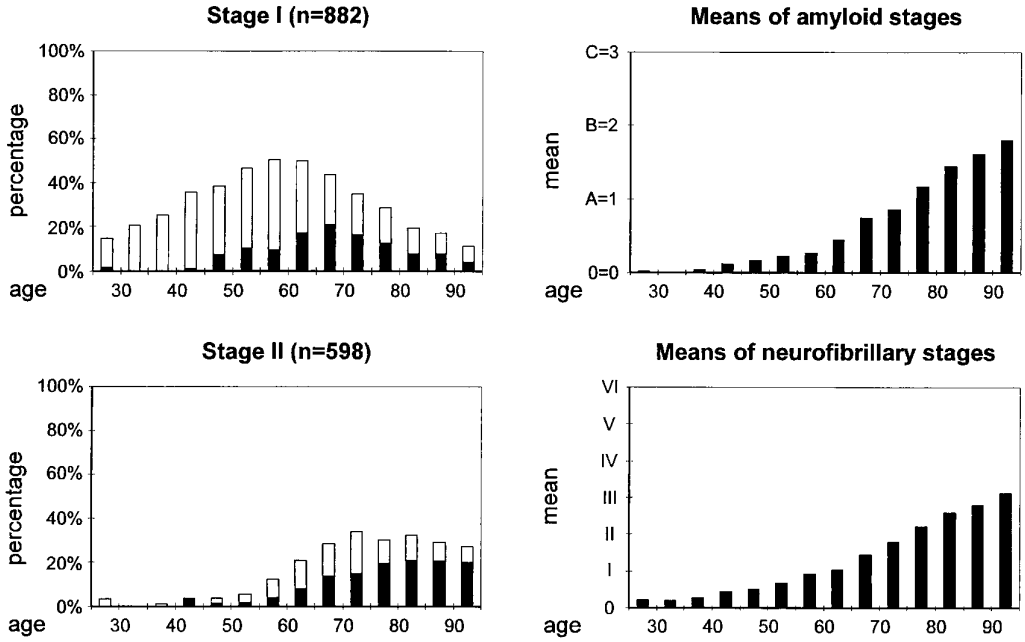

FIG. 4. Left: Relative frequency of cases showing stage I and stage II in the development of NFTs/NTs (same design as in Fig. 3). Initial neurofibrillary changes usually develop in the absence of amyloid deposits. Some individuals develop stage I pathology early in life. Old age is not a prerequisite for the evolution of the neurofibrillary changes. Note the shift towards higher age-categories with progress from stage I to stage II. Right: The arithmetic means of stages of amyloid deposits (A = 1, B = 2, C = 3) and neurofibrillary pathology increase with age. Age is a risk factor for AD.

dure are corroborated by the finding that early stages occur preferably in relatively young individuals, and the more advanced stages appear with increasing age (28). It is important to note that not a single stage I–VI case showed "ghost" tangles alone; all demonstrated fresh NFTs/NTs, indicating that the pathological process was continuing at the time of death. Spontaneous remission does not occur. Once the destructive process has begun it immutably progresses.

TABLE 4

PERCENTAGE OF THE VARIOUS COMBINATIONS BETWEEN AMYLOID (0, A, B, C) AND NFT/NT STAGES (0, I–II, III–IV, V–VI) IN THREE AGE-RANGES

Age (Years)	0	A	B	C
36–55				
0	53.30	1.32	0.44	0.00
I–II	34.70	5.05	2.64	0.22
III–IV	0.40	0.22	0.22	0.22
V–VI	0.00	0.00	0.00	0.22
56–75				
0	18.55	0.67	0.85	0.00
I–II	41.80	16.50	9.70	1.13
III–IV	3.20	1.04	2.64	1.98
V–VI	0.00	0.10	0.00	2.07
76–95				
0	1.46	0.20	0.20	0.00
I–II	22.20	14.65	12.30	2.54
III–IV	6.73	5.07	12.78	9.95
V–VI	0.10	0.00	1.46	10.34

A small proportion of cases develop amyloid deposits and/or NFTs/NTs at a surprisingly young age (Figs. 2 and 3). Advanced age is no prerequisite for the evolution of the changes. Development of the changes are frequently attributed to noxious influences expected to increase in severity in old age (peroxidative stress, mitochondrial dysfunction, imbalance of glucose metabolism) (2,5,16,29,30). The fact that initial lesions may develop in a young and otherwise healthy brain should stimulate studies to determine whether or not such influences can be demonstrated even in these very early stages.

As in many other neurodegenerative diseases, the pathological process underlying AD can be recognized over extended periods of time before the onset of clinical symptoms. Data on the appearance of stage I cases are of particular interest, because they provide information about the actual spread of the disease. To find the first neurofibrillary changes in a voluminous organ such as the human brain might seem to be an almost hopeless undertaking. However, with knowledge of the predilection sites of the initial NFTs/NTs, the task can be accomplished. Many of the stage I cases die of causes other than AD, and only a proportion of them live long enough to arrive at end stages V–VI. In higher age categories, the relative frequency of stage I/II cases increases, reaches a culmination point, then decreases. At stages III–IV, severe destruction of the cortex is already observed; however, it is focused on the entorhinal region and adjoining areas. Because of the probable

presence of initial symptoms and the characteristic brain destruction, stage III–IV cases are considered to correspond to clinically incipient AD (4,14,18,24). Stages V/VI correspond to the clinical picture of fully developed AD. They are increasingly prevalent with increasing age (Fig. 3, fourth row).

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FORECASTING THE GLOBAL BURDEN OF ALZHEIMER'S DISEASE

Ron Brookmeyer [*] Elizabeth Johnson [†]
Kathryn Ziegler-Graham [‡] H. Michael Arrighi [**]

[*]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, rbrook@jhsph.edu

[†]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health

[‡]St. Olaf College

[**]Elan Pharmaceuticals

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Ron Brookmeyer, Elizabeth Johnson, Kathryn Ziegler-Graham, and H. Michael Arrighi

Abstract

Background: The goal was to forecast the global burden of Alzheimer's disease and evaluate the potential impact of interventions that delay disease onset or progression. Methods: A stochastic multi-state model was used in conjunction with U.N. worldwide population forecasts and data from epidemiological studies on risks of Alzheimer's disease.

Findings: In 2006 the worldwide prevalence of Alzheimer's disease was 26.6 million. By 2050, prevalence will quadruple by which time 1 in 85 persons worldwide will be living with the disease. We estimate about 43% of prevalent cases need a high level of care equivalent to that of a nursing home. If interventions could delay both disease onset and progression by a modest 1 year, there would be nearly 9.2 million fewer cases of disease in 2050 with nearly all the decline attributable to decreases in persons needing high level of care.

Interpretation: We face a looming global epidemic of Alzheimer's disease as the world's population ages. Modest advances in therapeutic and preventive strategies that lead to even small delays in Alzheimer's onset and progression can significantly reduce the global burden of the disease.

Forecasting the Global Burden of Alzheimer's Disease

Ron Brookmeyer[1]

Elizabeth Johnson[1]

Kathryn Ziegler-Graham[2]

H. Michael Arrighi[3]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore MD

[2]St Olaf College, Northfield MN;

[3] Elan Pharmaceuticals, San Diego CA

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INTRODUCTION

As the world population ages, enormous resources will be required to adequately care for persons afflicted with Alzheimer's disease. Research is actively underway to develop interventions to both delay disease onset and slow progression of disease. Effective interventions may significantly reduce the prevalence and incidence of Alzheimer's disease, improve the quality of life both of the patients and their caregivers, and reduce the resources needed to provide adequate institutional and home health care. Several treatments to help slow disease progression, and prevention strategies including lifestyle changes are being investigated (1).

Uncertainty exists in the estimates of the global burden of Alzheimer's disease and the potential impact of interventions. Recently, Alzheimer's Disease International, an international consortium of Alzheimer's associations, produced estimates of the worldwide prevalence of people with dementia (2). These estimates were based on a Delphi consensus study of 12 international experts who systematically reviewed published studies. The consensus method involved a qualitative assessment of evidence by each expert, and then those experts were given an opportunity to revise their estimates of prevalence after reflecting on the input of their colleagues. The resulting Delphi consensus estimates have been considered some of the best currently available estimates of worldwide prevalence. Yet, because the Delphi approach is not based on an underlying quantitative model, the Delphi study cannot be readily used to forecast the potential impact of new interventions on health care needs. Furthermore the study did not take into account the severity of disease. Disease severity is an important consideration for assessing the global burden of Alzheimer's disease because the resources needed to care for patients with advanced disease are very different than for patients early in the disease process. The objective of this article is to forecast the global burden of Alzheimer's disease based on a

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mathematical model that incorporates the aging of the world's population. The model is used to forecast the world-wide prevalence of Alzheimer's disease, evaluate the impact of interventions, and incorporate disease severity.

METHODS

The Multi-State Model

Our methodology is based on a multi-state probabilistic model for the incidence and progression of Alzheimer's' disease. The method extends a single stage disease model used for U.S. projections (3) by including early and late stages of disease. According to the model, healthy persons have an annual probability of onset of Alzheimer's disease which begins in an early stage and ultimately progresses to late stage disease. Persons with early stage disease have an annual probability of progressing to late stage disease. The definitions of early and late stage disease including the mean durations are discussed below. Persons are at risk of death during each state. The model is illustrated schematically in figure 1. The transition probabilities between states are the probabilities of moving from one state to the next. We allow some of these transition probabilities to depend not only on age but also calendar year to account both for birth cohort effects (e.g. death rates change over time) and the impact of new interventions that could potentially delay disease onset and progression. The model is implemented as a discrete time stochastic model in which transitions occur only at the beginning of a calendar year, and it is possible that persons may have multiple transitions in a year (e.g. disease onset followed by death could occur in the same year).

We derived formulas for the age-specific prevalence rates of early stage and late stage disease in terms of the model in figure 1. The transition probabilities are inputs into these

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formulas. We performed a number of analyses and systematic reviews of published literature, to estimate the transition probabilities (described below.) Then, we forecast disease prevalence by multiplying the formulas for age–specific prevalence rates by demographic population projections. We used the United Nations worldwide population projections (4). Those projections are in terms of 5 year age groups which we interpolated to obtain projections by single year of age. We performed analyses separately by gender, and for each of six regions of the world. Then, we evaluated the potential effects of interventions that delay disease onset, delay disease progression or both by modifying the transition probabilities under different scenarios. We multiplied the transition probabilities by various factors (relative risks) to model the potential effects of the interventions. We translated these relative risks into average delays in disease onset and progression (in the absence of competing causes of death) as an alternative way to express the efficacy of intervention programs. We considered the impact of interventions that begin in the year 2010. The technical details including the formulas for the age specific prevalence rates and computing software are available from the authors at www.biostat.jhsph.edu/project/globalAD/index.htm.

Transition Probabilities

In this section, we discuss inputs for each of the transition probabilities of figure 1.

Incidence rates

We estimated age-specific probabilities of disease onset by performing a systematic review of published Alzheimer's disease incidence rates. Jorm and colleagues (5) reviewed the worldwide literature on Alzheimer's disease incidence rates. We updated the Jorm review to include additional recent studies reporting age-specific incidence rates of Alzheimer's disease.

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We fit a linear regression equation to the log of the age-specific incidence rate for each of 27 studies in our review because incidence rates appeared to grow exponentially with age. We then averaged the rates from the fitted regression lines to obtain an equation for the age-specific incidence rate. We found that the annual age-specific incidence of Alzheimer's disease at age *t* expressed in per cent per year (for *t* greater than 60) is given by:

$$\text{Incidence rate (\% per year)} = .132e^{.121(t-60)}. \qquad (1)$$

Equation 1 implies that incidence grows exponentially with a doubling time of about 5.7 years. We found no significant geographic differences in the doubling times of Alzheimer's incidence ($p=.3$), suggesting that any geographic variation may be due to different criteria and thresholds for diagnosis. We used equation 1 for the incidence rates ($r_{t,y}$ in figure 1) in our analyses. We accounted for uncertainty in equation 1 by performing a sensitivity analysis that used a range based on the upper and lower 10th percentiles of the distribution of fitted incidence rates from all the studies. This range spanned from about half to double the incidence estimates from equation 1. For example, the predicted annual incidence at age 80 is 1.48 % per year with range of 0.67% to 3.41%. The ranges we cite in the results section account for this uncertainty in incidence rates. We also performed sensitivity analyses to the assumption that incidence continues to grow exponentially at the oldest ages by holding incidence rates constant after age 90.

Disease Progression

Alzheimer's disease is a progressive disease and persons who have the disease longer often require a higher level of care. Considerable variability exists in the world's literature on the rate of Alzheimer's disease progression which results from differences in definitions of severe disease among studies, and heterogeneity in the disease course among patients. The Consortium to Establish a Registry for Alzheimer's disease suggested that 6 years is the mean

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time from mild to severe disease using the Clinical Dementia Rating scale (5). Similarly, a study examining the time for patients needing care equivalent to placement in a health related facility, such as a nursing home, also obtained an estimate of about 6 years (7). We defined late stage disease to refer to the period when patients need such a high level of care. We used an annual transition probability from early to late stage disease of .167 in our model which corresponds to a mean duration of early stage disease of approximately 6 years. The model accounts for variability in the duration of early disease course (the 25th, 50th and 75th percentiles of the distribution of durations of early stage disease are approximately 1.7, 4.2 and 8.3 years respectively). We performed sensitivity analyses to the underlying disease progression rate (γ) We recognize that the rate of disease progression could depend on age or gender; however, we do not believe at this time the epidemiological data is sufficient to more precisely characterize rates of disease progression.

Death rates

We assumed that the effect of Alzheimer's disease was to increase the background mortality rates (d_{ty}). We modeled this excess mortality by an additive model for the death rates whereby the death rates for patients with late stage disease (d^*) are:

$$d^*_{ty} = d_{ty} + k \qquad (2)$$

where d are the background mortality rates, and k is the excess mortality associated with Alzheimer's disease (the subscripts indicate that the model accounts for age (t) and calendar year (y)). Then, we calibrated the parameter k to published studies on Alzheimer's survival using least squares and obtained k =.11. For example, the model predicted that the median survival times for males diagnosed with Alzheimer's at ages 65, 75 and 85 were 7.9, 5.7 and 3.3 years, respectively; the predicted median survival times for females diagnosed at ages 65, 75 and 85

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were 9.1, 7.2 and 4.3 years respectively. These model predictions are in good agreement with published studies on Alzheimer's disease (8-10), and in fact were within 6 months of empirical findings (10). The interpretation of this model is that the effect of Alzheimer's disease on mortality is to add 11% per year to the background mortality rates once the disease has progressed to late stage. We also performed sensitivity analyses to evaluate the effect of excess mortality over background during both early and late stage disease.

We assembled U.S. death rates by gender and age from 1959 to the present as a basis for the background death rates (d_{ty}) (11). We recognize that variation is considerable in background mortality rates throughout the world. Accordingly, we performed sensitivity analyses of our results to these background mortality rates. Forecasts of disease prevalence also require assumptions about the background mortality rates into the future. We extrapolated recent past trends in mortality to obtain predictions of future mortality rates. We fit regression models to the mortality rates over a 15 year period (between 1988 and 2002) for each year of age, to obtain estimates of the annual percent change in mortality rates that were then used to predict future background mortality.

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RESULTS

In 2006, there were 26.6 million cases of Alzheimer's disease in the world (range 11.4-59.4). We predict that by the year 2050 the worldwide prevalence of Alzheimer's will grow fourfold to 106.8 million (range 47.2-221.2). Table 1 shows the geographic distribution of the burden of disease. We estimate that 48% of the worldwide cases are in Asia and that percentage will grow to 59% by 2050.

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Figure 2 shows the 2006 age-specific prevalence rates of Alzheimer's derived from our model. For example, the prevalence rates at ages 65, 75 and 85 were 0.9%, 4.2% and 14.7% respectively. Figure 2 also shows the age-specific prevalence rate by stage of disease from which one can calculate the percent of cases with late stage disease. For example, the model predicts the percentage of 65 year old cases with late stage disease is 34% and increases to 45% among 85 year old cases. Overall, we estimate about 11.6 (43%) of the 26.6 million worldwide cases living today have late stage disease (table 1). Figure 3 shows the growth in the prevalence of Alzheimer's disease cases through 2050 by stage of disease and by gender. We estimate that about 62% of worldwide cases are female reflecting the lower background mortality rates among women.

We evaluated the potential effects of interventions that could either delay disease onset or disease progression under 6 scenarios. Prevention programs that could delay onset by 1 or 2 years correspond to a relative risk (i.e., the multiplier of the transition probability) of .88 and .77 respectively. Therapeutic treatment interventions that delay disease progression by 1 and 2 years correspond to relative risks of .85 and .75 respectively. Table 2 shows the effects that such interventions could have on the global burden of Alzheimer's disease by the year 2050. Delaying disease onset by an average of 2 years would decrease worldwide prevalence of Alzheimer's by 22.8 million cases (scenario A). Even a modest one year delay in disease onset would result in 11.8 million fewer cases worldwide (scenario B). A therapeutic intervention that delays disease progression by an average of 2 years with no effect on disease onset would actually result in a net increase in global prevalence of 5.2 million cases because of a rise in the number of early stage cases (scenario C). However, under scenario C, there would also be a decrease of nearly 7 million late stage cases. Interventions even modestly delaying both disease

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onset and progression can significantly decrease the global burden of disease. For example, if both disease onset and disease progression are delayed by 1 year (scenario F) , there would be nearly 9.2 million fewer cases of disease and nearly all of that decline is attributed to decreases in the numbers of cases with late stage disease.

The sensitivity of our results were evaluated with respect to a number of model assumptions. Equation 1 assumes that the age-specific incidence rate continues to grow exponentially even in the oldest ages. If however, incidence rates plateau and remain constant after age 90 instead of continuing to raise exponentially, then a modest 4% decline is observed for the 2050 estimate of the worldwide prevalence of Alzheimer's disease. We find that estimates of worldwide prevalence are not especially sensitive to the shape of the incidence curve at the oldest ages because the oldest ages represent a relatively small segment of the population.

Sensitivity of our results to the background death rates was also examined. Surprisingly, when the background mortality rates were inflated by 20%, the absolute age-specific prevalence rates in figure 2 decreased very slightly, in fact by at most 3 per 1000. While surprising that the model for the age specific prevalence rates is not sensitive to the background mortality rates, the reason is that the age-specific prevalence rate is the ratio of persons with disease to persons alive, and if the background death rates increase, then *both* the numerator and denominator decrease, and the net effect is that the ratio itself does not change much.

We also considered the sensitivity of our results to our model for Alzheimer's mortality. Initially, we had assumed that excess mortality from Alzheimer's occurred only during late stage disease. If excess mortality also occurs during early stage of disease which was say, half the excess of that in late stage disease (i.e., we added $k/2$ to the background death rates in early

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stage) , our estimate of worldwide prevalence in 2006 would decline by about 14%, and the percentage of cases classified as late stage would slightly increase from 43% to 46%.

We considered the sensitivity of our results to the progression rate from early to late stage disease. If the average duration of early stage disease was in fact greater than the 6 years we assumed, then the percentage of prevalent cases that have late stage disease should be smaller than estimated. That phenomenon reflects the epidemiological concept that prevalence increases with duration. For example, if the mean durations of early stage disease were 4, 6, and 8 years, then with all other factors fixed) the estimated worldwide prevalence in 2006 of late stage Alzheimer's disease would be 13.9, 11.6 and 9.8 million cases respectively; and the percentages of prevalent cases that are classified as late stage would be 56%, 43% and 35% respectively.

DISCUSSION

Our model indicates that 26.6 million persons worldwide are currently living with Alzheimer's disease (range 11.4 to 59.4). We project that by the year 2050 worldwide prevalence will quadruple to 106.2 million with 1 in 85 persons living with Alzheimer's disease. The increase is a result of the aging of the world's population. The United Nations Population Division projects that the number of persons at least 80 years of age will increase by a factor of about 3.7 by the year 2050. The Alzheimer's Disease International study concluded there were 24.3 million persons with dementia in the world using a Delphi consensus methodology (2). Wimo and colleagues (12) estimated 25.5 million cases of dementia worldwide in 2000 by multiplying age-specific prevalence rates derived from epidemiological surveys by population estimates. Our estimates, which refer specifically to Alzheimer's disease cases rather than

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dementia more generally, are broadly consistent with these estimates which were obtained using different methodologies.

An advantage of the modeling methodology used in this paper is that the effects of interventions may be evaluated. We find that the impact of interventions depend on whether the interventions delay onset of disease, delay progression of disease, or a combination of both. Interventions can differentially affect the stage-specific prevalence depending on which stage of the disease natural history is targeted. We find that interventions that both delay disease onset and delay progression by even a modest amount would result in significant reductions in the global burden of disease. In related work, Sloane and colleagues (13) evaluated the impact of therapeutic advances in the United States. They found, as did we, that therapies that only delayed disease progression would lead to a decrease in advanced disease. But they also found no overall increase in Alzheimer's prevalence which was in contrast to our finding of a net increase (scenario C in table 2). We find that therapeutic advances that delay disease progression would lead to an increase in overall disease prevalence but on average the prevalent cases would have less severe disease.

There are important sources of uncertainty in our results. Main sources of uncertainty are the age-specific Alzheimer's disease incidence rates, which are reflected in the wide ranges of our forecasts. Data was not sufficient to obtain separate incidence rates for each geographic region, and we used equation 1 for all regions. The majority of published studies on age specific incidence rates of Alzheimer's disease are derived from populations in developed countries, and there is a critical need for additional studies in developing countries. We cannot say whether geographic variation in Alzheimer's incidence rates result from real differences in underlying incidence or rather differences in methodology and diagnostic criteria of the epidemiological

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studies. Our wide ranges on our estimates account for this uncertainty. However, we did not find any significant geographic differences in the doubling times of the age specific incidence rates. Accordingly, our finding about the *proportionate i*ncrease in Alzheimer's disease, namely a quadrupling in prevalence by 2050, is reasonably precise, even if the absolute number of cases is more uncertain. Indeed, we conclude Alzheimer's disease prevalence will quadruple by 2050 regardless of whether we use the lower or upper limits of our range of disease incidence rates. That conclusion does however depend on the accuracy of the U.N demographic projections of the aging of the world population.

The resources needed to care for an Alzheimer's patient depends on stage of disease. Adult day care programs may be adequate in the early stages, while a high level of care, equivalent to that of nursing homes, will be needed in the late stages. Assessments of the global burden of disease should account for disease stage. We recognize that currently there is no single staging system that is accurate, reproducible and routinely used worldwide. Nevertheless, we believe the two stage model of disease progression used here, produces useful estimates of the numbers of patients requiring a high level of care roughly equivalent to that provided by a health care facility such as a nursing home. Epidemiological surveys of the percentage of cases with severe disease have ranged between 2% to over 50% (14-16). Such wide variation could result either from differences in survey methodology and diagnostic criteria, or sampling enrollment biases. Our modeling approach produces estimates in the upper end of the range. As more information becomes available about disease progression rates the multi-state model can be used with updated input parameters for the transition probabilities. A web site that allows users to input their own transition probabilities and population data, and then implements the multi-state

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model to obtain forecasts of the global burden of Alzheimer's disease is available from the authors.

As the world's population ages, we will face a looming epidemic of Alzheimer's disease. Health care systems will be challenged to meet the needs of patients and their caregivers. The worldwide costs will be huge (17). Prevention of Alzheimer's is an ambitious goal (1, 18) that may not be fully achievable in the near term, although delaying disability may be achievable. We find that modest advances in therapeutic and preventive strategies resulting in even small delays in Alzheimer's disease onset and progression can significantly reduce the global burden of the disease.

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Table 1:

Projections of Alzheimer's disease prevalence (in millions) in 2006 and 2050 by regions and stage of disease

	Prevalence (in millions)					
	2006			2050		
	Overall	Early Stage	Late Stage	Overall	Early Stage	Late Stage
Africa	1.33	0.76	0.57	6.33	3.58	2.75
Asia	12.65	7.19	5.56	62.85	34.84	28.01
Europe	7.21	4.04	3.17	16.51	9.04	7.47
Latin Am. / Caribbean	2.03	1.14	0.89	10.85	5.99	4.86
North America	3.10	1.73	1.37	8.85	4.84	4.01
Oceania	0.23	0.13	0.10	0.84	0.46	0.38
Total	26.55	14.99	11.56	106.23	58.75	47.48

Note: Regions defined according to the United Nations Population Division (4):Oceania includes Australia, New Zealand, Melanesia, Micronesia, and Polynesia.

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Table 2:

Impact of interventions on world-wide prevalence of Alzheimer's disease. Table shows change in prevalence in 2050 associated with interventions begun in 2010 compared to baseline scenario of no intervention.

Intervention Scenario	Mean Delay (in years)		Change in Worldwide Prevalence (in millions)		
	Onset	Progression	Overall	Early Stage	Late Stage
A	2	0	- 22.76	- 12.28	- 10.48
B	1	0	- 11.76	- 6.32	- 5.44
C	0	2	+ 5.23	+ 12.14	- 6.91
D	0	1	+ 2.84	+ 6.54	- 3.70
E	2	2	- 18.48	- 2.66	- 15.82
F	1	1	- 9.19	- 0.48	- 8.71

Note: These estimates refer to the changes in prevalence compared to the baseline scenario of no intervention. Under the baseline scenario of no intervention, in 2050 there will be 106.23 million cases worldwide of which 58.75 and 47.48 million cases have early and late stage disease respectively (from Table 1).

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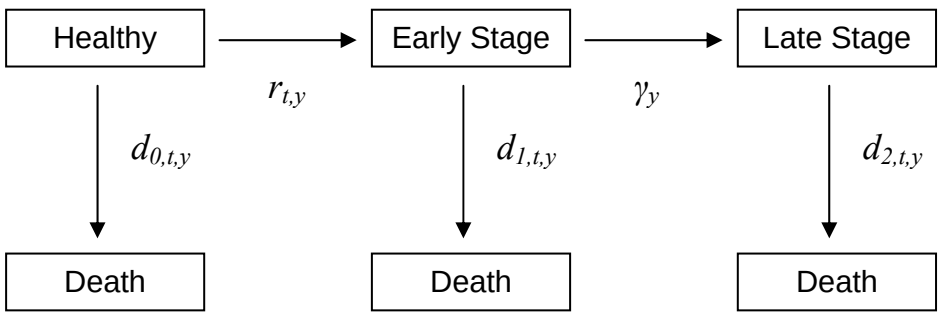

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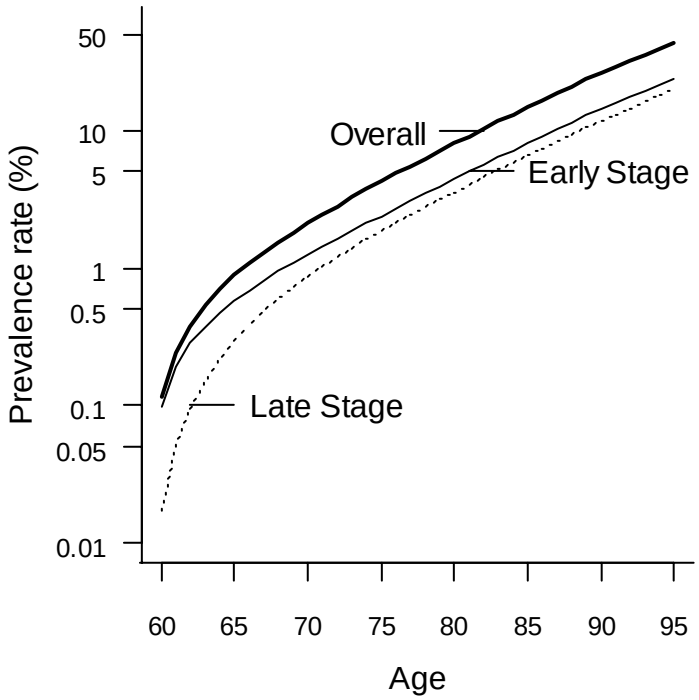

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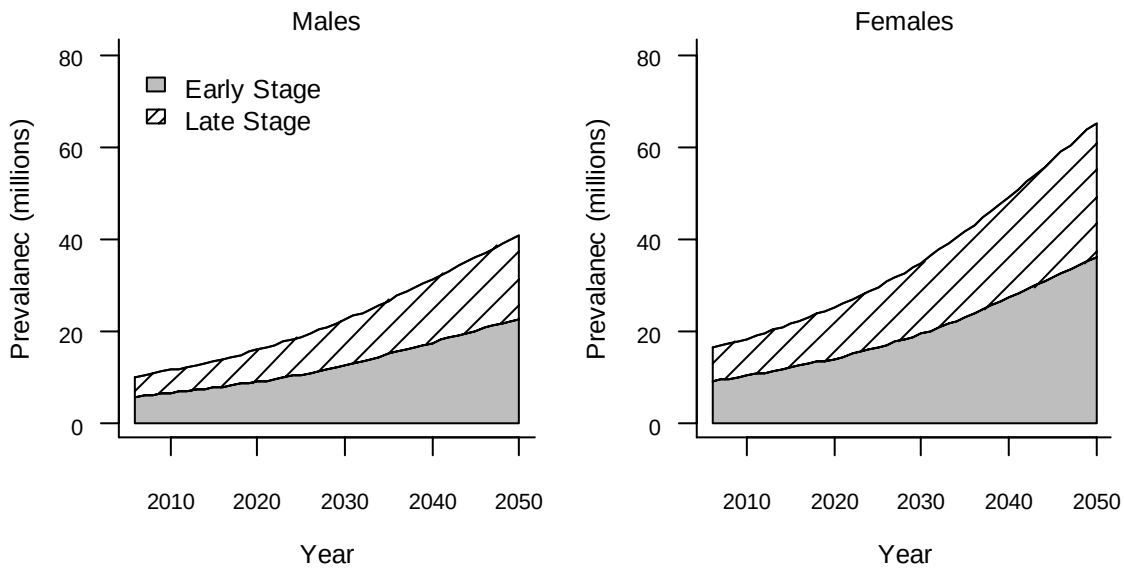

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Presynaptic nigro-striatal function in a group of Alzheimer's disease patients with parkinsonism: evidence from a dopamine transporter imaging study

R. Ceravolo[1], D. Volterrani[2], G. Gambaccini[1], S. Bernardini[1], C. Rossi[1], C. Logi[1], G. Tognoni[1], G. Manca[2], G. Mariani[2], U. Bonuccelli[1], and L. Murri[1]

[1] Department of Neuroscience, and
[2] Center of Nuclear Medicine, University of Pisa, Italy

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Summary. The occurrence of parkinsonism in Alzheimer's disease (AD) is quite common, however the molecular and neurochemical changes underlying such extrapyramidal features in AD have been not fully understood. Post-mortem as well as in vivo imaging study have produced conflicting results as regards the existence of dopaminergic changes in AD. Aim of the present study was to investigate *in vivo* the nigro-striatal dopaminergic function in a group of AD patients with parkinsonism. Thirteen patients with AD and extrapyramidal features not related to past neuroleptic use (AD-P) underwent SPECT with ^{123}I-FP-CIT, a ligand of dopamine transporter, and the data were compared with those obtained in 15 patients with Diffuse Lewy Body Dementia (DLBD), 20 patients with Parkinson's disease (PD), and 8 healthy elderly controls. The analysis of the data was performed by regions-of-interest approach and calculations of the striatal-to-non specific (occipital lobes) radioactivity ratios were made. The ^{123}I-FP-CIT striatal uptake in patients with AD-P was similar to that obtained in the control population. Both the DLBD and PD groups showed significantly lower ^{123}I-FP-CIT uptake in all striatal areas with respect to AD-P and control groups ($p < 0.005$). The lack of dopamine transporter changes in our series of AD-P patients can indicate that dopaminergic presynaptic function is preserved in this population and that different dopaminergic changes such as postsynaptic ones, or different neurotransmitter alterations might underlie the extrapyramidal features in AD.

Keywords: Parkinsonism, Alzheimer's disease, dopamine transporter imaging.

Introduction

The occurrence of parkinsonism in Alzheimer's disease (AD) is quite common particularly in the later stages (Stern et al., 1996; Tsolaki et al., 2001). It has also been hypothesized that the presence of extrapyramidal signs might characterize a clinical subtype with a faster progression (Mortimer et al., 1992; Chui et al., 1994; Lopez et al., 1999). Recently the progression of parkinsonian-like signs in older age has been reported to be associated with decline in cognitive function and the development of AD (Wilson et al., 2003). The main diagnostic challenge is between diffuse Lewy Body Dementia (DLBD) and Alzheimer's disease with parkinsonism, and the clinical criteria have been reported to have mainly low sensitivity when Lewy bodies coexist with the pathological abnormalities of AD (Lopez et al., 2002).

Several conflicting evidences regarding the existence of nigrostriatal neurochemical abnormalities in AD *in vitro* (Murray et al., 1995; Sahlberg et al., 1998; Piggott et al., 1999) as well as *in vivo* (Tyrrell et al., 1990; Donnemiller et al., 1997; Rinne et al., 1998) have been reported. Similarly *in vitro* and *in vivo* studies on striatal dopamine D1 and D2 receptor numbers in AD patients have produced heterogeneous results (Reisine et al., 1984; Pizzolato et al., 1996; Piggott et al., 1999; Donnemiller et al., 1997; Kemppainen et al., 2000).

The investigation of the pre-synaptic dopaminergic system is actually possible also by SPECT imaging, using ligands for the dopamine reuptake system (dopamine transporter-DAT) that measure the reuptake of dopamine from the synaptic cleft into the presynaptic terminals (Fischman et al., 1998). This molecular neuro-imaging approach is a powerful, reliable, objective method for in vivo detecting the dysfunction of nigro-striatal pathway, so allowing a simple distinction between parkinsonism (including PD, Multiple System Atrophy, Cortical-basal degeneration) and pseudo-parkinsonism, such as essential tremor, dopa-responsive dystonia, lower body parkinsonism, iatrogenic parkinsonism (Asenbaum et al., 1998). A few recent studies have been performed in order to assess the role of SPECT imaging of DAT for *in vivo* distinction between AD and DLBD resulting in the lack of nigrostriatal dopaminergic degeneration in AD without parkinsonian-like symptomatology (Walker et al., 2002; Ceravolo et al., 2003). However no SPECT imaging study of DAT has been carried out in order to evaluate if parkinsonism in AD is related to possible changes in striatal dopaminergic pre-synaptic system.

In this study, we investigated the nigro-striatal dopaminergic function *in vivo* by means of DAT imaging in a group of AD patients with parkinsonism, with respect to PD and DLBD patients, in order to evaluate the presence of presynaptic dopaminergic changes underlying the extrapyramidal features in AD.

Methods

Patients

Thirteen patients (six women, seven men; mean age 71.3 ± 4.5 years; disease duration: 3.9 ± 2.5 years) with AD were studied. All patients fulfilled the clinical diagnosis of probable AD according to NINCS-ADRDA criteria (McKhann et al., 1984). All patients with AD included in the

study had parkinsonism, mainly rigidity and bradykinesia (postural tremor was present in two subjects). The parkinsonism was assessed by a neurologist trained in movement disorders and evaluated by the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987). In particular, the parkinsonian features in AD patients were well characterized and different from forms of akinetic crisis often related to cognitive decline. Fifteen patients (seven women, eight men; mean age 70.5 ± 5.3 years; disease duration: 2.7 ± 2.3 years) with DLBD (diagnosis performed according to the Consensus LBD criteria) (Mc Keith et al., 1996) and twenty patients with Parkinson's disease (PD) (seven women, thirteen men; mean age 66.8 ± 8.1 years; disease duration: 4.3 ± 1.9 years) (according to the UK Parkinson's disease Society Brain Bank criteria) (Hughes et al., 1992) were also recruited. Eight healthy elderly controls (three women, five men; mean age 65.5 ± 9.3 years) were included from partners of patients which had no neurologic or psychiatric disease and were taking no regular medication. For each patient and control a full neuropsychological investigation using tests assessing attention, memory, language, visuospatial and visuoconstructive abilities was performed. In addition a Mini-Mental State examination was carried out in all patients and controls. History of neuroleptic use was exclusion criterion. All the patients and controls underwent also a magnetic resonance imaging or computed tomography brain scan.

FP-CIT SPECT scanning

SPECT studies were carried out at the Center of Nuclear Medicine, University of Pisa. Thyroid metabolism was blocked with potassium iodate, as recommended, to reduce possible irradiation of the gland. Scanning took place between three and four hours after injection of ^{123}I-FP-CIT (185 MBq). All subjects were scanned with a double-head scanner (Optima NT, ELGEMS, Milwaukee, USA). The images were acquired on a 128×128 matrix, and the overall scanning time for each patient was 30–45 minutes. All the images were automatically reconstructed, and after uniform correction for tissutal attenuation, the transaxial pictures were re-oriented along the fronto-occipital line. All scans were analyzed by DV, who was unaware of the diagnostic status of the subjects. Usually 5–8 slices were acquired starting at the cerebellum level upwards to include the basal ganglia. Regular circular regions of interest were used to calculate the average striatal (caudate nucleus, putamen) to non-specific (areas with little or no dopamine receptors, such as occipital lobes) radioactivity ratios, for both hemispheres. Statistical comparisons between groups were performed by Mann Whitney signed rank U test.

Results

Clinical characteristics of the cohort

There were no significant difference between the four groups with respect to family history of PD or AD, past psychiatric history, history of smoking and alcohol consumption, years of education. There were differences between patients with DLBD and those with AD on the results of neuropsychological investigations, the former being more severely demented (Mini-Mental State Examination, mean $\pm$ SD value: DLBD, 16.5 ± 6.2 versus AD 19.1 ± 5.3). PD patients and controls resulted not demented. The mean motor UPDRS score for AD subjects was 9.7 ± 3.9, whereas for PD subjects 13.7 ± 5.1 and for DLBD subjects 16.8 ± 7.8.

^{123}I-FP-CIT scan results

The ^{123}I-FP-CIT uptake (semi-quantitative measures as specific/non-specific binding ratios) in patients with AD and parkinsonism was similar to that in the control subjects in putamen (AD: right (means $\pm$ standard deviations) 2.62 ± 0.09; left 2.67 ± 0.03 versus controls, right 2.60 ± 0.16; left

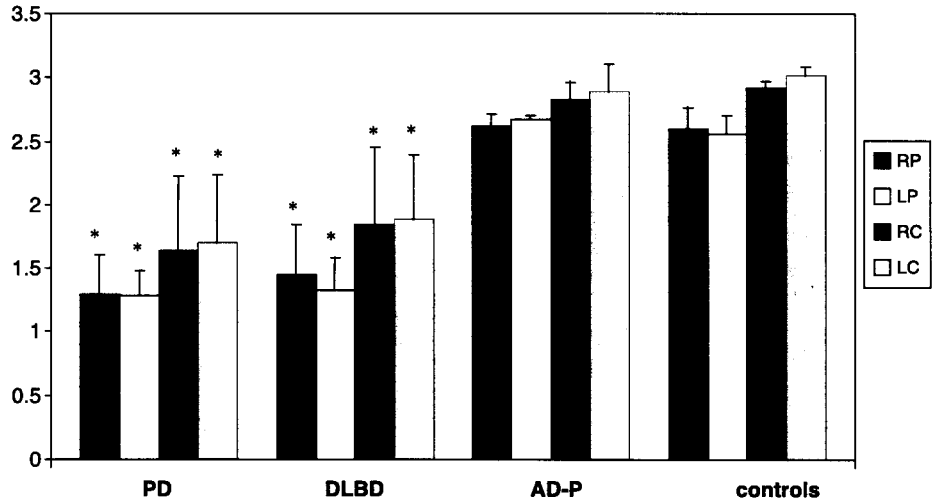

Fig. 1. ^{123}I-FP-CIT uptake values, expressed in terms of semi-quantitative measures as striatal/non-specific (occipital) binding ratios, in patients affected by Alzheimer's disease with parkinsonism (AD-P), Parkinson's disease (PD), diffuse Lewy body dementia (DLBD), and healthy controls. $^{*}p<0.005$

2.56 ± 0.14) as well as in caudate nucleus (AD, right 2.83 ± 0.13, left 2.89 ± 0.22 versus controls, right 2.92 ± 0.05, left 3.01 ± 0.08) (Fig. 1).

The ^{123}I-FP-CIT binding values in PD patients were 1.29 ± 0.31 for right putamen, 1.28 ± 0.20 for left putamen, 1.64 ± 0.59 for right caudate nucleus, and 1.70 ± 0.54 for left caudate (Fig. 1). In DLBD group the binding measures were 1.45 ± 0.39 for right putamen, 1.33 ± 0.25 for left putamen, 1.84 ± 0.61 for the right caudate, and 1.88 ± 0.51 for the left caudate (Fig. 1). Both the DLBD and PD groups showed significantly lower ^{123}I-FP-CIT uptake in all striatal areas than the AD group and controls ($p<0.005$) (Fig. 1). There were highly significant differences between DLBD and AD, and DLBD and controls for all striatal binding measures ($p<0.005$) (Fig. 2). Finally there were highly significant differences in all binding measures between PD and controls ($p<0.001$) and between PD and AD ($p<0.005$) (Fig. 2). Since the motor impairment as assessed by UPDRS was quite different between AD with parkinsonism and DLBD and PD group, in order to avoid such confounding factor in evaluating nigro-striatal function, a subgroup of DLBD and PD with mild parkinsonism was choosen (4 DLBD patients, UPDRS mean $\pm$ SD: 11.0 ± 2.2; 6 PD patients, UPDRS 10.6 ± 1.5). In this "mild" DLBD group the binding measures were 1.29 ± 0.31 for right putamen, 1.28 ± 0.20 for left putamen, 1.64 ± 0.59 for the right caudate, and 1.70 ± 0.54 for the left caudate. In "mild" PD subgroup the binding measures were 1.45 ± 0.39 for right putamen, 1.33 ± 0.25 for left putamen, 1.95 ± 0.51 for the right caudate, and 1.98 ± 0.51 for the left caudate. Both these DLBD and PD "mild" subgroups showed significantly lower ^{123}I-FP-CIT uptake in all striatal areas than the AD group and controls ($p<0.005$).

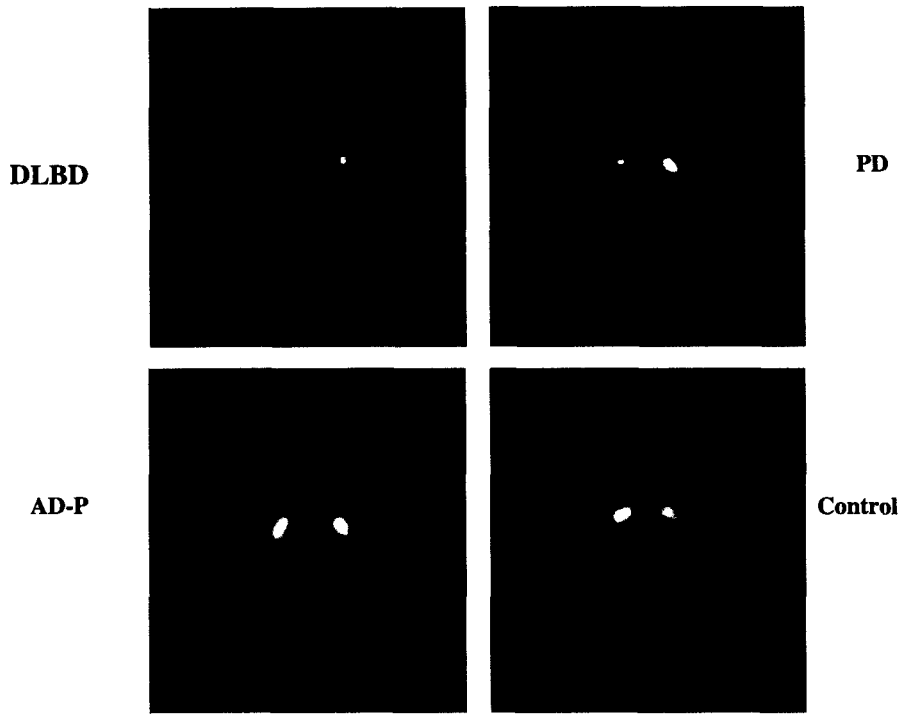

Fig. 2. ^{123}I-FP-CIT SPECT images obtained in single cases of diffuse Lewy body dementia (DLBD), Parkinson's disease (PD), Alzheimer's disease with parkinsonism (AD-P), and healthy control

Discussion

This study confirms that DLBD and AD, also when parkinsonism occurs, could be distinguished *in vivo* by DAT imaging approach. This observation is in agreement with pathological findings of a consistent loss of substantia nigra neurons and depletion of striatal dopamine content in DLBD (Piggott et al., 1999). In previous studies a significantly reduced striatal uptake of 18F-Dopa on PET investigation has been reported in subjects affected by DLBD (Hu et al., 2000). Also by using B-CIT, another ligand of DAT, and SPECT, Donnemiller et al. (1997) reported in a small group of patients with DLBD a significantly lower striatal uptake in comparison with AD and control subjects. Recent SPECT investigations of DAT by means of FP-CIT showed in DLBD patients a significantly lower uptake of radioactivity than patients with AD in the caudate nucleus and anterior and posterior putamen (Walker et al., 2002; Ceravolo et al., 2003). In such studies however the occurrence of parkinsonism in AD subjects and the molecular counterparts of this feature was not focused.

The lack of DAT changes in AD with parkinsonism as found in the present study, can indicate that dopaminergic presynaptic function is preserved and that pathways other than dopaminergic ones are underlying the extrapyramidal features in AD. Extrapyramidal signs are frequently associated with AD: in particular AD patients can show gait disturbances, reduced arm swing in walking,

bradykinesia and symmetric rigidity, and generally these patients are not affected by rest tremor (Tsolaki et al., 2001).

In cross-sectional studies 20% to 50% of clinical patients with AD have parkinsonism (Chui et al., 1985; Mayeux et al., 1985); when followed longitudinally parkinsonism developed in approximately half the patients with AD. The wide range of prevalence of parkinsonism in AD may be due both to methodologic factors, such as the assessment measures of parkinsonism, and to potentially confounding variables, such as neuroleptic use and level of participation in follow-up. These motor manifestations may represent either stages or subgroups of AD because of their high prevalence and it has been hypothesized that the presence of parkinsonism significantly predicts faster cognitive decline in AD (Chui et al., 1994). A recent study has confirmed that AD patients who developed parkinsonism, had faster functional decline and shorter survival time than those without parkinsonism (Lopez et al., 2000). Parkinsonism in AD could be due to the presence of Lewy bodies in patients with clinically diagnosed AD, however some patients with parkinsonism and AD have no Lewy bodies in cortical and subcortical structures (Lopez et al., 2000). Extrapyramidal symptoms in AD may be associated with neuro-fibrillary tangles in the substantia nigra (Liu et al., 1997) or to alterations in biogenic amine system (Zubenko et al., 1991) or a marked loss of dopamine D2 receptors (Joyce et al., 1998).

Post-mortem studies have suggested that there might be changes in the brain dopaminergic system in AD (Nazarali and Reynolds, 1992). Reports of nigrostriatal neurochemical abnormalities vary in AD with some reports of little or no loss in dopamine uptake *in vitro* (Murray et al., 1995; Piggott et al., 1999) or *in vivo* (Tyrrell et al., 1990; Donnemiller et al., 1997) and other reports of reduced dopamine uptake sites *in vitro* (Sahlberg et al., 1998) and *in vivo* (Rinne et al., 1998). There are reports that substantia nigra neuron numbers and striatal dopamine concentration are not changed (Perry et al., 1993; Love et al., 1996; Liu et al., 1997; Piggott et al., 1999), however there are a few reports of decreased substantia nigra neuronal density (Kazee et al., 1995; Tabaton et al., 1985). This variability of evidences of dopaminergic activities in AD may be due to the wide eterogeneity within the cases included and the symptomatology presented (Forstl et al., 1994; Victoroff et al., 1996). Also the potential inclusion of patients with DLBD, misdiagnosed as having AD, in such studies could be another factor contributing to the non consistency of the findings of dopaminergic changes in AD (Ellis et al., 1996; Karla et al., 1996).

In vivo imaging studies have also produced conflicting results. The study of the pre-synaptic dopaminergic system using 18F-Dopa which primarily reflects the activity of dopa-decarboxylase and the subsequent storage of 18F-Dopa in the vesicles, and PET, showed no changes in AD patients (Tyrrell et al., 1990). DAT imaging studies with SPECT reported no striatal changes in AD with respect to DLBD patients (Donnemiller et al., 1997; Walker et al., 2002; Ceravolo et al., 2003). In a PET study Rinne et al. (1998) observed in a group of AD patients a reduction of striatal uptake of a DAT ligand (11C-CFT) that well correlated with the severity of parkinsonism. However parkinsonism in this series of AD patients was quite severe, and alternative diagnosis might be

possible. Furthermore some AD patients with parkinsonism in this study had striatal uptake values within the control range. It should be considered that presynaptic dopaminergic imaging studies, such as 18F-Dopa PET or DAT imaging studies, are very sensitive techniques able to detect the dysfunction also in a pre-clinical phase (Schwarz et al., 2000; Berendse et al., 2001). It could mean that, if parkinsonism in AD is related to a pre-synaptic nigro-striatal dysfunction, it should be detected regardless of the severity of parkinsonism by means of a DAT imaging study.

Post-mortem studies concerning the numbers of striatal D1 and D2 dopaminergic receptors had controversial results as the numbers are either decreased or unchanged in different studies (Reisine et al., 1984; Seeman et al., 1987). No change of D2 and D1 receptors binding has been recently reported in AD, whereas D2 binding resulted significantly reduced in the caudal putamen of DLBD patients (Piggott et al., 1999). In SPECT studies with IBZM, a D2 dopaminergic post-synaptic ligand, a decreased number of striatal D2 receptors was found in AD without extrapyramidal symptoms (Pizzolato et al., 1996), whereas no change of striatal binding was reported in AD patients in other studies (Walker et al., 1997; Donnemiller et al., 1997). The lack of change in D2 receptor binding also confirmed in a recent PET study (Kemppainen et al., 2000) is consistent with the present report of preserved presynaptic dopaminergic nigrostriatal function. All these evidences also agree with the clinical observation that parkinsonism occurring in AD does not respond to dopaminergic medications. In our series of AD patients with parkinsonism we found that dopamine transporter function, as assessed by means of DAT SPECT, is within normal range. This finding might suggest that other than striatal dopaminergic changes involving nuclei beyond the nigrostriatal pathway or other parts of the basal ganglia-thalamocortical circuit could contribute to extrapyramidal symptoms in AD. It should be noted that our study population is not so enough large to allow definitive conclusions regarding the molecular basis of parkinsonism in AD, and our results warrant further confirmations on larger populations.

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Authors' address: R. Ceravolo, MD, Department of Neuroscience, University of Pisa, Via Roma 67, I-56100 Pisa, Italy, e-mail: r.ceravolo@neuro.med.unipi.it

The Neuropsychiatric Inventory:
Comprehensive assessment of psychopathology in dementia

J.L. Cummings, MD; M. Mega, MD; K. Gray, MD; S. Rosenberg-Thompson, RN, MN; D.A. Carusi, BS; and J. Gornbein, DrPH

Article abstract—We developed a new instrument, the Neuropsychiatric Inventory (NPI), to assess 10 behavioral disturbances occurring in dementia patients: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity. The NPI uses a screening strategy to minimize administration time, examining and scoring only those behavioral domains with positive responses to screening questions. Both the frequency and the severity of each behavior are determined. Information for the NPI is obtained from a caregiver familiar with the patient's behavior. Studies reported here demonstrate the content and concurrent validity as well as between-rater, test-retest, and internal consistency reliability; the instrument is both valid and reliable. The NPI has the advantages of evaluating a wider range of psychopathology than existing instruments, soliciting information that may distinguish among different etiologies of dementia, differentiating between severity and frequency of behavioral changes, and minimizing administration time.

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Neuropsychiatric disturbances are common manifestations of dementing disorders. Alzheimer's disease (AD) is accompanied by delusions, agitation, anxiety, and personality changes[1-6]; frontotemporal dementias are evidenced by apathy, euphoria, irritability, and disinhibition[7,8]; and vascular dementia produces apathy, irritability, and lability.[7,9,10] Neuropsychiatric disorders may be the presenting manifestations of dementing disorders, appearing before cognitive alterations and heralding the onset of the brain disease.[11-13] Neuropsychiatric manifestations change as the dementias progress, requiring reevaluation and implementation of new interventions in the course of the illness.[14] Neuropsychiatric disturbances add to caregiver burden and are a major cause of institutionalization of dementia patients.[15-17] Some behavioral changes have prognostic significance. Delusions, for example, are associated with more rapid decline in intellectual function in AD.[18-22] The neuropsychiatric aspects of dementia syndromes are often treatable with psychotropic medications.[2,7,23] Thus, neuropsychiatric features of dementias have important diagnostic, prognostic, and management implications.

The assessment and measurement of neuropsychiatric disturbances in dementia present unique challenges. At the time of the interview, patients may not exhibit, remember, or report their symptoms; some neuropsychiatric disorders, such as delusions and hallucinations, are entirely subjective and if not described by the patient must be inferred from their behavior; the magnitude of behavior changes may be related to either their severity or their frequency; and patients may simultaneously exhibit dementia, depression, and anxiety, making it difficult to distinguish among types of behavioral change. Several tools are available to assess behavior in dementia patients. The principal instruments currently in use include the BEHAVE-AD,[2] the Hamilton Depression Rating Scale (HDRS),[24] the Neurobehavior Rating Scale,[25] the Columbia University Scale for Psychopathology in Alzheimer's Disease,[26] and the Cornell Scale for Depression in Dementia.[27] The BEHAVE-AD[2] is the instrument most widely used for the evaluation of dementia-related behavioral changes. Developed specifically to assess patients with AD, the BEHAVE-AD addresses delusions, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances, and anxieties and phobias. It does not evaluate other types of behavioral change commonly accompanying AD (eg, apathy or irritability) or occurring in other types of dementia (eg, disinhibition in frontotemporal dementias).

From the Departments of Neurology (Drs. Cummings and Mega, and D.A. Carusi) and Psychiatry and Biobehavioral Science (Drs. Cummings and Gray, and S. Rosenberg-Thompson), UCLA School of Medicine, Behavioral Neuroscience Section, Psychiatry Service; West Los Angeles Veterans Affairs Medical Center (Drs. Cummings and Gray); and the Biomathematical Consulting Unit, Department of Biomathematics (Dr. Gornbein), UCLA School of Medicine, Los Angeles, CA.

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Address correspondence and reprint requests to Dr. Jeffrey L. Cummings, Neurobehavior Unit, Psychiatry Service (116AF), West Los Angeles VAMC, 11301 Wilshire Boulevard, Los Angeles, CA 90073.

Depression is frequently associated with dementia. Major depressive episodes are common in vascular dementia and in the subcortical dementias accompanying movement disorders such as Parkinson's disease.[7] Depressive symptoms occur in up to 40% of AD patients.[2,5,9,28] The HDRS[24] is frequently used to assess depression in dementia; it is usually administered with a scripted text.[29] The reliability of the instrument is acceptable.[30] Developed for use in nondemented patients, the HDRS assesses several areas that occur both in depression and in nondepressed demented patients—agitation, weight loss, insomnia, impaired concentration—making it difficult to know whether the scale score reflects depression or dementia. The HDRS also depends on gathering information from demented patients who may not remember their symptoms; the validity of the alternative strategy of asking a spouse about a patient's mood is uncertain.

The Neurobehavior Rating Scale was developed for assessment of behavioral changes following head trauma.[25] It is also used to evaluate behavioral changes in dementia and distinguishes behaviors in AD from those of vascular dementia.[28] The instrument has 28 items, each receiving a scale score of 0 to 6 after exploratory questions have been asked. It thus requires considerable time to administer and cannot be readily used in routine clinical settings. Scores are based on patient observation by the clinician and may underestimate psychopathology not evident during the examination.

A number of other instruments have recently become available that focus on the assessment of behavioral changes in dementia. These include the Columbia University Scale of Psychopathology in Alzheimer's Disease[26] and the Cornell Scale for Depression in Dementia.[27] These tools provide advances over earlier instruments, but they assess a relatively restricted range of behavior and lack differential diagnostic capability. These scales have substantially advanced understanding of the behavioral aspects of dementias and each has an important place in the armamentarium used by clinicians to assess neuropsychiatric disturbances, but development is warranted of new instruments that apply to other behaviors commonly observed in dementia patients.

We developed the Neuropsychiatric Inventory (NPI) to assess a wide range of behaviors encountered in dementia patients, to provide a means of distinguishing frequency and severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. We report the content validity, concurrent validity, internal consistency reliability, item independence, between-rater reliability, and test-retest reliability of the NPI. Relationships between NPI scores and age and dementia severity as well as the NPI profiles of 40 normal controls are also described. These studies demonstrate that the NPI is psychometrically secure and can be used to efficiently and comprehensively assess the neuropsychiatric aspects of dementing disorders. This is not a diagnostic study; profiles for different dementias and the ability of the NPI to distinguish among different types of dementia will be reported later.

Methods. *Content.* The behavioral domains to be assessed were chosen after a comprehensive review of the literature pertaining to behavior occurring in different dementias[1-7] and preliminary studies of behavioral changes in patients with AD, vascular dementia, and frontotemporal dementias.[4,8-10,12,14,28,31-33] Ten behavioral domains are evaluated by the NPI. The domains and a sample question from each are as follows: delusions (Does the patient believe that others are stealing from her or him?); hallucinations (Does the patient talk to people who are not there?); agitation/aggression (Is the patient uncooperative, resistive to help from others?); dysphoria (Does the patient say or act as if she or he is sad or in low spirits?); anxiety (Does the patient say that she or he is worried about planned events?); euphoria (Does the patient find humor in and laugh at things that others do not find funny?); apathy (Does the patient seem less spontaneous and less active than usual?); disinhibition (Does the patient say crude things or make sexual remarks that he or she would not usually say?); irritability/lability (Does the patient have sudden flashes of anger?); and aberrant motor activity (Does the patient pace around the house without apparent purpose?). These domains were chosen because they are commonly affected in dementias and because the items have the potential to distinguish among dementias that produce different types of behavioral disturbances (eg, more disinhibition in frontotemporal dementias, more indifference in AD, more depression in vascular dementia[8,9,12,28]).

Screening and assessment questions. One important goal of the NPI is to facilitate behavioral assessment by minimizing the time required to complete the evaluation while providing a comprehensive characterization of abnormal behavior manifested by the patient. This goal was accomplished by developing screening questions that provide an overview of each specific behavioral domain. Information is gathered from caregivers familiar with the patient's behavior. To serve as an informant, the caregiver must have at least daily contact with the patient. Using scripted questions, the caregiver is asked whether the patient's behavior changed after the onset of the dementia and if the altered behavior has been present during the past month or other specific period. If the caregiver indicates that the abnormal behavior was present, the behavioral domain is then explored with either seven or eight subquestions (illustrated above) that provide more detailed information about the specific features of the behavioral disturbance. After the subquestions are answered, the caregiver is asked to rate the severity (1 = mild, 2 = moderate, 3 = severe) and frequency (1 = occasionally, less than once per week; 2 = often, about once per week; 3 = frequently, several times per week but less than every day; 4 = very frequently, once or more per day or continuously) of the behavior. The questions are read aloud by the examiner; defined anchor points for severity and frequency allow caregivers to provide a ratable answer. Using this approach, domains with a negative response to the screening question are not explored, while data regarding the characteristics, severity, and frequency are garnered for each domain with a positive response to the screening question. Caregivers provide the information for the NPI because patients may not remember their behavior when asked, may not exhibit abnormal behavior while with the clinician, and often cannot grasp scaling concepts necessary for determining severity and frequency. Information from observing the patient is not used in scoring the NPI because the examiner is usually not in a position to determine the frequency of behaviors or the range of sever-

ity of behaviors that may be exhibited. If the clinician is aware of information that contradicts the caregiver's report, the information from the NPI is invalid and should be discarded.

After the assessment strategy and behavioral domains were chosen, administration instructions were developed and the NPI was administered to the caregivers of 20 dementia patients to determine the sensitivity of the screening questions. This was done by asking both the screening questions and all the subquestions and determining the number of instances in which a caregiver responded negatively to the screening questions and positively to one of the subquestions.

Content validity. The NPI addresses behaviors that have been subjected to relatively little investigation, such as apathy, irritability, disinhibition, and euphoria. Concurrent validity could not be assessed when there was no standard instrument with which the NPI could be compared. To determine the content validity of the NPI, a Delphi panel was developed and asked to rate the scale items. The NPI was submitted to 10 nationally and internationally known experts in geriatric psychiatry, behavioral neurology, or neuropsychology (Delphi panel members are listed in the Acknowledgments). Each panel member rated the screening questions and the subquestion section of each behavioral domain as to whether the essential elements of the behavior were captured. Screening questions and subquestions were rated between 1 (well assessed) and 4 (poorly assessed); operationalized criteria for scoring were provided.

Concurrent validity. Concurrent validity was determined by comparing the scores on the relevant subscales of the NPI with the appropriate scales of two instruments currently in widespread use. The NPI, the BEHAVE-AD, and the HDRS were administered to the caregivers of 40 patients with dementia syndromes. The dementias were of a variety of types (AD, vascular dementia, mixed AD-vascular dementia, frontotemporal dementias, and miscellaneous); cognitive impairment had a broad spectrum of severity; and the patients exhibited a wide range of behavioral disorders of varying severity. The delusions, hallucinations, dysphoria, anxiety, agitation/aggression, and aberrant motor behavior subscales of the NPI were compared with the Delusions, Hallucinations, Affective disturbances, Anxiety and phobias, Aggressiveness, and Activity disturbances subscales of the BEHAVE-AD; the Dysphoria subscale of the NPI was compared with the depression score of the HDRS.

Between-rater reliability. Between-rater reliability was determined by having two raters score the NPI responses of a caregiver. Raters were familiarized with the instrument through the administration instructions and by observing several interviews conducted by experts using the NPI. Two raters were present during the same interview, which was conducted by one of the raters. The two raters were not the same in each interview. Raters participating in this aspect of NPI assessment included a behavioral neurologist, four behavioral neurology fellows, a geriatric psychiatry fellow, and a premedical student. Each rater was blind to the rating chosen by the other, and raters did not confer on responses before giving the ratings to a third individual who recorded the data. Between-rater reliability interviews were conducted with 45 caregivers.

Test-retest reliability. Test-retest reliability was determined by conducting a second NPI interview with caregivers within 3 weeks of an initial interview. The second interview was conducted over the telephone by a clinician not involved in the first interview. Twenty caregivers participated in the test-retest reliability assessment of the NPI.

Normal control subjects. To determine the rate of behaviors assessed by the NPI in the nondemented population, 40 spouses of nondemented individuals were interviewed using the NPI. The subjects were residents of a Southern California retirement community (Leisure World). Each member of a couple was administered the Mini-Mental State Examination[34] (MMSE), and the spouse was asked if the partner exhibited any signs of dementia or memory loss. If the partner's MMSE score was 25 or above and the spouse denied any concern about the partner's intellectual function, then the spouse was interviewed using the NPI, providing data pertaining to the partner. As with patient caregivers, the interviewees were asked about behavior that differed from the partner's usual behavior and had occurred within the preceding 4 weeks.

Statistical analyses. A variety of statistical procedures were used to assess the psychometric properties of the NPI. Concurrent validity was determined by calculating the Spearman correlation coefficients between the NPI subscale scores and the subscales of the BEHAVE-AD or HDRS. Similar methods were used to explore the relationships between NPI subscale scores and age and MMSE scores. Cronbach's coefficient alpha[35] was determined to assess internal consistency reliability, and Pearson's correlations were calculated for the item-independence study. Percent-agreement analyses were used for between-rater reliability, and correlation coefficients were generated for test-retest reliability calculations. When a synoptic score was superior for clinical or analytic purposes, the product of the frequency and the severity (severity of the behavior multiplied by how often it occurred) was used as an overall measure of the magnitude of the behavioral disturbance.

Results. *Patients, caregivers, and controls.* Caregivers providing behavioral information in this study were all family members of outpatients attending a university or a Veterans Affairs dementia clinic or of subjects participating in a clinical trials program. Forty caregivers participated in the concurrent validity study. The patients on whom information was collected were 22 men and 18 women aged 56 to 90 years (mean, 75.7). All patients were assessed with the MMSE[34] and had scores ranging from 0 to 29 (mean, 19.2). Twenty of these patients had AD, nine had vascular dementia, and 11 had other types of dementing disorders. Patients with AD met the criteria of the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association[36] for probable AD; patients with vascular dementia met criteria of the National Institute of Neurological Disease and Stroke[37] for probable vascular dementia.

Forty-five NPI assessments were included in the interrater reliability study. Participants were caregivers of outpatients in a dementia clinic or of patients who were on stable doses of medication in a clinical trials program. Their patients were 26 men and 19 women; patient MMSE scores ranged from 1 to 29 (mean, 17.4). Forty-two of the patients had AD, one had vascular dementia, and two had other types of dementing illnesses. A subgroup of 20 of the caregivers participated in the test-retest reliability study. The patients of all these caregivers had AD. Another subgroup of 20 caregivers of patients with a variety of dementias provided the data used in determining the

sensitivity of the screening questions.

Forty normal control subjects participated in the study. MMSE scores ranged from 25 to 30 (mean, 28.4). There were 20 men and 20 women.

Screening question sensitivity. The principal requirement when using the screening question strategy is to show that the screen detects nearly all the psychopathology that would be found if all the questions on the scale were asked. Among the 20 patients evaluated in this portion of the NPI assessment, there were nine false-negative responses (20 patients × 10 behaviors per patient = 200 behaviors; nine "misses" = 4.5%). A false-negative rate of under 5% was deemed acceptable.

False-positive responses also occurred where caregivers responded positively to the screen but negatively to all subquestions. This occurred primarily in the dysphoria section (four of nine false-positive responses) of the NPI. Caregivers responded affirmatively to screening questions using the word "depression" but applied the word in a nonclinical sense to describe behavior determined by the clinician to be unrelated to depressive symptomatology.

Content validity. The results of the Delphi panel assessment of the content validity of the NPI are shown in table 1. A score of 1 indicated that the domain was well assessed and a score of 4 indicated that the domain was poorly assessed by the NPI screening questions and subquestions. Each group of questions except those assessing "troublesome behavior" received scores of less than 2, indicating high content validity. "Troublesome behavior" was reformulated as "aberrant motor behavior" in accordance with the recommendations of the Delphi panel.

Item and summary scores. Table 2 shows the NPI subscale scores for the 40 subjects in the concurrent validity study. These data show that a wide range of psychopathology was present in the study subjects although the mean scale scores tended to be low. Apathy was the behavior most commonly recorded; agitation/aggression, dysphoria, anxiety, irritability/lability, and aberrant motor behavior were also frequently described by caregivers. Euphoria was the behavior least often observed and with the most restricted range of expression; this reflects the small number of patients with euphoric behavior included in the sample.

Concurrent validity. Concurrent validity was determined by comparing the NPI subscales with the appropriate subscales of the BEHAVE-AD and the total score of the HDRS. Table 3 presents the correlations of the BEHAVE-AD and the HDRS with the NPI sub-

Table 1. Delphi panel member responses regarding the content validity of the Neuropsychiatric Inventory (NPI)

Behavior	Panel member scores: Screening question (mean)	Panel member scores: Subquestions (mean)
Delusions	1-2 (1.5)	1-2 (1.4)
Hallucinations	1-2 (1.3)	1-3 (1.3)
Dysphoria	1-2 (1.2)	1-2 (1.3)
Anxiety	1-2 (1.5)	1-2 (1.5)
Euphoria	1-2 (1.6)	1-2 (1.3)
Aggression	1-2 (1.3)	1-2 (1.2)
Apathy	1-3 (1.3)	1-2 (1.4)
Irritability	1-2 (1.3)	1-2 (1.7)
Disinhibition	1-2 (1.2)	1-2 (1.2)
Troublesome behavior*	1-3 (2.2)	1-3 (2.0)

* This section was reformulated in accord with the recommendations of the Delphi panel members and appears as "aberrant motor behavior" on the current NPI and in the remainder of the analyses.

Table 2. Scores of the Neuropsychiatric Inventory subscales (frequency and severity) derived from the concurrent validity study, interrater reliability test results, and results of the study of test-retest reliability

Behavior	Frequency mean (SD; range*)	Severity mean (SD; range)	Between-rater agreement: Frequency (%)	Between-rater agreement: Severity (%)	Test-retest reliability: Frequency Correlation (p)	Test-retest reliability: Severity Correlation (p)
Delusions	0.48 (1.11; 0-4)	0.28 (0.60; 0-2)	100	100	0.92 (0.0001)	0.80 (0.0001)
Hallucinations	0.25 (0.71; 0-3)	0.15 (0.36; 0-1)	97.9	97.9	0.98 (0.0001)	1.0 (0.0)
Agitation/Aggression	1.28 (1.52; 0-4)	0.70 (0.82; 0-3)	95.7	95.7	0.51 (0.02)	0.75 (0.0002)
Dysphoria	1.35 (1.56; 0-4)	0.70 (0.82; 0-3)	97.9	97.9	0.79 (0.0001)	0.84 (0.0001)
Anxiety	1.40 (1.71; 0-4)	0.68 (0.86; 0-3)	93.6	100	0.71 (0.0004)	0.51 (0.02)
Euphoria	0.13 (0.52; 0-3)	0.08 (0.27; 0-1)	100	100	†	†
Apathy	2.83 (1.55; 0-4)	1.35 (0.83; 0-3)	97.9	89.4	0.74 (0.0002)	0.68 (0.001)
Disinhibition	0.65 (1.23; 0-4)	0.35 (0.66; 0-2)	100	100	0.97 (0.0001)	0.87 (0.0001)
Irritability/Lability	1.23 (1.58; 0-4)	0.58 (0.81; 0-3)	95.7	97.9	0.53 (0.02)	0.51 (0.02)
Aberrant motor behavior	1.26 (1.8; 0-4)	0.41 (0.64; 0-2)	100	97.9	0.78 (0.0001)	0.77 (0.0001)

* Range refers to the range of behaviors reported by caregivers included in this study.
† No patient in the test-retest sample was judged to be euphoric, and the reliability of this item could not be assessed.

Table 3. Correlation of Neuropsychiatric Inventory (NPI) scores and scores of the BEHAVE-AD and the Hamilton Depression Rating Scale (HDRS)

	NPI correlations (p)		
	Frequency	Severity	Product of severity × frequency
BEHAVE-AD			
Delusions with NPI delusions	0.75 (0.01)	0.80 (0.01)	0.76 (0.01)
Hallucinations with NPI hallucinations	0.74 (0.01)	0.63 (0.01)	0.74 (0.01)
Aggression with NPI aggression	0.78 (0.01)	0.56 (0.01)	0.66 (0.01)
Anxiety and phobias with NPI anxiety	0.66 (0.01)	0.60 (0.01)	0.60 (0.01)
Affective disturbance with NPI dysphoria	0.54 (0.01)	0.47 (0.01)	0.33 (0.05)
Activity disturbance with NPI aberrant motor behavior	0.73 (0.01)	0.75 (0.01)	0.77 (0.01)
Global with NPI global	0.66 (0.0001)	0.71 (0.0001)	0.66 (0.0001)
HDRS with NPI dysphoria	0.70 (0.01)	0.59 (0.01)	0.62 (0.01)

scale frequency, severity, and product of frequency times severity. All correlations reached the 0.05 significance level and all but one reached the 0.01 significance level, indicating that the NPI is not significantly different from the BEHAVE-AD or the HDRS in its quantification of behavioral symptoms. The weakest correlation was between the Affective Disturbance subscale of the BEHAVE-AD and the Dysphoria subscale of the NPI (frequency × severity $r = 0.33$, $p = 0.05$). The relationship between the HDRS total score and the Dysphoria scale of the NPI was better (frequency × severity $r = 0.62$, $p = 0.01$). The correlation between the NPI Dysphoria scale and the HDRS total ($r = 0.62$) was comparable to the relationship between the BEHAVE-AD Affective Disturbance subscale and the HDRS total ($r = 0.61$). Overall, the analysis demonstrates an acceptable level of concurrent validity compared with the standard instruments.

Internal consistency reliability. Cronbach's coefficient alpha was calculated to determine the internal consistency (internal consistency reliability) among the items from the 40 NPIs generated during the concurrent validity study. Cronbach's alpha for overall reliability was 0.88. Cronbach's alpha varied between 0.87 and 0.88 for both severity and frequency of individual items, establishing a high level of internal consistency reliability.

Item independence. Twenty-two percent of the items showed significant relationships (Pearson correlation coefficients >0.01), and these largely reflected the expected patterns of behavior. For example, hallucination severity was correlated with delusion severity, and depression frequency was related to anxiety (frequency and severity) and apathy (frequency and severity). Seventy-eight percent of the items showed no significant relationships, indicating that they are independent of each other and are assessing differer behaviors.

Frequency and severity. Differences emerged be tween frequency and severity in this analysis. Disir hibition frequency and severity were strongly corr lated with agitation frequency (0.004 and 0.001, re spectively) but not with agitation severity; anxiet frequency and severity were correlated with apath frequency (0.005 and 0.043, respectively) but not wit apathy severity; disinhibition frequency and severit were correlated with apathy frequency (0.019 an 0.034, respectively) but not apathy severity; and di inhibition frequency and severity were correlate with frequency of aberrant motor behaviors (0.02 and 0.018, respectively) but not their severity. Severity and frequency were significantly correlated for all items ($p = 0.0001$ for all correlations). This indicates that frequency and severity, while closely related, identify different aspects of some behavioral disturbances.

Between-rater reliability. Between-rater reliability was determined using a percent-agreement approach. Between-rater agreement was very high (table 2). Overall, this analysis demonstrates that the NPI is highly reliable when used by different examiners. No trends emerged regarding use of the tool by individuals with different types of training, suggesting that it can be reliably used by individuals with different levels of training when they are provided with appropriate instruction for its use.

Test-retest reliability. Table 2 presents the test-retest reliability measures for each of the NPI scales and the overall reliability for severity and frequency. Test-retest reliabilities of all scored measures were significantly correlated; overall correlations were 0.79 for frequency ($p = 0.0001$) and 0.86 for severity ($p = 0.0001$). The weakest correlations (all $p = 0.02$) were for agitation frequency, anxiety severity, and irritability severity. The lower test-retest reliability of these measures may reflect more variability in these behaviors or it may be more difficult for spouses to reliably assess and report these behaviors in response to NPI questions. The second interview was conducted over the telephone and elicited information indistinguishable from that of the personal interview. This suggests that the NPI can be used as a telephone interview instrument, but in this study, the telephone interview always followed the face-to-face interview and the results may have been affected by the earlier encounter.

Relationship of item scores to dementia severity and age. Four of the 10 items (frequency × severity) of the NPI had significant relationships with the MMSE: delusions ($r = -0.31$, $p = 0.05$), anxiety ($r = -0.32$, $p = 0.05$), disinhibition ($r = -0.31$, $p = 0.05$), and aberrant motor behavior ($r = -0.39$, $p = 0.05$). These behaviors received higher scores in patients with the lower MMSE scores. Apathy was the only NPI item that showed a significant relationship with age; older patients were rated as more apathetic ($r = 0.38$, $p = 0.05$).

Normal control subjects. Forty normal control subjects participated in the study. The maximum possi-

ble score (frequency × severity) of any NPI subscale is twelve. In the normal control sample, all NPI scores were zero except for depression, disinhibition, and irritability. Mean depression score (severity × frequency) was 0.25 (range, 0 to 6); mean disinhibition score was 0.13 (range, 0 to 4); and mean irritability score was 0.05 (range, 0 to 2). None of the subscale scores was significantly correlated with the MMSE score. Thus, spouses of normal control subjects did not endorse delusions, hallucinations, agitation, anxiety, euphoria, apathy, or aberrant motor behaviors as characteristic behaviors of their partners. Depression, disinhibition, and irritability were identified at low rates among the normal controls.

In the course of examining the normal control subjects, two individuals had MMSE scores in the abnormal range (24 or less), and both had elevated scores on NPI subscales compared with cognitively intact individuals (these two patients were not included among the 40 controls analyzed above). This observation suggests that the NPI may identify deviations from normal behavior in the elderly when cognitive impairments are mild and the individual has not yet exhibited sufficient intellectual decline to mandate clinical assessment.

Interpretation. The NPI provides scores for 10 subscales. Each scale is scored for frequency and severity, and a total subscale score can be calculated by multiplying frequency and severity. Elevation of the subscale score beyond that noted among the controls indicates that behavior changes in that domain are present. We did not establish cutoff scores or determine what score might correlate with a clinical diagnosis such as major depressive episode (Dysphoria scale), manic episode (Euphoria scale), or anxiety disorder (Anxiety scale). Categorical diagnoses such as these are made on the basis of clinical information complementary to that obtained with the NPI. The presence of any delusions or hallucinations is abnormal, and depression scores above 6, disinhibition scores above 4, and irritability scores above 2 were not present among normal persons. Scores on the other scales—agitation, euphoria, apathy, and aberrant motor behavior—were not found among normal subjects and, when present, can be regarded as evidence of an abnormality. A global score for the NPI can be generated by summing the total scores (frequency multiplied by severity) of the individual subscales. This global score sums many disparate behaviors (eg, psychosis and apathy) and can be regarded only as an imprecise guide to the total behavioral disturbance exhibited by the patient.

Discussion. This study establishes the validity and reliability of the NPI, a new instrument for the assessment of psychopathology in patients with dementia. The content validity study employing a Delphi panel demonstrated that the NPI effectively captures a wide range of psychopathology, and the concurrent validity study showed that the NPI quantitates psychopathology as well as standard instruments such as the BEHAVE-AD and the HDRS. An item analysis indicated that there is high internal consistency item reliability and that the behavioral domains assessed are largely independent of each other. Between-rater reliability was high, and the test-retest reliability study demonstrated that responses to NPI questions are stable over short intervals (up to 3 weeks). The screening questions were shown to have a less than 5% false-negative rate for detecting psychopathology that would be discovered by completing the entire interview. The results establish the NPI as an instrument in which the clinician can have confidence as a means of assessing and quantitating behavioral changes in dementia.

The NPI has several advantageous features when compared with existing instruments. The screening-question approach allows the clinician to focus on areas of psychopathology while not expending time on unrewarding avenues of inquiry. The caregiver of a patient with little psychopathology is asked only the screening questions in the 10 behavioral domains, and the interview can be completed in 7 to 10 minutes. Caregivers of patients with more psychopathology will require longer interviews.

The NPI explores a wide range of psychopathology. In addition to delusions, hallucinations, depression, anxiety, and agitation that are assessed with instruments currently in use, the NPI also assesses apathy, irritability/lability, disinhibition, and euphoria. Routine investigation of these behavioral domains will allow more comprehensive understanding of the behavioral changes present in any specific dementia patient and may help to distinguish among different types of dementias. In this study assessing a population comprised largely of AD patients, apathy and irritability were among the most commonly recorded behaviors.

The NPI is scored on the basis of information provided by the caregiver and thus avoids the problems inherent in observer-based strategies of asking questions of demented patients or observing behavior for only restricted periods of time. The dysphoria section of the NPI does not include neurovegetative or somatic items and thus avoids the possible confounding effects of the overlapping features of dementia and depression. The NPI distinguishes between behavior severity and frequency, a feature potentially useful in assessing interventions that may affect only one of these behavioral dimensions.

Although we subjected the NPI to comprehensive studies, several areas of application remain unexplored. First, most of the patients in the current studies had AD, and the differential diagnostic utility of the instrument is not established. Second, some behaviors (eg, euphoria) were uncommon in the current study population, and the NPI's ability to assess these behaviors has not been fully determined. Third, the NPI has not been used in treatment studies, and its utility in monitoring behavioral changes related to psychotropic drugs or behavioral interventions remains to be determined. Fourth, the NPI is based on information gathered from caregivers and is subject to bias if the caregiver lacks or distorts information.

With these provisos, the NPI is a useful, psychometrically sound, and efficient means of assessing a wide range of neuropsychiatric alterations in dementia patients.

Note. The Neuropsychiatric Inventory described in this report will be provided on request.

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Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria

Bruno Dubois, Howard H Feldman*, Claudia Jacova, Steven T DeKosky, Pascale Barberger-Gateau, Jeffrey Cummings, André Delacourte, Douglas Galasko, Serge Gauthier, Gregory Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Yaakov Stern, Pieter J Visser, Philip Scheltens*

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INSERM U610, Hôpital de la Salpêtrière , Paris, France, and Université Pierre et Marie Curie–Paris6, Paris, France (B Dubois MD); **Division of Neurology, University of British Columbia and Vancouver Coastal Health, Vancouver BC, Canada** (H H Feldman MD, C Jacova PhD); **Department of Neurology, University of Pittsburgh, Pittsburgh, USA** (S T Dekosky MD); **INSERM U593, Université Victor Segalen Bordeaux 2, France** (P Barberger-Gateau MD); **University of California at Los Angeles Alzheimer's Disease Center, USA** (J Cummings MD); **CHU de Lille, Centre INSERM JPA, Bâtiment Gérard Biserte, Lille, France** (A Delacourte PhD); **Department of Neurosciences, University of California, San Diego, California, USA** (D Galasko MD); **McGill Center for Studies in Aging, Douglas Hospital, Montreal, Quebec, Canada** (S Gauthier MD); **Department of Neurology; University of Kentucky Medical Center; Sanders-Brown Center on Aging; Lexington, USA** (G Jicha MD); **Department of Behavioral Neurology and Cognitive Neuroscience, Tohoku University Graduate School of Medicine, Aoba-ku, Sendai, Japan** (K Meguro MD); **Wolfson Research Centre, Institute for Ageing and Health, Newcastle General Hospital, Newcastle upon Tyne, UK** (J T O'Brien MD); **Neurology Department, Memory Clinic, Lille University Hospital, France** (F Pasquier MD); **Centre Mémoire de Ressources et de Recherche, Pavillon M, Hôpital Pasteur, Nice, France** (P Robert MD); **Dementia Research Group, Department of**

The NINCDS–ADRDA and the DSM-IV-TR criteria for Alzheimer's disease (AD) are the prevailing diagnostic standards in research; however, they have now fallen behind the unprecedented growth of scientific knowledge. Distinctive and reliable biomarkers of AD are now available through structural MRI, molecular neuroimaging with PET, and cerebrospinal fluid analyses. This progress provides the impetus for our proposal of revised diagnostic criteria for AD. Our framework was developed to capture both the earliest stages, before full-blown dementia, as well as the full spectrum of the illness. These new criteria are centred on a clinical core of early and significant episodic memory impairment. They stipulate that there must also be at least one or more abnormal biomarkers among structural neuroimaging with MRI, molecular neuroimaging with PET, and cerebrospinal fluid analysis of amyloid β or tau proteins. The timeliness of these criteria is highlighted by the many drugs in development that are directed at changing pathogenesis, particularly at the production and clearance of amyloid β as well as at the hyperphosphorylation state of tau. Validation studies in existing and prospective cohorts are needed to advance these criteria and optimise their sensitivity, specificity, and accuracy.

Background

For research purposes, the diagnosis of Alzheimer's disease (AD) is based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR)[1] and the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS–ADRDA) working group.[2] These accepted criteria are fulfilled in a two-step diagnostic process where there is initial identification of a dementia syndrome and then the application of criteria based on the clinical features of the AD phenotype. The DSM-IV-TR criteria require the presence of both a memory disorder and impairment in at least one additional cognitive domain, both of which interfere with social function or activities of daily living (ADL).[1] ADL impairment has come to define the threshold for the diagnosis of dementia beyond the identification of a cognitive abnormality. The NINCDS–ADRDA clinical criteria of probable AD do not require evidence of interference with social or occupational functioning but they include the specification that the onset of AD is insidious and that there is a lack of other systemic or brain diseases that may account for the progressive memory and other cognitive deficits. The currently accepted criteria support a probabilistic diagnosis of AD within a clinical context where there is no definitive diagnostic biomarker. A definite diagnosis of AD is only made according to the NINCDS–ADRDA criteria when there is histopathological confirmation of the clinical diagnosis. [2]

Since the publication of the NINCDS–ADRDA criteria in 1984, the elucidation of the biological basis of AD has advanced greatly, allowing an unprecedented understanding of the disease process. The clinical phenotype of AD is no longer described in exclusionary terms, but can be characterised more definitively on a phenotypic basis. Distinctive markers of the disease are now recognised including structural brain changes visible on MRI with early and extensive involvement of the medial temporal lobe (MTL), molecular neuroimaging changes seen with PET with hypometabolism or hypoperfusion in temporoparietal areas, and changes in cerebrospinal fluid biomarkers. A driving force behind this emerging identity of AD has been the intense research interest in characterising the earliest stages of AD that predate the crossing of the dementia threshold, defined by functional disability. **Prodromal AD** (see glossary, panel 1) must be distinguished within the broad and heterogeneous state of cognitive functioning that falls outside normal ageing.[3] This state has been described by a wide range of nosological terms including age-associated memory impairment, age-related cognitive decline, age-associated cognitive decline, mild cognitive disorder, mild neurocognitive disorder, cognitively impaired not demented, and mild cognitive impairment.[4–9] **Mild cognitive impairment** (panel 1) is the most widely used diagnostic term for the disorder in individuals who have subjective memory or cognitive symptoms, objective memory or cognitive impairment, and whose activities of daily living are generally normal. Progression to clinically diagnosable dementia occurs at a higher rate from mild cognitive impairment than from an unimpaired state, but is clearly not the invariable clinical outcome at follow-up.[10] A more refined definition of AD is still needed to reliably identify the disease at its earliest stages.

The case for revising the research criteria for AD diagnosis

There are several factors that highlight the need to update the current research criteria for AD.

Panel 1: Glossary of terms

Mild cognitive impairment
Variably defined but includes subjective memory or cognitive symptoms or both, objective memory or cognitive impairment or both, and generally unaffected activities of daily living; affected people do not meet currently accepted dementia or AD diagnostic criteria

Amnestic mild cognitive impairment
A more specified term describing a subtype of mild cognitive impairment, in which there are subjective memory symptoms and objective memory impairment; other cognitive domains and activities of daily living are generally unaffected; affected people do not meet currently accepted dementia or AD diagnostic criteria

Preclinical AD
The long asymptomatic period between the first brain lesions and the first appearance of symptoms and which concerns normal individuals that later fulfil AD diagnostic criteria

Prodromal AD
The symptomatic predementia phase of AD, generally included in the mild cognitive impairment category; this phase is characterised by symptoms not severe enough to meet currently accepted diagnostic criteria for AD

AD dementia
The phase of AD where symptoms are sufficiently severe to meet currently accepted dementia and AD diagnostic criteria

Insufficient diagnostic specificity

The DSM-IV-TR and NINCDS–ADRDA criteria have been validated against neuropathological gold standards with diagnostic accuracy ranging from 65–96%.[11–14] However, the specificity of these diagnostic criteria against other dementias is only 23–88%.[13,14] The accuracy of these estimates is difficult to assess, given that the neuropathological standard is not the same in all studies. Nevertheless, the low specificity must be addressed through both revised AD and accurate non-AD dementia diagnostic criteria.

Improved recognition of non-AD dementia

Since the publication of the NINCDS–ADRDA criteria, operational definition and characterisation of non-AD dementias has improved. Entities for which there are diagnostic criteria include the frontotemporal lobar degenerations (frontotemporal dementia frontal variant, semantic dementia, progressive non-fluent aphasia),[15–17] corticobasal degeneration,[18,19] posterior cortical atrophy,[20] dementia with Lewy bodies,[21] and vascular dementia.[22,23] Varma and colleagues[13] showed that many of these disorders can fulfil the NINCDS–ADRDA criteria and it is likely that they have been included in AD research studies. Meanwhile, for each of these disorders, criteria have been developed that aim for high specificity. The development of disease-specific criteria that are applicable in some cases before dementia is fully manifested has enabled the criteria to be used without going through the two-step process of dementia recognition (the syndrome) followed by the specific disease (the aetiology). For example, the identification of a dementia syndrome is not required for the diagnosis of primary progressive aphasia, corticobasal degeneration, or posterior cortical atrophy even though a dementia as currently defined will occur during or at the end of the course of these diseases.[3] The histopathological diagnosis of the non-AD dementias has also advanced. In the example of frontotemporal lobar degeneration, the identification of ubiquitin-immunoreactive cytoplasmic and intranuclear inclusions as an important pathology in patients has reduced the neuropathological diagnostic prevalence of dementia lacking distinctive histopathology from 40% to 10% in autopsy series.[24–26] There is no doubt that progress in the clinical definition of non-AD dementia improves the sensitivity of the currently accepted diagnostic criteria for AD by reducing the level of uncertainty.

Improved identification of AD phenotype

When the NINCDS–ADRDA criteria were first published, the authors noted that they were not yet fully operational because of insufficient knowledge about the disease.[2] Since then, the clinical phenotype of AD has been much more clearly elucidated. In most patients with AD (86–94%), there is a progressive amnestic core that appears as an impairment of episodic memory.[27–29] The pathological pathway of Alzheimer's related changes has been fully described[30,31] and involves the medial temporal structures (eg, entorhinal cortex, hippocampal formation, parahippocampal gyrus) early in the course of the disease. Moreover, the episodic memory disorder of AD correlates well with the distribution of neurofibrillary tangles within the MTL[32] and with MRI volumetric loss of the hippocampus,[33] structures known to be critical for episodic memory. The availability of neuroimaging techniques that can reliably measure the MTL have further supported this vital cliniconeuroanatomic correlation.

Need to test early intervention

The rapid growth of knowledge about the potential pathogenic mechanisms of AD including the amyloidopathy and tauopathy has spawned numerous experimental therapeutic approaches to enter into clinical trials. There is accruing evidence that, years before the onset of clinical symptoms, there is an AD process evolving along a predictable pattern of progression in the brain.[30,31] The neurobiological advantage of earlier intervention within this cascade is clear. Earlier intervention with disease-modifying therapies[34] is likely to be more effective when there is a lower burden of amyloid and hyperphosphorylated tau

Clinical Neurology, Institute of Neurology, London, UK (M Rossor MD); **Department of Clinical Neurosciences, Brown University, Providence, RI, USA** (S Salloway MD); **Cognitive Neuroscience Division of the Taub Institute, Presbyterian Hospital, New York, USA** (Y Stern PhD); **and Department of Neurology and Alzheimer Center, VU University Medical Center, Netherlands** (P J Visser MD, P Scheltens MD)

Correspondence to: Bruno Dubois, INSERM U610, Salpêtrière Hospital, 47 Bld de l'Hôpital, Paris 75013, France **bruno.dubois@psl.aphp.fr**

*These authors contributed equally to this work

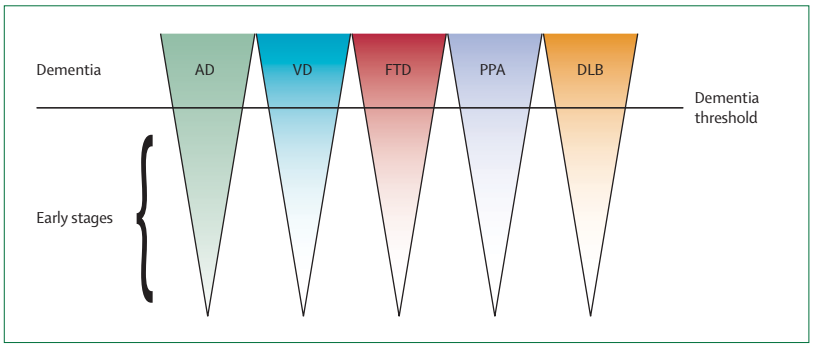

Figure: **Alzheimer's disease starts and should be identified before the occurrence of full-blown dementia (as for other dementing conditions)**
AD=Alzheimer's disease; VD=vascular dementia; FTD=frontotemporal dementia; PPA=primary progressive aphasia; DLB=dementia with Lewy bodies.

and may truncate the ill effects of secondary events due to inflammatory, oxidation, excitotoxicity, and apoptosis. Early intervention may also be directly targeted against these events because they may play an important part in early phases of AD. By the time there is clear functional disability, the disease process is significantly advanced and even definitive interventions are likely to be suboptimal. Revised research criteria would allow diagnosis when symptoms first appear, before full-blown dementia, thus supporting earlier intervention at the prodromal stage (figure).

Problems with definition of mild cognitive impairment

One of the proposed advantages of mild cognitive impairment has been its potential usefulness for clinical trials directed at delaying the time to onset of AD. A series of large randomised controlled trials with both non-steroidal anti-inflammatory drugs and acetylcholinesterase inhibitors have sought to establish the usefulness of these drugs in delaying the conversion of mild cognitive impairment to AD. However, the lessons learned have highlighted the problems of mild cognitive impairment within this type of randomised controlled trial. With only small variations in the inclusion criteria for mild cognitive impairment, four trials (ADCS-MIS, InDDEx, Gal-Int 11, and Rofecoxib) have had a very wide range of annual rates of progression to **AD dementia** (panel 1, 4·8–16%).[35–38] The intention in these trials on mild cognitive impairment was to include many individuals with prodromal AD (ie, individuals with symptoms not sufficiently severe to meet currently accepted diagnostic criteria) that later progress to meet these criteria. When the mild cognitive impairment inclusion criteria of these trials were applied to a cohort of memory clinic patients in an observational study, they had diagnostic sensitivities of 46–88% and specificities of 37–90% in identifying prodromal AD.[39] Given these numbers, these trials have clearly treated many patients who do not have AD or are not going to progress to AD for a long time. This has diluted the potential for a significant treatment effect and may have contributed to the negative outcomes where none of these drugs were successful at delaying the time to diagnosis of AD.[37–38] These trials have also incurred significant costs where sample sizes of 750 to 1000 have been called for with durations of 3–4 years. Increasing the severity of mild cognitive impairment needed for inclusion in trials might improve sensitivity, specificity, and predictive values. However, participants would then be much closer to the current dementia threshold and would have a greater pathological burden, making the clinical gain marginal and disease modification difficult.

Neuropathological findings in mild cognitive impairment have also reinforced the heterogeneity of the clinical disorders subsumed under the definition mild cognitive impairment. To address the recognised clinical and pathological heterogeneity, it has been proposed that subtyping of mild cognitive impairment might be useful.[40,41] The term **amnestic mild cognitive impairment** (panel 1) has been proposed to include individuals with subjective memory symptoms, objective memory impairment, and with other cognitive domains and activities of daily living generally assessed as being normal.[9] However, only 70% of a selected cohort of people with amnestic mild cognitive impairment clinically identified to have progressed to dementia actually met neuropathological criteria for AD.[42] This finding indicates that applying the criteria for this subtype of mild cognitive impairment clinically, without other objective evidence such as neuroimaging or results of cerebrospinal fluid analyses, will lack specificity for predicting the future development of AD since at least 30% of these will have non-AD pathology. If 30% of cases enrolled in a study that assesses drugs targeting amyloid or neurofibrillary tangles were to have non-AD pathology, there would be a substantial loss of power and possibly a conclusion that a medication was not effective. If all cases could be ascertained as having AD, a positive outcome might result. Thus, the most accurate determination that an individual has prodromal AD is critical.

In the planning of trials of disease-modifying treatment, special care will be needed to limit not only the exposure of potentially toxic therapies to those with prodromal AD but also to reliably exclude those who are destined to develop non-AD dementia. Our proposal for multidimensionally established identification of AD would have potential superiority to the intrinsically heterogeneous state of mild cognitive impairment and would advance the concept of mild cognitive impairment to its natural next level of more desirably identifying prodromal AD.

Unclear distinction between mild cognitive impairment and AD

The transition from mild cognitive impairment to AD has been an a priori primary endpoint in several randomised controlled trials.[37,38,43] There is an inherent arbitrariness in

determining a binary outcome, that is, conversion or no conversion, when the underlying disease is a continuous process. Individual clinicians' experience in dementia diagnosis and the quality of the information they receive on the cognitive and functional status of patients will affect the threshold of detection of the transition to AD.[27] Our revised research criteria will eliminate the mild cognitive impairment construct, thus bypassing the binary outcome in the clinical categorisation process associated with it as well as problems with reliability.

New biomarkers for AD

Over the past two decades since the NINCDS–ADRDA criteria were published, great progress has been made in identifying the AD-associated structural and molecular changes in the brain and their biochemical footprints. MRI enables detailed visualisation of MTL structures implicated in the core diagnostic feature of AD.[44] PET with fluorodeoxyglucose (FDG) has been approved in the USA for diagnostic purposes and is sensitive and specific in detecting AD in its early stages.[45] Cerebrospinal fluid biomarkers for detecting the key molecular pathological features of AD in vivo are available and can be assessed reliably.[46] Their diagnostic predictability has been extended to mild cognitive impairment.[47] In vivo imaging of pathology-specific proteins (Pittsburgh compound B [PiB], FDDNP)[48,49] are advancing in their development and potentially in our ability to accurately identify prodromal and even **preclinical AD** (panel 1). The growing body of evidence about AD biomarkers allows us to incorporate these into our new diagnostic research criteria for AD.

Objectives

An international working group was convened in 2005 to discuss the opportunity for developing a diagnostic framework for AD that would include the prodromal stages and the integration of biomarkers and to define the future goals and steps for the validation of such a framework. This paper provides the consensus recommendations of the working group and sets out the framework for revised research criteria for AD that would apply both in the early stages and across the full spectrum of the illness.

Methods

15 international dementia experts were invited by two of the authors (Dubois and Scheltens) to attend a satellite workshop at the Second Congress of the International Society for Vascular Behavioural and Cognitive Disorders (Vas-Cog) in Florence on June 9, 2005. The participants were each asked to present the evidence base of published literature around a range of topics including clinical, functional, neuropsychiatric and behavioural, cognitive, neuroimaging, neuropathology, and laboratory markers pertinent to the early stages of AD, and to provide expert opinion where there was no published evidence. A draft document outlining revised diagnostic criteria was subsequently developed by the lead authors (Dubois, Feldman, and Scheltens) and then refined in further correspondence with conference participants. Additional members were then recruited into the working group to broaden the perspective before the finalisation and submission of the current proposed AD research criteria for publication.

Proposed diagnostic criteria for probable AD

The proposed framework for revised criteria for probable AD retains the designation of probable AD. It does not include a designation of possible AD because of the incompatibility of this definition with diagnostic criteria that are highly specific for AD. The framework addresses the disease presentation that is typical for AD. We exclude atypical presentations including focal cortical syndromes (primary progressive aphasia, visuospatial dysfunction) where an antemortem diagnosis would at best receive the designation of possible AD from the framework. This may change in the future as work on diagnostic biomarkers advances and reliance on a well characterised clinical phenotype is lessened. In the absence of completely specific biomarkers, the clinical diagnosis of AD can still be only probabilistic, even in the case of typical AD. To meet criteria for probable AD, an affected individual must fulfil criterion A (the core clinical criterion) and at least one or more of the supportive biomarker criteria: B, C, D, or E (panel 2).

Core diagnostic criterion: early episodic memory impairment (A)

1. Gradual and progressive change in memory function at disease onset reported by patients or informants for a period greater than 6 months

The reporting of subjective memory complaints is a common symptom in an ageing population,[50] at a prevalence that far exceeds the risk of being classified as having AD. Subjective memory complaints in elderly people may result from normal ageing or various medical disorders, and they are commonly associated with depression.[51–53] However, such self-reported symptoms are associated with a high risk of future development of AD[54,55] and, therefore, should be carefully taken into account. The perceptions of patients' symptoms from an informant or proxy are perhaps more significant as they are more strongly related to objective memory performance[51] and are predictive of progression to AD.[52] To satisfy criterion A, memory symptoms must start gradually and show progressive decline over at least 6 months. Particular attention should be paid to intraindividual decline, which improves the identification of those individuals with prodromal AD.[56]

2. Objective evidence of significantly impaired episodic memory on testing

A diagnosis of AD requires an objective deficit on memory testing (recall deficit with intrusions). Tests of

Panel 2: **Diagnostic criteria for AD**

Probable AD: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria

A. Presence of an early and significant episodic memory impairment that includes the following features:

1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features

B. Presence of medial temporal lobe atrophy

- Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)

C. Abnormal cerebrospinal fluid biomarker

- Low amyloid β_{1-42} concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
- Other well validated markers to be discovered in the future

D. Specific pattern on functional neuroimaging with PET

- Reduced glucose metabolism in bilateral temporal parietal regions
- Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family

Exclusion criteria

History

- Sudden onset
- Early occurrence of the following symptoms: gait disturbances, seizures, behavioural changes

Clinical features

- Focal neurological features including hemiparesis, sensory loss, visual field deficits
- Early extrapyramidal signs

Other medical disorders severe enough to account for memory and related symptoms

- Non-AD dementia
- Major depression
- Cerebrovascular disease
- Toxic and metabolic abnormalities, all of which may require specific investigations
- MRI FLAIR or T2 signal abnormalities in the medial temporal lobe that are consistent with infectious or vascular insults

Criteria for definite AD

AD is considered definite if the following are present:

- Both clinical and histopathological (brain biopsy or autopsy) evidence of the disease, as required by the NIA-Reagan criteria for the post-mortem diagnosis of AD; criteria must both be present[139]
- Both clinical and genetic evidence (mutation on chromosome 1, 14, or 21) of AD; criteria must both be present

delayed recall discriminate very mild AD from normal healthy controls with high accuracy (>90%).[57] Such tests also predict prodromal AD better than other memory or non-memory measures, with accuracy greater than 80%.[57–63] Delayed recall is a reliable predictor of AD in individuals with mild cognitive impairment.[64,65] A meta-analysis of 47 studies calculated pooled effect sizes between incident AD and control groups. Episodic memory yielded the largest pooled effect sizes (>1 SD), along with executive functioning and perceptual speed.[66] Within episodic memory, delayed recall testing showed a larger effect size than immediate recall testing.

Impaired delayed recall is not itself evidence of an AD-related memory disorder. Genuine deficits in encoding and storage processes that are characteristic for AD must be distinguished from non-AD deficits that can also affect delayed recall, including attentional difficulties that may be present in depression,[67] or inefficient retrieval strategies associated with normal ageing,[68] frontotemporal dementia,[69] or subcortical-frontal dementias.[70] The accurate diagnosis of the episodic memory deficit of AD can be improved by use of test paradigms that provide encoding specificity.[71] Within such paradigms, test materials are encoded along with specific cues—for example, semantic cues, which are used to control for an effective encoding and are subsequently presented to maximise retrieval. Coordinated encoding and retrieval paradigms of this type include the free and cued recall test[71] or similar cued recall paradigms.[72,73] Within these neuropsychological test paradigms, measures of sensitivity to semantic cueing can successfully differentiate patients with AD from healthy controls, even when patients are equated to controls on mini-mental state examination scores or when disease severity is very mild.[72,74,75] Buschke and co-workers derived sensitivity and specificity estimates of 93% and 99%, respectively, for the discrimination of patients with mild AD from healthy people with such a strategy.[72] Patients with non-AD disorders including progressive supranuclear palsy and Parkinson's and Huntington's diseases do almost as well as control individuals under encoding specificity conditions whereas patients with AD do not normalise their recall deficit.[70] Patients with very mild AD also have a measurable reduction in sensitivity to cueing.[75] Reduced benefit from cueing at recall reliably identifies prodromal AD.[73]

3. The episodic memory impairment can be isolated or associated with other cognitive changes at onset of AD or as AD advances

In most cases, even at the earliest stages of the disease, the memory disorder is associated with other cognitive changes. As AD advances, these changes become notable and can involve the following domains: executive function (conceptualisation with impaired abstract thinking; working memory with decreased digit span or mental ordering; activation of mental set with decreased verbal fluencies); language (naming difficulties and impaired

comprehension); praxis (impaired imitation, production, or recognition of gestures); and complex visual processing and gnosis (impaired recognition of objects or faces). The emergence of neuropsychiatric symptoms, including apathy or delusions, also constitutes a clinical marker of disease.[76,77] Neuropsychiatric symptoms cannot be a core diagnostic feature because they are less specific and generally occur at a high prevalence later in the course of the disease. When there is evidence of impairment in multiple cognitive domains, functional disability, and neuropsychiatric symptoms, a more widespread diffusion of neuronal lesions in cortical and subcortical structures can be established.[30] However, even in these more advanced cases, there should be evidence of an early and previous episodic memory deficit as a mandatory requirement for the diagnosis of AD.

Supportive features

Atrophy of medial temporal structures on MRI (B)

Atrophy of the MTL on MRI seems to be common in AD (71–96%, depending on disease severity), frequent in mild cognitive impairment (59–78%), but less frequent in normal ageing (29%).[78,79] MTL atrophy is related to the presence of AD neuropathological and its severity, both in terms of fulfilment of AD neuropathological criteria and Braak stages.[44,80] MRI measurements of MTL structures include qualitative ratings of the atrophy in the hippocampal formation[81] or quantitative techniques with tissue segmentation and digital computation of volume.[82] Both techniques can reliably separate AD group data from normal age-matched control group data, with sensitivities and specificities greater than 85%.[83–85] Hippocampal volumes can distinguish AD equally at younger (≤70 years) and old ages (>70 years).[86] Qualitative measures have been useful in distinguishing patients with AD from those with non-AD dementia including vascular, frontotemporal, and dementia of unspecified cause, with combined mini-mental state examination and MTL atrophy ratings yielding sensitivity and specificity greater than 85%.[87]

In studies of mild cognitive impairment, the accuracy of MTL atrophy measures in identifying prodromal AD has been generally lower, possibly because individuals who did not meet currently accepted AD diagnostic criteria at study completion included some cases that would have done so at a later time. Qualitative MTL ratings can identify prodromal AD; however the sensitivities and specificities, respectively, of 51–70% and 68–69%[88–91] at present limit their usefulness. The predictive usefulness of quantitative measures of hippocampal volume in identifying prodromal AD is inconsistent.[88,89,92–94] Measures of hippocampal subfields might be more useful than measures of the entire structure.[95,96] Other structures or combinations of structures within and beyond the MTL may prove to be more sensitive to early AD pathology. For example, entorhinal cortex volume identifies prodromal AD more accurately than hippocampal volume, with a sensitivity of 83% and specificity of 73%.[97] There are, however, technical difficulties in measuring this region that must be resolved.[98,99] Combinations of MTL volumes and lateral temporal lobe or anterior cingulate volumes also detect prodromal AD with variable success (sensitivity 68–93%, specificity 48–96%).[100,101]

There is a strong correlation between MTL volumes and episodic memory performance.[33,102] In turn, there is a potential incremental value of MTL measurement beyond the episodic memory impairment in the identification of prodromal AD. In several studies, MTL measures (quantitative and qualitative) contributed independently of memory scores to the identification of prodromal AD.[90,93] The reported accuracy of identifying prodromal AD increased from 74% to 81%[89] and from 88% to 96%[88] when MTL measures were added to age and memory scores, respectively.

Inclusion of MTL atrophy as a diagnostic criterion of AD, irrespective of the age at onset,[86] mandates exclusion of other causes of MTL structural abnormality including bilateral ischaemia, bilateral hippocampal sclerosis, herpes simplex encephalitis, and temporal lobe epilepsy. T2 weighted MRI, coupled to history and examination, and potentially adjunctive directed tests such as cerebrospinal fluid analysis and EEG should facilitate this discrimination.[103,104]

Abnormal cerebrospinal fluid biomarkers (C)

In the NINCDS–ADRDA guidelines, cerebrospinal fluid examination was recommended as an exclusion procedure for non-AD dementia, due to inflammatory disease, vasculitis, or demyelination.[2] Since then, there has been a lot of research into the usefulness of AD-specific biomarkers that are reflective of the central pathogenic processes of amyloid β aggregation and hyperphosphorylation of tau protein. These markers have included amyloid β_{1-42} (Aβ42), total tau (t-tau), and phospho-tau (p-tau).[105–107] In AD, the concentration of Aβ42 in cerebrospinal fluid is low and that of t-tau is high compared with those in healthy controls.[105,106] Concentrations of different phosphorylated tau epitopes may also be high.[108,109] Aβ42 concentration in the cerebrospinal fluid is normal in patients with depression and decreased in dementia with Lewy bodies, frontotemporal lobar degeneration, and vascular dementia.[110] This lack of specificity is not fully explained, but may relate to the lack of histopathological verification or the presence of comorbid AD. T-tau concentration is normal in depression, may be slightly raised in dementia with Lewy bodies and frontotemporal lobal degeneration, and is very high in Creutzfeldt-Jakob disease.[110,111] Measurement of the concentration of p-tau, notably p-tau 231, increases the specificity for AD, especially in contrast to frontotemporal lobar degeneration.[109] The pooled sensitivity and specificity for Aβ42 in AD versus controls from 13 studies involving 600 patients and 450 controls were

86% and 90%, respectively.[110] For t-tau, the sensitivity was 81% and the specificity 90%, pooled from 36 studies with 2500 patients and 1400 controls.[110] Across 11 studies with a total of 800 patients and 370 controls, p-tau had a mean sensitivity of 80% when specificity was set at 92%, but sensitivities varied widely among studies using different methods.[110] By use of a combination of concentrations of Aβ42 and t-tau for AD versus controls, high sensitivities (85–94%) and specificities (83–100%) can be reached.[110]

Several recent studies have specifically addressed the value of cerebrospinal fluid biomarkers in identifying prodromal AD. Combinations of abnormal markers (low Aβ42, high t-tau, high p-tau 181) reached a hazard ratio of 17 to 20 for predicting AD in a follow-up of 4–6 years.[47] Sensitivities and specificities in this study were >90% and >85%, respectively, which agreed with those in a similar one with much shorter follow-up (1 year).[47,112] This high diagnostic usefulness of cerebrospinal fluid markers in the mild cognitive impairment stage supports their incremental value over memory impairment in the diagnostic scheme and justifies their inclusion as a diagnostic criterion.

Using an adapted spinal needle (Sprotte 24 g), lumbar puncture can be done with a very low rate of clinically significant adverse events and with a good acceptability in cognitively impaired people and healthy adults of all ages.[113]

Specific metabolic pattern evidenced with molecular neuroimaging methods (D)

PET and single photon emission computed tomography (SPECT) are in vivo nuclear radioisotopic scans that can measure blood flow (99mTc-HMPAO or 133Xe), glucose metabolism (18F-FDG PET), and, more recently, protein aggregates of amyloid and tau. Within an AD diagnostic framework their ideal role is to increase the specificity of clinical criteria.

A reduction of glucose metabolism as seen on PET in bilateral temporal parietal regions and in the posterior cingulate is the most commonly described diagnostic criterion for AD.[114] A recent meta-analysis of nine studies reported that for the discrimination of patients with AD from healthy controls, pooled sensitivities and specificities were 86% for temporoparietal hypometabolism. There is a wide range for both sensitivities and specificities, without clear explanation of this variability.[115] When histopathological examination has been used as the gold standard, sensitivity is 88–95% and specificity is 62–74%.[114,115] Because of cognitive reserve, the reduction in temporoparietal glucose metabolism diagnostic for AD might vary with educational attainment or IQ at any level of clinical severity.[116]

PET has been successful in distinguishing dementia with Lewy bodies from AD, with sensitivity of 86–92% and specificity of 80–81% when visual-association cortex was considered.[117,118] Discrimination from frontotemporal dementia has also been achieved, with sensitivity and specificity of 78% and 71%.[119] There has been limited accuracy in differentiating AD from vascular dementia (sensitivity 75–88%, specificity 18–53%).[120,121]

The usefulness of FDG-PET in the detection of prodromal AD has only just begun to be addressed in studies with small samples of patients with mild cognitive impairment and limited follow-up (≤3 years). Metabolic reductions in the anterior cingulate, posterior cingulate, and temporal, parietal, and medial temporal cortices detected prodromal AD, with accuracy estimates ranging from 75% to 84%.[122–124] The potential incremental value of PET over other diagnostic markers in identifying prodromal AD is poorly defined. PET may be more accurate when delayed recall scores are severely impaired (sensitivity and specificity >90%).[125]

There are promising PET techniques that provide in-vivo visualisation of amyloid and potentially neurofibrillary tangles. Studies using PiB (*N*-methyl-[^{11}C]2-(4Ľ-methylaminophenyl)-6-hydroxybenzothiazole) and FDDNP (2-(1-[6-[(2-[^{18}F]fluoroethyl](methyl)amino]-2-naphthyl]ethylidene)malononitrile) have shown a pattern of increased radioligand retention in patients with AD compared with control individuals that is consistent with AD pathology.[48,49,126] Furthermore, positive cortical PiB binding has been associated with low cerebrospinal fluid Aβ42 concentrations in AD.[127] These protein visualisation techniques clearly have the potential of increasing the usefulness of PET in AD within the diagnostic framework, but their diagnostic accuracy, in particular their specificity for AD, requires further investigation as there is evidence of high AD-like PiB retention in some healthy people and some people with mild cognitive impairment.[127–129] AD-like PiB retention in healthy people might signal a preclinical AD state in asymptomatic individuals who later meet currently accepted dementia and AD diagnostic criteria, whereas in mild cognitive impairment it might reveal prodromal AD. Longitudinal follow-up is essential for the verification of the presumption that these are indeed preclinical and prodromal AD cases and not false positives.[128]

Because SPECT is more widely available and cheaper than PET, it has received much attention as an alternative to PET. However, at present, the technique is not included in these proposed criteria as the diagnostic accuracy estimates for this modality generally fall below the requisite 80% levels specified by the Reagan Biomarker Working Group.[130] 99M Tc-HMPAO SPECT identifies diagnosed AD with moderate sensitivity (77–80%) and specificity (65–93%). A pattern of bilateral temporal parietal hypoperfusion increases diagnostic certainty over clinical diagnosis alone.[131]

According to a recent meta-analysis SPECT distinguished AD from non-AD in studies including healthy controls with pooled weighted sensitivities ranging from 65% to 71%, with a specificity of 79%.[132] There are few SPECT studies that have adequately addressed the comparison between AD and non-AD

dementias. The few that did provided a pooled weighted sensitivity and specificity for AD versus frontotemporal dementia of 71% and 78%, respectively, and for AD versus vascular dementia of 71% and 75%, respectively.[132] More specific ligand methods, for example dopamine SPECT scanning with fluoropropyl-CIT, may have particular utility in distinguishing dementia with Lewy bodies and Parkinson's disease dementia from AD (sensitivity 88%, specificity 85%).[133–135]

Two small retrospective SPECT studies of mild cognitive impairment suggest that hypoperfusion in parietal and temporal lobe regions, and in the precuneus, may be brain functional patterns occurring very early in AD. In both studies, patterns of regional blood flow on SPECT distinguished prodromal AD with accuracy greater than 80%.[135,136] These studies require replication with larger samples and prospective methodology before the technique can become a recommended criterion. The thioflavin derivative IMPY (6-iodo-2-(4′-dimethylamino-) phenyl-imidazo[1,2-a]pyridine), which targets amyloid plaques for in vivo imaging in SPECT has not yet been investigated in living patients with either AD or mild cognitive impairment, but this ligand might help measure amyloid plaque burden in the future, thus providing an additional new approach and usefulness for functional imaging.[137]

Familial genetic mutations (E)

Three autosomal dominant mutations that cause AD have been identified on chromosomes 21 (amyloid precursor protein), 14 (presenilin 1), and 1 (presenilin 2).[138] The presence of a proband with genetic-testing evidence of one of these mutations can be considered as strongly supportive for the diagnosis of AD for affected individuals within the immediate family who did not themselves have a genetic test for this mutation. If individuals with a positive mutation history of the described type present with the core amnestic criterion A, they will be considered to meet criteria for AD within the revised diagnostic framework. The gold standard for definite diagnosis of AD in this setting would of course be genetic testing and verification of a genetic mutation in these individuals.

Exclusion criteria

Probable AD diagnosis cannot be established if the illness begins with a sudden onset, has focal neurological findings including hemiparesis, sensory loss, visual field deficits, or where there are seizures, gait disturbances, or extrapyramidal signs at the onset or very early in the course of the illness. Other medical, neurological, or psychiatric disorders that could otherwise account for the deterioration in memory and related symptoms must be excluded. The diagnosis should be questioned in case of the following red flags: early behavioural disturbances (particularly disinhibition, euphoria, or psychosis), early extrapyramidal symptoms, early visual hallucinations, early visuospatial impairment, marked fluctuations in cognition and REM sleep behavioural disorders. The presence of cerebrovascular lesions, particularly white-matter lesions and lacunar infarctions both symptomatic and asymptomatic, are common with ageing. To establish probable AD, cerebrovascular disease that is sufficiently severe to account for the cognitive and functional deficits must be excluded. Probable AD cannot be diagnosed if the symptom profile suggestive of dementia with Lewy bodies (pronounced fluctuations in attention and cognition, recurrent prominent visual hallucinations, and motor parkinsonism) or if any other non-AD dementia is present. The presence of a delirium or toxic metabolic cause for the cognitive disorder precludes a diagnosis of probable AD (at least until the delirium has cleared) as does an unexplained altered state of consciousness.

Discussion

This working group has identified, by consensus, that new research criteria are timely, realistic, and feasible. Our proposed AD diagnostic framework (panel 2)[139] is anchored around a core clinical phenotype supported by brain-structure abnormalities, molecular imaging impairment, biochemical changes, or genetic mutations associated with AD. The timeliness of these criteria is underscored by the many drugs in development that are directed at changing the disease pathogenesis through amyloid immunotherapy, gamma or beta secretase inhibitors and modulators, alpha secretase activators, tau kinase inhibitors, and nerve growth factors. Further new approaches directed at tau and tangles are foreseen. There is a neurobiological imperative to identify AD before the point of disease where irreversible pathological injury would prevent effective intervention.[140] The proposed criteria should allow an earlier and more specific AD diagnosis than their predecessor, the NINCDS–ADRDA criteria.

These proposed criteria move away from the traditional two-step approach of first identifying dementia according to degree of functional disability, and then specifying its cause. Rather, they aim to define the clinical, biochemical, structural, and metabolic presence of AD. The cornerstone clinical criterion A specifies that there is an episodic memory deficit within test conditions of encoding specificity. This criterion should allow 86–94% of cases to be included.[28,29] Beyond this core criterion, the presence of at least one biological footprint of the disease, either by criterion B (structural imaging), criterion C (cerebrospinal fluid), criterion D (molecular imaging), or criterion E (dominant mutation within the immediate family) is also needed to establish a positive diagnosis. The requirement, for diagnosis, of a clinical phenotype in combination with any one of the supportive features currently represents the most balanced approach because the clinical phenotype of AD is better known than its biological phenotype. We have no empirical basis at this

time for assigning different weightings to the supportive features or recommending combinations of features or, alternatively, requiring the presence of all. However, as new evidence accrues on biological markers for AD, especially those detecting AD-pathology specific markers such as amyloid imaging, the weighting of the supportive features may change. Other combinations may prove to have greater diagnostic accuracy or new features may be introduced. This will evolve as data sets gathered with all modalities are assessed.

We recognise that these criteria represent a cultural shift requiring more biologically focused work-up than previous approaches; however, this seems to be the best way to integrate the profound advances into the clinical arena. When effective disease-modifying medications are available, the argument for such biologically based studies will be even more compelling. Some research needs will be better addressed with a more stringent approach requiring that each diagnostic criterion be met. For example, proof-of-principle studies may benefit from the most highly selected AD study samples where the presence of all supportive features might be specified. This could maximise specificity for AD, but impose a substantial loss of sensitivity that would need to be re-addressed in later stages of development.

There are important differential diagnostic challenges that can be anticipated with the application of the proposed criteria. Of primary concern are non-AD amnestic disorders that can be associated with MTL damage including bilateral ischaemic injury, hippocampal sclerosis, limbic encephalitis, and temporal lobe epilepsy. Non-AD neurodegenerative disorders including tangle-only pathological changes and argyrophilic grain disease may also involve the MTL and limbic system.[42] Depression can present with episodic memory impairment and MRI changes in hippocampal volume.[141] These disorders could potentially satisfy criteria A and B, and in turn, where possible, must be ruled out in each instance. Careful clinical assessment with the use of specific memory tests, careful attention to T2 signal abnormalities within the MTL, and other investigations as clinically indicated will be called for to establish the AD diagnosis. We also cannot exclude that the non-AD dementias including frontotemporal lobar degeneration, vascular dementia, and dementia with Lewy bodies may in some cases have the core clinical amnestic presentation specified in this framework. These non-AD dementias may also have positive molecular imaging or cerebrospinal fluid findings as has been shown in the reviewed evidence. If a non-AD cause is suspected, it must be ruled out carefully on a case-by-case basis by applying in parallel the diagnostic criteria for the other disorders.

We have specifically not addressed the issue of mixed disease for two reasons. First, in many instances mixed stands for comorbid disease being present but not being the principal cause of the dementia syndrome. As such, nothing has changed over current practice. Second, by narrowing the definition to a strict memory presentation with additional evidence for underlying AD pathological change, the chance of a patient fulfilling more than one set of criteria, as was the case with the NINCDS–ADRDA criteria, has actually been reduced. Even when a patient has abundant white-matter changes on MRI, thought to be of vascular origin, the presence of criterion A and the absence of overt dementia in the sense of the NINDS–AIREN criteria (ie, involvement of other cognitive domains), renders the patient more likely to have AD (with concomitant vascular disease) than vascular dementia. The MRI changes may still be used to guide therapy towards secondary prevention.

Moreover, the proposed criteria depict typical AD. There are also atypical forms of neuropathologically confirmed AD.[28,29] These forms clearly deviate from the described amnestic presentation and include focal cortical syndromes, particularly posterior cortical degeneration where there is visual or visuospatial impairment, or frontal forms with prominent behavioural symptoms. The non-memory clinical phenotype might be influenced by the apolipoprotein genotype.[142] Estimates of the relative prevalence of these atypical presentations have ranged from 6% to 14%.[28,29] These presentations will still clearly elude diagnosis according to the revised criteria as they did in the NINCDS–ADRDA criteria. Their inclusion in research protocols remains too uncertain to be made with sufficient reliability and for this reason we have excluded them from the present diagnostic framework.

The strength of these proposed research criteria is the introduction of neurobiological measures on to the clinically based criteria. There are, however, many limitations and steps still needed. In their current formulation, these proposed diagnostic criteria still require decisions around how they are to be put into practice. For example, for the core criterion of significant episodic memory impairment, we have identified the memory test paradigms that can distinguish AD-associated deficits from other memory difficulties, but we have not defined a magnitude of deficit or the comparative norms that should be used. In structural imaging, we have not presented a specific best test or method for MTL atrophy. There remains uncertainty as to the most effective method of assessment, qualitative or quantitative, and for the latter, the specific region within the MTL for measurement. There is no specification of the amount of atrophy that is optimally diagnostic of AD. Within molecular neuroimaging, there are similar open questions with regard to which regions are optimally diagnostic, whether a qualitative versus quantitative approach should be taken, and what degree of hypometabolism is diagnostic. Finally, we have not specified which cerebrospinal fluid marker or combination of markers should be used to support a positive diagnosis. Concentrations of cerebrospinal fluid

markers vary substantially with different assays but also with the same assay done in different centres,[110] raising important questions about measurements and sources of error. Although most of these questions will receive empirical answers in the future, this will not entirely resolve an issue that is also philosophical, around whether an approach primarily based on applied clinical judgment or one based on fully operational definitions will work better for the research diagnosis of AD. At this point we favour the former approach of clinical judgment being applied to the determination of each criterion.

Validation studies of the proposed diagnostic criteria will clearly be needed because, inherent in this new definition of AD is the assumption that they indicate the presence of the neurodegenerative process of AD, including those cases presenting very early in the course of the disease. Their validity will need to be established for different types of discrimination and at different time points in the disease course, including discrimination of early AD from normal ageing, and AD from non-AD dementias. Two major strategies can be used for the validation of the proposed criteria. First, the criteria can be applied retrospectively to existing cohorts that have detailed investigations including neuropsychology, MRI, cerebrospinal fluid analysis, and PET. The current large cohort studies of the European Alzheimer Disease Consortium (EADC), the Alzheimer Disease Cooperative Study (ADCS), the Alzheimer Disease Neuroimaging Initiative (ADNI), and other ongoing studies[88,143] will provide ideal sources within which to validate the diagnostic criteria of probable AD. Because these are all multicentre studies, they will also allow the assessment of measurement reliability across centres as a step towards standardising measurements and putting our proposed criteria into practice. Second, new prospective cohorts should be acquired that are followed to post-mortem. This prospective validation approach will need to focus on non-demented individuals with and without cognitive complaints. At their initial study visit, individuals should be assessed in parallel with the newly proposed criteria for AD and with the criteria for mild cognitive impairment. In subsequent visits, the stability of the diagnosis under these proposed criteria should be determined. In addition, the standard NINCDS–ADRDA criteria for AD should be applied. The first validation measure will be the sensitivity and specificity of our proposed criteria, obtained at baseline, for predicting cognitive decline as well as eventually meeting the existing AD criteria. In addition, the present criteria should be compared with the NINCDS–ADRDA criteria to verify whether we achieve the goal of increasing the specificity for diagnosis. Ultimately, the sensitivity and specificity for the pathological diagnosis of AD and other dementias will need to be assessed. In all future studies using these criteria, the supportive features used and the number of patients that have a positive MRI, or cerebrospinal fluid test, or PET or SPECT should be specified. Validation studies will necessarily begin with selected samples—for example those accrued in the ADCS, EADC, and ADNI—but validation will eventually need to be extended to unselected heterogeneous community samples. The most informative studies are those that will use the four criteria on patients at different stages of the disease, including the prodromal stage, with a long-term follow-up including post-mortem examination.

We recognise that the proposed research criteria require significant expertise, technical skills, and financial resources to allow the comprehensive assessment of MRI, PET, and cerebrospinal fluid. MRI will be contraindicated in some patients or not easily available in some countries, as may be the case for cerebrospinal fluid biomarkers or molecular neuroimaging with PET or SPECT. The multidisciplinary approach that is required for our diagnostic framework may not yet be feasible in all memory clinics and certainly not in most epidemiological studies. The validation studies being proposed will need to take place within highly specialised AD centres, and if successful, the research criteria will need to be adapted for use in standard clinical settings. We foresee that technically less demanding criteria for clinical settings might develop from the more technically challenging research criteria once these are validated.

Finally, these proposed criteria acknowledge the progress that has been made in the past two decades in refining our understanding of the neurobiology and clinical phenomenology of AD. Their usefulness will be determined in the future as investigators apply the criteria in a variety of research studies and as key issues in their application are resolved.

Contributors

Each of the authors has contributed to the writing and the revision of the paper and has approved the final version. In addition, most of the authors (16 out of 19) participated in the Florence meeting (June 2005) and in the related discussions about the revised criteria.

Conflicts of interest

We have no conflicts of interest.

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NEUROLOGY

The FAB: A frontal assessment battery at bedside

B. Dubois, A. Slachevsky, I. Litvan and B. Pillon

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The FAB

A frontal assessment battery at bedside

B. Dubois, MD; A. Slachevsky, MD; I. Litvan, MD; and B. Pillon, PhD

Article abstract—*Objective:* To devise a short bedside cognitive and behavioral battery to assess frontal lobe functions. *Methods:* The designed battery consists of six subtests exploring the following: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. It takes approximately 10 minutes to administer. The authors studied 42 normal subjects and 121 patients with various degrees of frontal lobe dysfunction (PD, n = 24; multiple system atrophy, n = 6; corticobasal degeneration, n = 21; progressive supranuclear palsy, n = 47; frontotemporal dementia, n = 23). *Results:* The Frontal Assessment Battery scores correlated with the Mattis Dementia Rating Scale scores (rho = 0.82, $p < 0.01$) and with the number of criteria (rho = 0.77, $p < 0.01$) and perseverative errors (rho = 0.68, $p < 0.01$) of the Wisconsin Card Sorting Test. These variables accounted for 79% of the variance in a stepwise multiple regression, whereas age or Mini-Mental State Examination scores had no significant influence. There was good interrater reliability ($\kappa = 0.87$, $p < 0.001$), internal consistency (Cronbach's coefficient alpha = 0.78), and discriminant validity (89.1% of cases correctly identified in a discriminant analysis of patients and controls). *Conclusion:* The Frontal Assessment Battery is easy to administer at bedside and is sensitive to frontal lobe dysfunction.

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Assessing frontal lobe function and thus being able to identify a dysexecutive syndrome are helpful for the diagnosis and prognosis of brain diseases such as frontotemporal dementias[1] and for evaluation of the severity of brain injuries. It can also help to identify vascular dementias[2] and parkinsonian disorders, particularly progressive supranuclear palsy (PSP), in which the presence of frontal lobe dysfunction supports the diagnosis.[3] It may also be useful for differentiating between degenerative disorders involving subcortical structures and for evaluating the progression of these disorders over time.[4]

The functions of the frontal lobes are difficult to assess clinically. There is no test that reliably identifies a dysexecutive syndrome.[5] In practice, extensive neuropsychological batteries are needed to assess the frontal lobe processes.[6,7] Given the modular functional organization of the frontal lobes,[8,9] searching for a possible dysexecutive syndrome requires time-consuming tests exploring functions associated with different frontal areas. Therefore, there is a need for a brief tool exploring different domains of executive function that are impaired in several neurologic diseases.

We devised a bedside battery to assess the presence and severity of a dysexecutive syndrome affecting both cognition and motor behavior, and to evaluate it for 1) content and concurrent validity, 2) discriminant validity, comparing normal controls and patients with various degrees of executive dysfunction, and 3) interrater reliability.

Methods. *Description of the Frontal Assessment Battery (FAB).* According to current theories, the frontal lobes control conceptualization and abstract reasoning, mental flexibility, motor programming and executive control of action, resistance to interference, self-regulation, inhibitory control, and environmental autonomy.[6,10-14] Each of these processes is needed for elaborating appropriate goal-directed behaviors and for adapting the subject's response to new or challenging situations—functions that are mediated by the prefrontal cortex. For that reason, the designed battery consists of six subtests, each exploring one of the aforementioned functions related to the frontal lobes. Moreover, these subtests were chosen because the score of each of them significantly correlated with frontal metabolism, as measured in terms of the regional distribution of 18-fluorodeoxyglucose in a PET study of patients with frontal lobe damage of various etiologies.[9] The processes studied and the corresponding subtests of the FAB are presented below. The content, instructions and scoring of each subtest are provided in the Appendix. The total scores are calculated by adding the notes of the six subtests. The overall duration of the battery is approximately 10 minutes.

1. Conceptualization: Abstract reasoning is impaired in frontal lobe lesions.[11] This function is currently investi-

See also pages 1601, 1609, and 1613

From INSERM EPI 007 and Fédération de Neurologie (Drs. Dubois, Slachevsky, and Pillon), Hôpital de la Salpêtrière, Paris, France; and Cognitive Neuropharmacology Unit (Dr. Litvan), Henry M. Jackson Foundation, Bethesda, MD.

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Address correspondence and reprint requests to Dr. Bruno Dubois, Fédération de Neurologie, Hôpital de la Salpêtrière, 47 Boulevard de l'Hôpital, 75651 Paris cedex 13, France; e-mail: b.dubois@psl.ap-hop-paris.fr

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Table *Study group characteristics*

Population	n	Age, y	MMSE	Mattis DRS	FAB
Controls	42	58.0 ± 14.4[a]	28.9 ± 0.8[a]	141 ± 2.4[a]	17.3 ± 0.8[a]
Patients	121	64.4 ± 9.3[a]	25.5 ± 4.8[a]	118.0 ± 19.1[a]	10.3 ± 4.7[a]
PD	24	59.4 ± 12.9[c,g]	28.0 ± 1.9[i,j]	134.0 ± 15.2[c,g,i]	15.9 ± 3.8[c,g,i]
MSA	6	65.0 ± 10.5	25.7 ± 3.9[j]	127.0 ± 16.2[e]	13.5 ± 4.0[e,f]
CBD	21	67.4 ± 8.1[b,c]	26.4 ± 3.8[b]	123.7 ± 15.0[b,c]	11.0 ± 3.7[b,c,d]
PSP	47	66.9 ± 7.0[g,h]	26.2 ± 3.7[h]	117.7 ± 15.2[g,h]	8.5 ± 3.4[d,f,g]
FTD	23	60.3 ± 8.5[b,h]	20.7 ± 6.3[b,h,i]	101.5 ± 20.0[b,e,h,i]	7.7 ± 4.2[b,e,i]

Values are presented as mean ± SD. Significantly different at $p < 0.05$ for: [a]controls and patients; [b]frontotemporal dementia (FTD) and corticobasal degeneration (CBD) patients; [c]PD and CBD patients; [d]progressive supranuclear palsy (PSP) and CBD patients; [e]FTD and multiple system atrophy (MSA) patients; [f]PSP and MSA patients; [g]PD and PSP patients; [h]FTD and PSP patients; [i]PD and FTD patients; [j]PD and MSA patients.

MMSE = Mini-Mental State Examination; DRS = Dementia Rating Scale; FAB = Frontal Assessment Battery.

gated by card-sorting tasks, proverb interpretation, or similarities.[15] The last task is easier for bedside assessment and scoring. Subjects have to conceptualize the links between two objects from the same category (e.g., an apple and a banana). Patients with frontal lobe dysfunction may be unable to establish an abstract link between the items (i.e., fruit), adhering to the concrete aspects of objects (i.e., both are yellow), or may be unable to establish a link of similarity (i.e., one is round but the other is elongated).

2. Mental flexibility: Patients with frontal lobe lesions are specifically disturbed in nonroutine situations in which self-organized cognitive strategies have to be built up.[16,17] Literal fluency tasks are unusual, require self-organized retrieval from semantic memory, and are easy to score. Frontal lesions, regardless of side, tend to decrease verbal fluency, with left frontal lesions resulting in lower word production than right frontal lesions.[18] In this task, subjects need to recall as many words as they can beginning with a given letter in a 1-minute trial.
3. Motor programming: Patients with frontal lobe lesions are also impaired in tasks requiring temporal organization, maintenance, and execution of successive actions.[12,13,19] In Luria's motor series, such as "fist–palm–edge," less severely impaired patients are unable to execute the series in correct order, whereas the most severely affected are unable to learn the series. Simplification of the task (two gestures instead of three) and perseveration (inappropriate repetition of the same gestures) may be observed.

   Sensitivity to interference: Deficits in behavioral self-regulation may be observed in tasks in which verbal commands conflict with sensory information. This occurs in the Stroop test, in which the subject must name the colors of words while inhibiting the natural tendency to read the words. This also occurs in the case of conflicting instructions, in which subjects must provide an opposite response to the examiner's alternating signal, e.g., tapping once when the examiner taps twice. Thus, subjects should obey verbal commands and refrain following what they see.[20] Patients with a frontal lobe lesion usually fail to obey the verbal command and tend to execute echopractic movements, imitating the examiner.[14]

   Inhibitory control: Withholding a response may be difficult for patients with damage to the ventral part of the frontal lobes.[21] In tasks anticipated to elicit a false-alarm motor response, these patients are often unable to inhibit inappropriate responses.[22] This difficulty in controlling impulsiveness can be assessed with the go–no go paradigm,[23] in which the subjects must inhibit a response that was previously given to the same stimulus, e.g., not tapping when the examiner taps twice.

   Environmental autonomy: Patients with frontal lobe lesions are excessively dependent on environmental cues.[24] Sensory stimuli can activate patterns of responses that are normally inhibited in normal controls. For example, the patient conceives the sight of a movement as an order to imitate (imitation behavior); the sight of an object implies the order to use it (utilization behavior); and the sight or sensory perception of the examiner's hands compels the patient to take them (prehension behavior). In some cases, the patients can elicit these behaviors even if they have been explicitly told not to do so. These abnormal behaviors (the spontaneous tendency to adhere to the environment) express the lack of inhibition normally exerted by the prefrontal cortex on the activation of patterns of behavior triggered by sensory stimulations.

Subjects. Subjects gave informed written consent to participate. Forty-two normal control subjects (mean ± SD; age, 58 ± 14.4 years), without any neurologic or psychiatric history, were included (table). All control subjects had a Mattis Dementia Rating Scale (DRS)[25] score >136 or a Mini-Mental State Examination (MMSE)[26] score >27.

To evaluate the discriminative power of the FAB, 121 patients with mild (PD, n = 24; multiple system atrophy [MSA], n = 6), moderate (corticobasal degeneration [CBD], n = 21), or severe (frontotemporal dementia [FTD], n = 23; progressive supranuclear palsy [PSP], n = 47) frontal lobe dysfunction[27,28] were included (see table). All patients underwent an extensive clinical evaluation to confirm their diagnosis and all met currently accepted diagnostic criteria. The diagnostic criteria for PD were based on the pres-

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ence of a parkinsonian syndrome with unilateral onset characterized by a resting tremor or an akinetorigid syndrome, a good response to levodopa that persisted at the time of evaluation, and the absence of exclusion criteria (e.g., supranuclear gaze palsy).[29,30] The diagnostic criteria for MSA included the presence of an extrapyramidal syndrome poorly responsive to levodopa, associated with an autonomic or urinary dysfunction in the absence of exclusion criteria.[31] The diagnostic criteria for CBD included a slowly progressive asymmetric akinetorigid syndrome and one or more of the following signs of cortical involvement: ideomotor apraxia, myoclonus, cortical sensory deficit, or alien limb syndrome.[32] The criteria for PSP included the presence of a gradually progressive disorder with an age at onset of 40 years or later; a supranuclear limitation of vertical gaze; a prominent postural instability, with falls occurring in the first year of symptom onset; and no evidence of another disease that could explain the symptoms; in the absence of exclusion criteria.[33] The diagnosis of FTD was based on a progressive onset of behavioral changes fulfilling the Lund and Manchester criteria,[1] a severe dysexecutive syndrome on neuropsychological evaluation, and the absence of any other neurologic disorder sufficient to explain the frontotemporal cortical deficit.[1] The neuropsychological evaluation of patients consisted of the MMSE[26] and Mattis DRS for all patients,[25] and the Wisconsin Card Sorting Test (CST)[34] for 86 patients. The MMSE ranges were 30 to 24 for patients with PD, 30 to 21 for patients with MSA, 30 to 13 for patients with CBD, 30 to 17 for patients with PSP, and 30 to 6 for patients with FTD.

Technical properties of the battery. Validation. *Concurrent validity.* The validity of the FAB, i.e. how well the battery evaluates the existence of a frontal lobe syndrome,[35] was analyzed by correlating the FAB total score with the patient's performance on 1) the Wisconsin CST, a test considered to be sensitive to executive dysfunction[36]; and 2) the Mattis DRS, a global scale reported to be correlated with the degree of executive dysfunction in neurodegenerative diseases.[4,25] For the Wisconsin CST, the number of criteria achieved and the number of perseverative errors were considered because both have been shown to be sensitive to frontal lobe dysfunction.[34] We performed a correlational validity study because there is no "gold standard" that determines the existence and severity of a frontal lobe syndrome.[35]

Discriminant validity. We determined the ability of the FAB to discriminate between normal control subjects and patients with cognitive impairment according to the Mattis DRS scale. Patients without cognitive impairment were excluded for this analysis. Only 95 patients with a Mattis DRS score below 136 were included.

The ability of the FAB to differentiate the frontal dysfunction of patients with cortical and subcortical lesions was studied by using a stepwise discriminant analysis in two groups of patients with frontal lobe dysfunction of different origins—subcortical (47 patients with PSP) and cortical (23 patients with FTD).

Reliability. Interrater reliability was determined by comparing the scores of two independent raters who were present during the administration of the FAB by one of them. Each rater was blind to the ratings made by the other. Interrater reliability was conducted in 17 patients and determined by calculating the kappa value.

We studied the internal consistency of the battery, i.e., the extent to which the six items of the FAB reflect the same underlying construct, by calculating the Cronbach's coefficient of alpha.[37]

Results. *Technical properties of the battery.* Validation. *Concurrent validity.* A correlation was found between the FAB scores and the Mattis DRS performance in 121 patients ($r = 0.82$, $p < 0.001$). Similarly, the FAB scores correlated with the number of criteria ($r = 0.77$, $p < 0.001$) and perseverative errors (rho = 0.68, $p < 0.001$) achieved in the Wisconsin CST. A stepwise multiple regression was used to evaluate the influence on the FAB performance of the following independent variables: age of patient, MMSE and Mattis DRS scores, and the number of criteria and perseverative errors in the Wisconsin CST. The Mattis DRS score and number of criteria achieved in the Wisconsin CST accounted for 79% of variance in the FAB ($F[2,82] = 152.9$; $p < 0.001$; $r^2 = 0.79$). Interestingly, age and MMSE scores had no significant influence.

Discriminant validity. The FAB discriminated between controls and patients after adjusting for age as a covariate (analysis of covariance: $F[1,131] = 17.24$; $p < 0.001$). The performance on the FAB correctly identified 89.1% of the cases (Wilke's lambda = 0.43, $F[1,135] = 176.2$; $p < 0.001$). A stepwise discriminant analysis in patients with FTD and PSP using the six FAB subscores as independent variables showed that similarities and prehension behavior correctly classified 69.7% of the patients (Wilke's lambda = 0.865; χ^2 [ddl = 2] = 10.6; $p = 0.005$).

Reliability. Two raters independently evaluating a subset of 17 patients with the FAB achieved an optimal interrater reliability ($\kappa = 0.87$, $p < 0.001$). The Cronbach's coefficient alpha between the items of the FAB of 121 patients was 0.78, suggesting good internal consistency.

Discussion. In order to provide a simple tool for assessing frontal lobe function that could be applied by any practitioner, we designed a short assessment battery, the FAB, based on our experience with focal frontal lobe lesions[24] and movement disorders associated with striatofrontal dysfunction.[4] Other tools have already been designed to evaluate frontal lobe function at the bedside.[38-41] A brief assessment of frontal and subcortical functions was proposed for patients with suspected subcortical pathology, but patients with AD scored significantly lower on this scale than those with Huntington's disease or PD.[38] The EXIT 25, an executive interview, correlates not only with tests sensitive to frontal lobe dysfunction but also with the MMSE ($r = -0.85$). This suggests that the EXIT 25 is also sensitive to functions that are not executive.[39] Another brief tool sensitive to executive control, the CLOX (a clock drawing test),[40] has been proposed, but only investigates one domain of cognitive function: drawing. Lastly, Ettlin and Kischka[41] proposed the "frontal lobe score," which is, however, not convenient for bedside assessment because it includes tasks such as the Trail-Making Test and takes up to 40 minutes to complete. The FAB is an easy test to administer, requires less than 10 minutes to complete, and is well accepted by patients. The six FAB subtests explore both cognitive

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and behavioral domains under the control of the frontal lobes, each of them having been shown to be significantly correlated with frontal lobe metabolic activity measured by 18-fluorodeoxyglucose using PET scan.[9] Moreover, each subtest is associated with specific areas of the frontal lobes on the basis of neuropsychological, electrophysiologic, and functional arguments: conceptualization with dorsolateral areas,[42,43] word generation with medial areas,[44,45] and inhibitory control with orbital or medial frontal areas.[46,47] Therefore, performance on the six subtests of the FAB can give a composite global score, which evaluates the severity of the dysexecutive syndrome and may suggest a descriptive pattern of executive dysfunction in a given patient.

The FAB presents good metric properties. The study demonstrated good internal consistency (Cronbach's alpha was 0.78),[37] optimal interrater reliability ($\kappa = 0.87$), and concurrent validity. Indeed, the FAB score was strongly associated with the performance of patients on the Mattis DRS (rho = 0.82) and Wisconsin CST (rho = 0.77 for the number of criteria), both of which evaluate different cognitive functions under frontal lobe control. These functions include initiation, conceptualization, and attention for the Mattis DRS scale[25] and conceptualization and cognitive flexibility for the Wisconsin CST. Several recent studies have demonstrated that performance in the Wisconsin CST is related to functional activity in the prefrontal cortex.[42,48-50] In contrast, the FAB score is correlated neither with the MMSE score, a measure of more general cognitive function, nor with age (see the results of the stepwise multiple regression). The battery also presents good discriminant validity, allowing differentiation to be made between control subjects and patients with frontal or subcorticofrontal cognitive impairment. However, the FAB global score does not allow discrimination between patients with predominantly subcortical (PSP) or cortical (FTD) dysfunction. Only two subtests discriminated between these patients to some extent—prehension behavior (more severely impaired in patients with PSP) and similarities (more severely impaired in patients with FTD). This result is not unexpected because patients with frontal and subcorticofrontal lesions usually present similar cognitive deficits and share only subtle neuropsychological differences.[51-53]

Some points should be stressed, however. Test–retest reliability was not assessed. The anatomic correlation of the different subtests of the battery was derived from data obtained with similar tests, but not from the subtests themselves. Finally, although highly significant correlations were shown between the FAB and tests sensitive to frontal lobe functions, but not between the FAB and MMSE, it would be necessary to demonstrate that patients with non–frontal lobe injuries perform at a higher level than that observed for patients with frontal lobe injuries, to definitively consider the FAB as a measure of frontal lobe dysfunction.

Appendix

Content, instructions, and scoring of the FAB

1. Similarities (conceptualization)

"In what way are they alike?"

A banana and an orange (In the event of total failure: "they are not alike" or partial failure: "both have peel," help the patient by saying: "both a banana and an orange are..."; but credit 0 for the item; do not help the patient for the two following items)

A table and a chair

A tulip, a rose and a daisy

Score (only category responses [fruits, furniture, flowers] are considered correct)

Three correct: 3

Two correct: 2

One correct: 1

None correct: 0

2. Lexical fluency (mental flexibility)

"Say as many words as you can beginning with the letter 'S,' any words except surnames or proper nouns."

If the patient gives no response during the first 5 seconds, say: "for instance, snake." If the patient pauses 10 seconds, stimulate him by saying: "any word beginning with the letter 'S.' The time allowed is 60 seconds.

Score (word repetitions or variations [shoe, shoemaker], surnames, or proper nouns are not counted as correct responses)

More than nine words: 3

Six to nine words: 2

Three to five words: 1

Less than three words: 0

3. Motor series (programming)

"Look carefully at what I'm doing."

The examiner, seated in front of the patient, performs alone three times with his left hand the series of Luria "fist–edge–palm." "Now, with your right hand do the same series, first with me, then alone." The examiner performs the series three times with the patient, then says to him/her: "Now, do it on your own."

Score

Patient performs six correct consecutive series alone: 3

Patient performs at least three correct consecutive series alone: 2

Patient fails alone, but performs three correct consecutive series with the examiner: 1

Patient cannot perform three correct consecutive series even with the examiner: 0

4. Conflicting instructions (sensitivity to interference)

"Tap twice when I tap once."

To be sure that the patient has understood the instruction, a series of three trials is run: 1-1-1. "Tap once when I tap twice." To be sure that the patient has understood the instruction, a series of three trials is run: 2-2-2. The examiner performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score

No error: 3

One or two errors: 2

More than two errors: 1

Patient taps like the examiner at least four consecutive times: 0

5. Go–No Go (inhibitory control)

"Tap once when I tap once."

To be sure that the patient has understood the instruction, a series of three trials is run: 1-1-1. "Do not tap when I tap twice." To be sure that the patient has understood the instruction, a series of three trials is run: 2-2-2. The examiner performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score

No error: 3

One or two errors: 2

More than two errors: 1

Patient taps like the examiner at least four consecutive times: 0

6. Prehension behavior (environmental autonomy)

"Do not take my hands."

The examiner is seated in front of the patient. Place the patient's hands palm up on his/her knees. Without saying anything or looking at the patient, the examiner brings his/her hands close to the patient's hands and touches the palms of both the patient's hands, to see if he/she will spontaneously take them. If the patient takes the hands, the examiner will try again after asking him/her: "Now, do not take my hands."

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Score

Patient does not take the examiner's hands: 3

Patient hesitates and asks what he/she has to do: 2

Patient takes the hands without hesitation: 1

Patient takes the examiner's hand even after he/she has been told not to do so: 0

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Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease

G. Fein, PhD; V. Di Sclafani, MPH; J. Tanabe, MD; V. Cardenas, PhD; M.W. Weiner, MD; W.J. Jagust, MD; B.R. Reed, PhD; D. Norman, MD; N. Schuff, PhD; L. Kusdra; T. Greenfield; and H. Chui, MD

Article abstract—*Background:* The cause of dementia in subcortical ischemic vascular disease (SIVD) is controversial. *Objectives:* To determine whether cognitive impairment in SIVD 1) correlates with measures of ischemic brain injury or brain atrophy, and/or 2) is due to concomitant AD. *Methods:* Volumetric MRI of the brain was performed in 1) elderly subjects with lacunes (L) and a spectrum of cognitive impairment—normal cognition (NC+L, n = 32), mild cognitive impairment (CI+L, n = 26), and dementia (D+L, n = 29); 2) a comparison group with probable AD (n = 28); and 3) a control group with normal cognition and no lacunes (NC). The authors examined the relationship between the severity of cognitive impairment and 1) volume, number, and location of lacunes; 2) volume of white matter signal hyperintensities (WMSH); and 3) measures of brain atrophy (i.e., hippocampal, cortical gray matter, and CSF volumes). *Results:* Among the three lacune groups, severity of cognitive impairment correlated with atrophy of the hippocampus and cortical gray matter, but not with any lacune measure. Although hippocampal atrophy was the best predictor of severity of cognitive impairment, there was evidence for a second, partially independent, atrophic process associated with ventricular dilation, cortical gray matter atrophy, and increase in WMSH. Eight autopsied SIVD cases showed variable severity of ischemic and neurofibrillary degeneration in the hippocampus, but no significant AD pathology in neocortex. The probable AD group gave evidence of only one atrophic process, reflected in the severity of hippocampal atrophy. Comparison of regional neocortical gray matter volumes showed sparing of the primary motor and visual cortices in the probable AD group, but relatively uniform atrophy in the D+L group. *Conclusions:* Dementia in SIVD, as in AD, correlates best with hippocampal and cortical atrophy, rather than any measure of lacunes. In SIVD, unlike AD, there is evidence for partial independence between these two atrophic processes. Hippocampal atrophy may result from a mixture of ischemic and degenerative pathologies. The cause of diffuse cortical atrophy is not known, but may be partially indexed by the severity of WMSH.

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Subcortical ischemic vascular disease (SIVD) is characterized by lacunar infarcts and deep white matter changes. The proportion of vascular dementia (VaD) attributed to SIVD ranges from 36 to 50%, with higher rates noted among African Americans[1] and Asian Americans[2] than whites.[3,4] A few studies report risk of dementia to be higher among subjects with lacunar infarcts versus other subtypes of stroke,[4] and among patients with AD with concomitant lacunar versus large-artery infarcts.[5] Thus, SIVD is an important subtype of VaD either alone or in combination with AD.

From Neurobehavioral Research, Inc. (Dr. Fein and V. Di Sclafani); Psychiatry Research (Dr. Cardenas) and Magnetic Resonance Unit (Drs. Tanabe, Weiner, and Schuff, and L. Kusdra and T. Greenfield), Department of Veterans Affairs Medical Center; the Departments of Radiology (Drs. Tanabe, Cardenas, Weiner, Norman, and Schuff) and Psychiatry (Dr. Weiner), University of California, San Francisco; the Center for Functional Imaging (Dr. Jagust), Lawrence Berkeley Laboratory, the Department of Neurology (Drs. Jagust and Reed), University of California, Davis; and the Department of Neurology (Dr. Chui), University of Southern California, Los Angeles.

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Address correspondence and reprint requests to Dr. Helena Chui, Geriatric Neurobehavior and Alzheimer Center, 800 Annex West, 7601 East Imperial Highway, Downey, CA 90242; e-mail: chui@hsc.usc.edu

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The FAB: A frontal assessment battery at bedside
B. Dubois, A. Slachevsky, I. Litvan and B. Pillon
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Global prevalence of dementia: a Delphi consensus study

Cleusa P Ferri, Martin Prince, Carol Brayne, Henry Brodaty, Laura Fratiglioni, Mary Ganguli, Kathleen Hall, Kazuo Hasegawa, Hugh Hendrie, Yueqin Huang, Anthony Jorm, Colin Mathers, Paulo R Menezes, Elizabeth Rimmer, Marcia Scazufca, for Alzheimer's Disease International

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Alzheimer's Disease International, London, UK (E Rimmer MA); Section of Epidemiology, Institute of Psychiatry, King's College, London, UK (C P Ferri PhD; Prof M Prince MD); Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK (Prof C Brayne PhD); University of New South Wales, Sydney, Australia (Prof H Brodaty MD); NEUROTEC- Karolinska Institute, Sweden (Prof L Fratiglioni PhD); Departments of Psychiatry and Epidemiology, School of Medicine and Graduate School of Public Health, University of Pittsburgh, Pittsburgh PA, USA (Prof M Ganguli MD); Center for Aging Research, Indiana University School of Medicine, IN, USA (K Hall PhD; Prof H Hendrie DSc); St Marianna University School of Medicine, Kanagawa, Japan (K Hasegawa MD); Institute of Mental Health, Peking University, Beijing, China (Prof Y Huang PhD); Department of Psychiatry, University of Melbourne, Melbourne, Australia (Prof A Jorm DSc); Measurement and Health Information, Evidence and Information for Policy, World Health Organization (C Mathers PhD); Department of Preventive Medicine, University of São Paulo, Brazil (P R Menezes PhD); and Department of Psychiatry, University of São Paulo, Brazil (M Scazufca PhD).

Correspondence to: Cleusa P Ferri, Section of Epidemiology, PO Box 060, De Crespigny Park, London SE5 8AF, UK c.ferri@iop.kcl.ac.uk

For more information about Alzheimer's Disease International see http://www.alz.co.uk

Summary

Background 100 years after the first description, Alzheimer's disease is one of the most disabling and burdensome health conditions worldwide. We used the Delphi consensus method to determine dementia prevalence for each world region.

Methods 12 international experts were provided with a systematic review of published studies on dementia and were asked to provide prevalence estimates for every WHO world region, for men and women combined, in 5-year age bands from 60 to 84 years, and for those aged 85 years and older. UN population estimates and projections were used to estimate numbers of people with dementia in 2001, 2020, and 2040. We estimated incidence rates from prevalence, remission, and mortality.

Findings Evidence from well-planned, representative epidemiological surveys is scarce in many regions. We estimate that 24·3 million people have dementia today, with 4·6 million new cases of dementia every year (one new case every 7 seconds). The number of people affected will double every 20 years to 81·1 million by 2040. Most people with dementia live in developing countries (60% in 2001, rising to 71% by 2040). Rates of increase are not uniform; numbers in developed countries are forecast to increase by 100% between 2001 and 2040, but by more than 300% in India, China, and their south Asian and western Pacific neighbours.

Interpretation We believe that the detailed estimates in this paper constitute the best currently available basis for policymaking, planning, and allocation of health and welfare resources.

Introduction

Auguste D, a patient of Alois Alzheimer, was a 51-year-old woman with a 5-year history of progressive cognitive impairment, hallucinations, delusions, and severely impaired social functioning. After her death on April 8, 1906, Alzheimer identified in her brain amyloid plaques, neurofibrillary tangles, and arteriosclerotic changes. World Alzheimer's Day, Sept 21, 2006, marks the centenary of the identification and naming of the clinico-pathological entity that we now recognise to be the main cause of dementia syndrome, and one of the most burdensome conditions of later life.

According to the Global Burden of Disease estimates for the 2003 World Health Report,[1] dementia contributed 11·2% of years lived with disability in people aged 60 years and older; more than stroke (9·5%), musculoskeletal disorders (8·9%), cardiovascular disease (5·0%), and all forms of cancer (2·4%). The disability weight for dementia, estimated by an international and multidisciplinary expert consensus, was higher than for almost any other health condition, apart from spinal-cord injury and terminal cancer. Although people with dementia are heavy consumers of health services, direct costs in developed countries arise mostly from community and residential care. Knapp and colleagues[2] estimated that in the UK, 224 000 of the 461 000 elderly people with cognitive impairment live in institutions at a cost of £4·6 billion (US$8·2 billion) every year, or 0·6% of the UK gross domestic product. Family caregivers remain the cornerstone of support for people with dementia, experiencing substantial psychological, practical, and economic strain.[3,4] Dementia care is particularly time intensive, and many caregivers need to cut back on work. In the USA, the annual cost of informal care was $18 billion per year in 1998 dollars.[5]

Such estimates of burden are critically dependent on the accuracy of the estimates of people living with the disease, which in turn depend on evidence from epidemiological surveys that are representative and well organised. For dementia in many world regions, such evidence is either incomplete or scanty in its coverage. Even when a wider evidence base is available for country or region-specific figures, these estimates are sometimes generated from single studies with little regard for their generalisability. Previous estimates of the number of people worldwide with dementia have tended to apply a uniform age-specific prevalence, assuming no important geographic variation.[6,7] Prevalence has been noted to be lower in developing countries,[8] strikingly so in some studies.[9,10]

Alzheimer's Disease International, the umbrella organisation for national Alzheimer's associations, convened an international group of experts to generate up-to-date evidence-based estimates for the prevalence and numbers of people with dementia in all regions of the world. Such figures would provide an authoritative and consistent foundation for global policymaking, and would assist national Alzheimer's associations to raise awareness of the size of the challenge faced by this and future generations.

Methods

Study design

We selected a Delphi consensus approach, guided by a systematic review of the published work on the prevalence of dementia from around the world. The essence of the Delphi consensus method is to derive quantitative estimates through the qualitative assessment of evidence. Studies of widely different design and quality can be assessed, much more than is usual in systematic reviews. When published information is scarce, experts can make inferences using other data from comparable contexts. Experts' estimates are aggregated and fed back anonymously to all participants, who then review their initial responses in view of group-wide choices.[11,12] The group does not need to meet. This practice confers anonymity and allows opinions to be expressed free from peer-group pressure.

We sought consensus on dementia prevalence for all regions of the world, in 5-year age bands from 60 to 84 years, and for those aged 85 years and older. We combined the sexes, and focused on dementia prevalence rather than subtypes such as Alzheimer's disease because most prevalence data was neither gender-specific nor distinguished by subtype. WHO has divided the countries of the world into 14 regions based on geography (AMRO [the Americas], EURO [Europe], EMRO [north Africa and the middle east], AFRO [Africa], SEARO [south Asia] and WPRO [western Pacific]) and patterns of child and adult mortality, from A (lowest) to E (highest).

The panel was selected to achieve global coverage. The 12 experts had done studies on the prevalence of dementia, meta-analyses on regional or global dementia prevalence or incidence, or were able to bring a global perspective to the exercise. Investigators who worked together gave only one combined estimate, since it would have been difficult for them to avoid interacting. Thus, we obtained ten prevalence estimates per age-group per region.

CF and MP did a systematic review of published work from around the world on the prevalence of dementia to assist the panel's decision making. This review consisted of a MEDLINE search covering the period from 1980 to 2004. Studies were identified with the terms: dementia, Alzheimer's disease, prevalence, and cross-sectional. Secondary references and review papers were also examined. Consensus panel members were asked to identify any omissions. The only inclusion criterion was that the study should be population-based. Although studies varied widely in quality, methodology, and dementia outcome definition, the evidence contributed by all could be judged and weighted appropriately by the expert panel.

The studies were examined and a detailed document synthesising the research evidence for the 14 WHO regions was sent to each expert. This consisted of methodological details (setting, sample size, one-phase or two-phase survey, implementation of two-phase design, response rates for both phases, diagnostic criteria) and a table that summarised the age-specific prevalence estimates from every study. 95% CIs were included where they were given in the paper, or could be calculated from information provided. CF and MP highlighted any apparent methodological deficiencies, most of which related to the design, conduct, and analysis of two-phase surveys. All information was given separately for each of the 14 WHO regions.

For the document synthesising research evidence on the prevalence of dementia worldwide see http://www.alz.co.uk/consensus

Procedures

Participants reviewed the document combining the research evidence and gave their own estimates for dementia prevalence in the 14 WHO regions, for men and women combined, in 5-year bands from 60 to 64 years up to 85 years and older. We did not specify how estimates were to be derived, although when regional data were not available, we requested that the participants make inferences where possible from data from other regions. We did provide information about factors of potential relevance, namely the development status and child and adult mortality of the regions. Participants could also comment on the rationale for their decision.

The ten estimates of age-specific prevalence were entered into a spreadsheet for every region. Individual responses were made anonymous so that the experts could identify their own responses but not those of others. The group response was summarised as the mean prevalence estimate. These spreadsheets were then returned to the members of the panel who were invited to reconsider in the light of their colleagues' prevalence estimates and any accompanying comments. If they chose to alter their estimates, they could see the effect of this change on the group mean. All participants responded in the second round.

Analysis

The levels of agreement between participants in the first and second round of the exercise were assessed with intraclass correlation coefficient (ICC) within age-groups for every region. The mean prevalence estimate and its SD were calculated for each age-group and each WHO region. These means were applied to the current age-specific population estimates for the 14 WHO world regions to arrive at total numbers affected worldwide and by region. Population projections (demographic statistics available from the UN) were used to estimate numbers likely to be affected in 2020 and 2040. These projections assume that current prevalence would be constant over time. The Global Burden of Disease project DISMOD-II software was used to derive estimated incidence rates for the year 2001 from prevalence, remission, and mortality.[13] Remission was assumed to be zero, and cause-specific mortality was modelled in terms of relative risks identified in

For The Global Burden of Disease project DISMOD-II software see http://www3.who.int /whosis

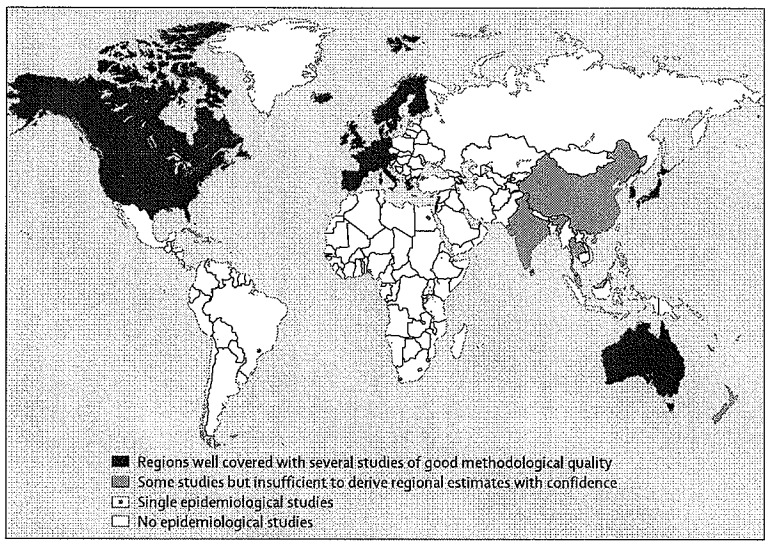

Figure 1: Prevalence studies worldwide

EURODEM: RR of 2·38 up to age 89, declining to 1·8 in women aged 90 and older and 1·6 in men aged 90 and older.[14]

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the extent of the global research evidence on the prevalence of dementia. The world regions coloured in red (North America, Europe, Japan, and Australia) are well covered with several studies of good methodological quality. Some epidemiological studies have been done in the regions coloured in pink, but they are insufficient in quality or quantity to provide representative estimates of the regional prevalence of dementia. Regions marked in white are completely or almost completely lacking in epidemiological studies; in these regions sites of single studies are marked with a red dot.

Agreement for AFRO E was poor in the first round (ICC=0·62 [95% CI 0·17–0·94]) but improved to 0·80 (0·56–0·96) in the second round. Otherwise, ICCs ranged from 0·88 to 0·99 in the first round, and from 0·95 to 0·99 in the second. There was an improvement in agreement for every region, other than EURO A and EURO C, for which agreement was already excellent (0·99) in the first round. Table 1 shows the mean and SD for the ten final prevalence estimates given by the 12 participants for all age-groups and the 14 WHO regions. The lowest estimates for all age-groups were given for AFRO D region followed by SEARO D, SEARO B, and AFRO E. DISMOD estimated that yearly incidence rates naturally follow the same regional pattern. When applying the prevalence figures from table 1 to the 2001 world population the estimated number of people with dementia worldwide is 24·3 million (table 2). Applying the DISMOD estimated incidence rates, we estimate 4.6 million new cases of dementia every year (about one new case every 7 s). The number of people living with dementia will almost double every 20 years, to 42·3 million in 2020 and 81·1 million in 2040. Although the expert consensus was for a higher prevalence of dementia in developed regions than developing regions, it is China and its developing western-Pacific neighbours that have the highest number of people with dementia (6 million), followed by western Europe with 4·9 million, and North America with 3·4 million. In 2001, 60·1% of all people with dementia lived in developing countries, rising to 64·5% in 2020 and 71·2% in 2040 (figure 2). At country level, the seven countries with the largest number of people with dementia in 2001 were: China (5·0 million), the European Union (5·0 million), USA (2·9 million), India (1·5 million), Japan (1·1 million), Russia (1·1 million), and Indonesia (1·0 million).

Projections for growth in the number of people with dementia indicate that regions fall into three broad groups (table 2). Developed regions start from a high base, but will experience a moderate proportionate increase (around 100% between 2001 and 2040). Latin America and Africa start from a low base but will experience a rapid increase in numbers (235–393%). India, China, and their south Asian and western-Pacific neighbours start from a high base and will experience rapid growth (314–336%). The consequences are striking. We predict that by 2040 China and its western-Pacific neighbours will have three times more people living with dementia than western Europe. Latin American countries today have half as many people

	Age-group (years)					
	60–64	65–69	70–74	75–79	80–84	≥85
EURO A	0·9 (0·1)	1·5 (0·2)	3·6 (0·2)	6·0 (0·2)	12·2 (0·8)	24·8 (1·0)
EURO B	0·9 (0·1)	1·3 (0·1)	3·2 (0·3)	5·8 (0·3)	12·2 (0·3)	24·7 (2·3)
EURO C	0·9 (0·1)	1·3 (0·1)	3·2 (0·2)	5·8 (0·2)	11·8 (0·5)	24·5 (1·8)
AMRO A	0·8 (0·1)	1·7 (0·1)	3·3 (0·3)	6·5 (0·5)	12·8 (0·5)	30·1 (1·1)
AMRO B	0·8 (0·1)	1·7 (0·1)	3·4 (0·2)	7·6 (0·4)	14·8 (0·6)	33·2 (3·5)
AMRO D	0·7 (0·1)	1·5 (0·3)	2·8 (0·4)	6·2 (1·1)	11·1 (2·0)	28·1 (5·2)
EMRO B	0·9 (0·3)	1·8 (0·1)	3·5 (0·3)	6·6 (0·2)	13·6 (0·8)	25·5 (2·3)
EMRO D	1·2 (0·3)	1·9 (0·2)	3·9 (0·3)	6·6 (0·4)	13·9 (1·3)	23·5 (2·3)
WPRO A	0·6 (0·1)	1·4 (0·1)	2·6 (0·3)	4·7 (0·6)	10·4 (1·2)	22·1 (3·5)
WPRO B	0·6 (0·1)	1·8 (0·2)	3·7 (0·4)	7·0 (0·9)	14·4 (1·9)	26·2 (3·9)
SEARO B	1·0 (0·1)	1·7 (0·2)	3·4 (0·2)	5·7 (0·5)	10·8 (1·2)	17·6 (2·7)
SEARO D	0·4 (0·1)	0·9 (0·1)	1·8 (0·2)	3·7 (0·4)	7·2 (1·2)	14·4 (2·7)
AFRO D	0·3 (0·1)	0·6 (0·1)	1·3 (0·2)	2·3 (0·5)	4·3 (1·0)	9·7 (1·9)
AFRO E	0·5 (0·3)	1·0 (0·4)	1·9 (0·9)	3·8 (1·7)	7·0 (3·6)	14·9 (7·2)

Table 1: Group mean consensus estimates (SD) for prevalence of dementia (%) for each region and age-group

	Population (millions), aged ≥60 years (2001)	Consensus dementia prevalence (%) at age ≥60 years	Estimated annual incidence per 1000	New dementia cases (millions) per year, 2001	Number of people (millions) with dementia, aged ≥60 years			Proportionate increase (%) in number of people with dementia	
					2001	2020	2040	2001–2020	2001–2040
Western Europe (EURO A)	89·6	5·4	8·8	0·79	4·9	6·9	9·9	43	102
Eastern Europe low adult mortality (EURO B)	27·4	3·8	7·7	0·21	1·0	1·6	2·8	51	169
Eastern Europe high adult mortality (EURO C)	44·6	3·9	8·1	0·36	1·8	2·3	3·2	31	84
North America (AMRO A)	53·1	6·4	10·5	0·56	3·4	5·1	9·2	49	172
Latin America (AMRO B/D)	40·1	4·6	9·2	0·37	1·8	4·1	9·1	120	393
North Africa and Middle Eastern Crescent (EMRO B/D)	27·5	3·6	7·6	0·21	1·0	1·9	4·7	95	385
Developed western Pacific (WPRO A)	34·5	4·3	7·0	0·24	1·5	2·9	4·3	99	189
China and developing western Pacific (WPRO B)	151·1	4·0	8·0	1·21	6·0	11·7	26·1	96	336
Indonesia, Thailand, and Sri Lanka (SEARO B)	23·7	2·7	5·9	0·14	0·6	1·3	2·7	100	325
India and south Asia (SEARO D)	93·1	1·9	4·3	0·40	1·8	3·6	7·5	98	314
Africa (AFRO D/E)	31·5	1·6	3·5	0·11	0·5	0·9	1·6	82	235
TOTAL	616·2	3·9	7·5	4·6	24·3	42·3	81·1	74	234

Table 2: **Number of people with dementia in 2001, projections for 2020 and 2040, and percentage increases, by WHO region**

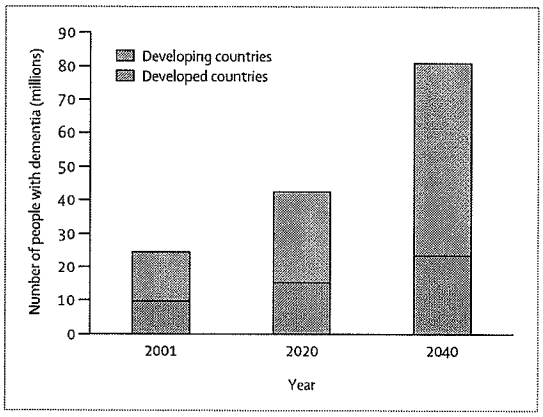

Figure 2: **Number of people with dementia in developed and developing countries**

with dementia (1·8 million) as North America (3·4 million), but by 2040 the numbers will be very similar (9·1 million and 9·2 million, respectively).

Discussion

We have generated expert consensus estimates of age-specific dementia prevalence for different world regions using the Delphi technique. We estimate that 24 million people have dementia today and that this amount will double every 20 years to 42 million by 2020 and 81 million by 2040, assuming no changes in mortality, and no effective prevention strategies or curative treatments. Of those with dementia, 60% live in developing countries, with this number rising to 71% by 2040. The rate of increase in numbers of people with dementia is predicted to be three to four times higher in developing areas than in developed regions.

In 1997, Prince[6] estimated that 18 million people would be living with dementia today. He assumed the same prevalence in all regions and did not allow for regional differences in age distribution in the older population. Wimo and colleagues[7], however, estimated a similar total number of people with dementia worldwide as our Delphi consensus; 25 million in 2000 rising to 63 million by 2030 and 114 million by 2050. They assumed the age-specific prevalence of dementia to be the same worldwide. They also calculated continent-specific numbers on the basis of published reviews. Wimo's figures differ substantially from our consensus for some regions; for example they estimate that there are 1·25 million people with dementia in Africa, but we estimated only 0·49. Compared with previous estimates, our consensus should be more sensitive to regional variation; the expert group reviewed all available evidence and its quality, and considered relevant regional characteristics.

The suggestion of a lower prevalence of dementia in developing regions than in developed regions[8] is reinforced by the consensus judgment of our panel. Our experts seemed to be strongly influenced by the one study of good methodological quality from sub-Saharan Africa,[10] for which the reported prevalence was very much lower than in developed countries. For south Asia (SEARO D), more weight seemed to be given to the similarly low estimates from the Ballabgarh rural north Indian study[9] than to studies in more developed sites in south India,[15,16] for which the reported prevalences are closer to those in Europe and North America. More research is needed to establish the generalisability of existing data and to explore differences between urban and rural areas.

Methodological factors might also be relevant; mild dementia could have been underdetected in the least developed regions because of difficulties in establishing social impairment. For China and its neighbours (WPRO B) the consensus prevalence estimates were very similar to those for Europe and North America. This finding is consistent with recent prevalence data from four Chinese cities, published after we had completed our consensus exercise.[17] The lower prevalence in Africa and south Asia, if genuine, might be partly explained by lower survival with dementia rather than lower incidence. However, incidence estimates in Nigeria and India are also much lower than in developed countries.[18,19] Differences in level of exposure to environmental risk factors might have contributed, with low levels of cardiovascular risk[18] and hypolipidaemia[19] in some developing countries both having been advanced as explanations. However, other risk factors, for example anaemia found to be associated with Alzheimer's disease in rural India,[20] will be more prevalent in developing countries. High levels of mortality in early life could also be implicated; constitutional and genetic factors that confer survival advantage in early years might go on to protect against neurodegeneration or delay its clinical manifestations.

Our estimates have limitations. Although the expert panel achieved high levels of consensus, this was often on the basis of scant epidemiological evidence. Some of the estimates, particularly for developing regions with few studies, may be reliable but invalid. Figure 1 signifies the need for much more epidemiological research on dementia, particularly in Latin America, Russia and eastern Europe, the middle east, and Africa. Our projections should be interpreted with caution for several reasons. First, these relied on demographic statistics, which might not be accurate for many parts of the world, especially for older age-groups. Second, we assumed that age-specific prevalence in each region would remain constant over time. In fact, changes in risk exposure might increase or decrease incidence. Improved medical and social care might reduce case mortality and increase prevalence. Interventions that delay onset would have substantial potential for reducing age-specific prevalence. Irrespective of any such effects, it seems probable that as early and late life patterns of morbidity and mortality converge with those of the developed west, dementia prevalence levels will do likewise.[21,22] The implication is that our projections for dementia in developing regions might be conservative. Efforts need to be made in all regions to monitor secular trends in incidence and prevalence associated with the epidemiological transition, and with changes in medical and social care.

We believe that the detailed estimates contained in this paper are the best currently available basis for policymaking, planning, and allocation of health and welfare resources. Primary prevention should focus on targets suggested by current evidence; risk factors for vascular disease, including hypertension, smoking, type 2 diabetes, and hyperlipidaemia.[23] The epidemic of smoking in developing countries and the high rising prevalence of type 2 diabetes in Asia are particular causes of concern. More work is needed to identify further modifiable risk factors.

Achieving progress with dementia care in developing countries has much to do with creating the climate for change. Poor awareness is a key public-health problem with important consequences: affected people do not seek help, and if they do health-care services tend not to meet their needs;[4] dementia is stigmatised, and sufferers can be excluded from residential care and denied admission to hospital;[24–26] no constituency is available to lobby government; and families tend to have less support or understanding from others and experience substantial strain.[4]

National Alzheimer's associations help to raise awareness and create a framework for positive engagement between policymakers, clinicians, researchers, caregivers, and people with dementia. Most of Alzheimer Disease International's 75 members are associations in developing countries. Their advocacy, empowered by evidence of prevalence, effect, and need will foster the development of more responsive services. For many low-income countries the most cost-effective approach will be community primary care to support and advise family caregivers.[4,24,26] Day care and residential respite care are expensive but important elements of a community service. Residential care is unlikely to be a government priority, but private nursing and residential care homes are already opening to meet the new demand. If government policies are well formulated and planned with the projections described in this paper in mind, the inevitable shift of resource expenditure towards older people can be predicted and its consequences mitigated.[27] The health and social care needs of the large and rapidly growing numbers of frail, dependent older people should be a matter of great concern for policymakers in developing regions.

Contributors

All authors participated in the study concept and design. C P Ferri and M Prince participated in the coordination of data collection, revision of literature provided to the panel, analysis and interpretation of data, and drafted the manuscript. C Mathers participated in the analysis. All authors critically reviewed the paper for important intellectual content. All authors were part of the consensus panel with the exception of C P Ferri (who managed the Delphi consensus exercise and prepared the anonymised syntheses of estimates) and E Rimmer.

Conflict of interest statement

We declare that we have no conflict of interest.

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"MINI-MENTAL STATE"

A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN*

MARSHAL F. FOLSTEIN, SUSAN E. FOLSTEIN
and
PAUL R. MCHUGH

Department of Psychiatry, The New York Hospital-Cornell Medical Center, Westchester Division, White Plains, New York 10605, U.S.A.
and
Department of Psychiatry, University of Oregon Medical School, Portland, Oregon 97201, U.S.A.

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INTRODUCTION

EXAMINATION of the mental state is essential in evaluating psychiatric patients.[1] Many investigators have added quantitative assessment of cognitive performance to the standard examination, and have documented reliability and validity of the several "clinical tests of the sensorium".[2,3] The available batteries are lengthy. For example, WITHERS and HINTON's test includes 33 questions and requires about 30 min to administer and score. The standard WAIS requires even more time. However, elderly patients, particularly those with delirium or dementia syndromes, cooperate well only for short periods.[4]

Therefore, we devised a simplified, scored form of the cognitive mental status examination, the "Mini-Mental State" (MMS) which includes eleven questions, requires only 5–10 min to administer, and is therefore practical to use serially and routinely. It is "mini" because it concentrates only on the cognitive aspects of mental functions, and excludes questions concerning mood, abnormal mental experiences and the form of thinking. But within the cognitive realm it is thorough.

We have documented the validity and reliability of the MMS when given to 206 patients with dementia syndromes, affective disorder, affective disorder with cognitive impairment "pseudodementia"[5,6]), mania, schizophrenia, personality disorders, and in 63 normal subjects.

DESCRIPTION OF THE MMS

The MMS is shown in the appendix. Questions are asked in the order listed and scored immediately. The tester (psychiatric resident, nurse, or volunteer) is instructed first to make the patient comfortable, to establish rapport, to praise successes, and to avoid

*Reprint request to M.F.F. now at Department of Psychiatry and Behavioral Science, Johns Hopkins Hospital, Baltimore, Md. 21205.

pressing on items which the patient finds difficult. In this setting most patients cooperate, and catastrophic reactions are avoided.

The MMS is divided into two sections, the first of which requires vocal responses only and covers orientation, memory, and attention; the maximum score is 21. The second part tests ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon similar to a Bender–Gestalt Figure; the maximum score is nine. Because of the reading and writing involved in Part II, patients with severely impaired vision may have some extra difficulty that can usually be eased by large writing and allowed for in the scoring. Maximum total score is 30. The test is not timed. Detailed instructions for administration are given in the appendix.

METHODS

The MMS was given to two groups of people that we will refer to as Samples A and B. In Sample A (Table 1) are 69 patients chosen specifically as clear examples of clinical conditions (29 with dementia syndromes due to a variety of brain diseases, 10 with affective disorder, depressed type with clinically recognizeable cognitive impairment, 30 with uncomplicated affective disorder, depressed type) and 63 normal, elderly persons similar in age to the patients. All the patients were tested shortly after admission to the New York Hospital Westchester Division, a private psychiatric hospital and the normal subjects were tested at a Senior Citizens Center and at a retirement apartment complex. Thirty-three of the 69 patients in Sample A were retested after treatment. The patients with dementia were treated according to their clinical conditions. They occasionally received tricyclic antidepressants or phenothiazines as well as treatment for medical illnesses. The patients with depression were treated with antidepressants and/or ECT. They also may have received medical treatments.

Sample B (Table 2) is a patient group formed by taking consecutive admissions to the hospital and giving them the MMS shortly after admission. It was intended to be a standardization sample and came eventually to consist of 137 patients (9 patients with dementia, 31 patients with affective disorder, depressed type, 14 patients with affective disorder, manic type, 24 with schizophrenia, 32 with personality disorder with drug abuse, and 27 with neurosis). These diagnoses were made by M.F. on review of the hospital chart employing the diagnostic criteria described below and without knowledge of the MMS scores. Subsets of patients from both Samples A and B were extracted for age-matched studies (Table 1B) concurrent validity (Table 3) and test-retest reliability (Table 4).

The following diagnostic criteria were used for both Sample A and B:

Dementia. A global deterioration of intellect in clear consciousness.

Affective disorder, depressed type, with cognitive impairment. A sustained feeling of depression with an attitude of hopelessness, worthlessness or guilt accompanied by disturbances in orientation and memory which occurred after the onset of the depression.

Affective disorder, depressed type, uncomplicated. A sustained feeling of depression with an attitude of hopelessness, worthlessness or guilt and with no notable cognitive defect.

Affective disorder, manic type. A sustained feeling of elevated mood with an attitude of overconfidence or exaggerated self-importance.

Schizophrenia. Either Schneider's first rank symptoms in the absence of affective symp-

TABLE 1.

Sample A

A. Mini Mental State Scores on Admission

Diagnosis	N	Age	Sex M/F	MMS $\bar{x}$	MMS S.D.	MMS Range	Mann-Whitney U	P
Dementia	29	80.8	12/17	9.6	5.8	0-22	45	<.001
Depression with cognitive Impairment	10	74.5	7/3	19.0	6.6	9-27	65.8	<.001
Affective Dis., Depressed	30	49.8	9/21	25.1	5.4	8-30	1178 (Z=6)	<.001
Normal	63	73.9	27/36	27.6	1.7	24-30		

B. Mini Mental Scores on Admission: Age-Matched Sample

Diagnosis	N	Age	Age Range	Sex M/F	MMS $\bar{x}$	MMS S.D.	MMS Range	Mann-Whitney U	P
Dementia	8	76	75-79	2/6	6.9	4.7	1-14	4	<.001
Depression with cognitive Impairment	8	76	70-86	5/3	18.4	5.7	9-27	8.5	<.006
Affective Dis., Depressed	8	74	69-79	1/7	26.1	4.4	17-30		

C. Mini Mental State Scores of Patients Tested Before and After Treatment

Diagnosis	N	Age	Sex M/F	MMS $\bar{x}$	MMS S.D.	MMS Range	MMS $\bar{x}$	MMS S.D.	MMS Range	$\bar{x}$ days between tests	Wilcoxon T (1 tail)	P
Dementia	14	81.4	6/8	10.5	6.6	0-22	11.1	5.7	1-19	29	20	NS
Depression with cognitive Impairment	7	75.0	5/2	18.3	5.0	13-27	23.4	2.4	21-26	36	1.0	<.025
Affective Dis., Depressed	12	58.9	3/9	25.5	5.0	14-30	27.2	3.7	16-30	51	10.5	<.025

TABLE 2.

Sample B

Diagnosis	N	Age	Sex M/F	MMS $\bar{x}$	MMS S.D.	MMS Range
Dementia	9	74.4	3/6	12.2	6.7	1-22
Depression	31	50.7	16/15	25.9	4.2	9-30
Mania	14	39.5	6/8	26.6	3.5	20-30
Schizophrenia	24	44.6	14/10	24.6	6.6	1-30
Personality Disorder with Drug Abuse	32	34.3	17/15	26.8	2.5	19-30
Neurosis	27	25.6	15/12	27.6	2.4	21-30

toms or the presence of a personality deterioration associated with thought disorder and emotional incongruence without first rank symptoms.

Personality disorder with drug abuse. Absence of all above symptoms with a history of drug abuse, including alcohol.

Neuroses. Presence of psychological symptoms appearing to arise from the combination of a particular life situation and vulnerable character but with the specific absence of symptoms characteristic of the other syndromes.

TABLE 3.

Sample for MMS - IQ Correlation

Diagnosis	N	Age	Sex M/F
Dementia	7	78	3/4
Depression with cognitive Impairment	8	76	6/2
Depression	8	55	3/5
Schizophrenia	2	68	1/1
Neurosis	1	22	0/1

TABLE 4.

Test-Retest Reliability

Type of Reliability	Sample Composition	N	Age	Sex M/F	MMS 1 $\bar{x}$	MMS 1 S.D.	MMS 1 Range	MMS 2 $\bar{x}$	MMS 2 S.D.	MMS 2 Range	# days between tests	Wilcoxon T (2 tail)	Wilcoxon P	Pearson r	Pearson P
24 hr. retest (1 tester)	various types of depressive symptoms	22	41.2	3/19	24.2	7.1	2-30	25.3	7.0	1-30	1	45	NS	0.887	<.0001
24 hr. retest (2 testers)	various types of depressive symptoms	19	45.6	7/12	23.9	4.7	13-30	25.2	5.1	13-30	1	22	NS	0.827	<.0001
28 day retest clinically stable patients	dementia, depression, schizophrenia	23	74.1	6/17	19.3	10.0	1-30	19.2	9.2	1-29	27.7	42	NS	0.988	<.0001

RESULTS

Validity

The MMS separated the three diagnostic groups in Sample A from one another and from the normal group. Of a total possible score of 30, the mean score for patients with dementia was 9·7, depression with cognitive impairment 19·0, and uncomplicated affective disorder, depressed 25·1. The mean score for normals was 27·6. Thus, the MMS scores agreed with the clinical opinion of the *presence* of cognitive difficulty and as the cognitive difficulty is usually less in depression than in dementia the scores dispersed in a fashion agreeing with the *severity* of the difficulty.

To be sure that these scores were not due to age effects and unrelated to clinical conditions an age-matched group was drawn from Sample A and showed an identical dispersal of scores according to diagnosis (Table 1b). Mean initial Mini-Mental Status score for

patients with depression under 60 yr-of-age was 24·5 and for patients over 60 was 25·7. These scores were not significantly different.

Thirty-three patients in Sample A were tested prior to and after treatment appropriate to their conditions. Patients with dementia most of whom have uncorrectable brain disease could be expected to show little change in a valid test of cognitive state, whereas those with depression and an associated cognitive difficulty (pseudo dementia) should show a considerable gain with treatment. These expectations are borne out in the results. There is no significant change in the MMS of dementia, a small but significant increase in the depressed patients, and a large and significant increase in those depressed patients with symptoms of cognitive difficulty.

Graphs charting the change-over time in the Mini-Mental State in three patients with improving cognitive states illustrate its usefulness serially and are further examples of how the MMS changes with the clinical state. The examples include a patient recovering from a head injury (Fig. 1), a patient recovering from a metabolic delerium (Fig. 2), and a patient recovering spontaneously over 2½ months from a depression accompanied by severe cognitive impairment (Fig. 3).

Sample B was drawn in order to improve the impression of validity by standardizing the

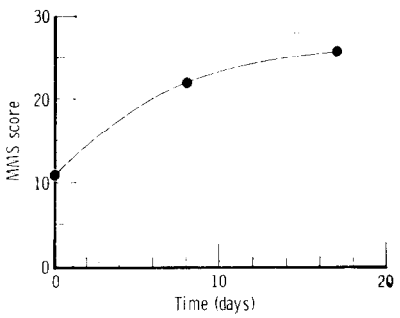

FIG. 1. Serial Mini-Mental State Scores of a patient recovering from a head injury.

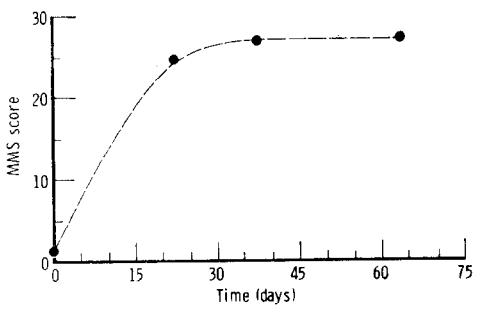

FIG. 2. Serial Mini-Mental State Scores of a patient recovering from a metabolic delerium.

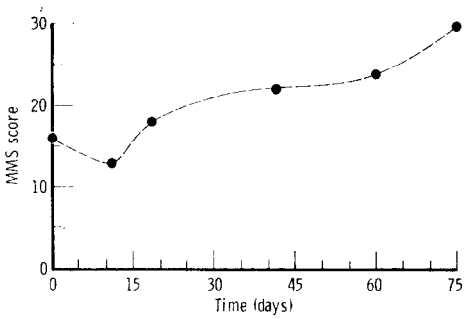

FIG. 3. Serial Mini-Mental State Scores of a patient recovering spontaneously from a depression accompanied by severe cognitive impairment.

MMS in a consecutive series of admission. One hundred and thirty-seven consecutive admissions were examined. Their mean MMS scores were: dementia 12·2; affective disorder, depressed 25·9; mania 26·6; schizophrenia 24·6; personality disorder with drug abuse 26·8; and neuroses 27·6. The minor differences in mean scores between Sample A and B for dementia and depression are not significant. In Sample B the means are similar for all diagnostic groups except dementia. However, amongst the groups with similar means those with depression and schizophrenia had a much wider range of scores than the other diagnostic groups or normal subjects in Sample A. Scores below 20 were found only in functional psychosis or dementia with but one exception; a score of 19 in a patient who had a history of drug abuse.

Concurrent validity was determined by correlating MMS scores with the Wechsler Adult Intelligence Scale, Verbal and Performance scores in a group of patients selected from Sample A and B because they had both a MMS and WAIS Performance in the same week. See Table 3 for the diagnostic and age distribution of this group. For Mini-Mental Status vs Verbal IQ, Pearson r was 0·776 ($p < 0·0001$). For Mini-Mental Status vs Performance IQ, Pearson r was 0·660 ($p < 0·001$).

Reliability

The MMS is reliable on 24 hr or 28 day retest by single or multiple examiners. When the Mini-Mental Status was given twice, 24 hr apart by the same tester on both occasions, the correlation by a Pearson coefficient was 0·887. Scores were not significantly different using a Wilcoxon T. To note examiner effect on 24 hr test retest reliability the MMS was given twice, 24 hr apart by two examiners. The Pearson r remained high at 0·827. The scores did not change; Wilcoxon T was not significant (Table 4). Thus the scores seem stable even when multiple examiners are used, the practice effect is small.

When elderly depressed and demented patients chosen for their clinical stability were given the Mini-Mental Status twice, an average of 28 days apart, there was no significant difference in these scores by the Wilcoxon T and the product moment correlation for test 1 vs test 2 was 0·98. (See Table 4.)

DISCUSSION

The MMS is a valid test of cognitive function. It separates patients with cognitive disturbance from those without such disturbance. Its scores follow the changes in cognitive state when and if patients recover. Its scores correlate with a standard test of cognition, the Wechsler Adult Intelligence Scale (WAIS).

Before considering its uses, it is an elementary but important point that as with any examination of cognitive performance, the MMS cannot be expected to replace a complete clinical appraisal in reaching a final diagnosis of any individual patient. Cognitive difficulties arise in a number of different clinical conditions. This is demonstrated by the overlapping of scores on the MMS in several categories here. Accurate diagnosis, including appraisal of the significance of cognitive disabilities documented in the MMS, depends on evidence developed from the psychiatric history, the full mental status examination, the physical status and pertinent laboratory data.

But the MMS does have a number of valuable features for clinical practice even though it cannot carry alone the diagnostic responsibility. As it is a quantified assessment of cognitive state of demonstrable reliability and validity, it makes more objective what is commonly a vague and subjective impression of cognitive disability during an assessment of a patient. It can provide this quantification easily requiring only a few minutes to complete. It can be repeated during an illness and shows little practice effect. Thus it is ideal for initial and for serial measurements of this important aspect of mental functioning and can demonstrate worsening or improvement of this feature over time and with treatment.

As with any other quantified assessment of cognitive function such as the WAIS with which it correlates so well, the MMS permits comparisons to be drawn between intellectual changes and other aspects of mental functioning. We have found it particularly useful in documenting the cognitive disability found in some patients with affective disorder (Post's pseudodementia) and the improvement of this symptom with appropriate therapy for the mood disorder. Other applications that demand a quantitative assessment of cognitive function might be expected.

The MMS as it is extracted from the clinical examination has an advantage in assessment of patients and clinical problems not so obvious in tests such as the WAIS that are designed for other purposes such as prediction of school or occupational performance. Thus failures in the MMS on orientation, memory, reading and writing have much clearer implications than do failures in digit symbol, picture completion or vocabulary subtests of the WAIS in terms of a patients capacity to care for himself. These implications from the MMS score are easily appreciated by other professionals such as lawyers, judges and social workers concerned with such issues as the patient's competency to manage his daily affairs. It can therefore aid in bringing to the patient the social supports that he needs.

Finally we have found the MMS useful in teaching psychiatric residents to become skilful in the evaluation of the cognitive aspects of the mental status. It provides them with a standard set of questions replacing what is often a bewildering variety of individual approaches. Those questions that it employs have obvious clinical pertinence and cover most of the categories of cognitive disability. Since it can be done quickly and gives a score it draws the resident's attention to global improvements or declines in cognitive state. It also though because special attention is focused on memory and language functions will reveal

the partial cognitive disabilities seen in the aphasic and the amnestic syndromes. As it becomes a routine, we have found an increase in resident interest and competence in assessing and managing the conditions that affect cognitive functioning such as dementia and delerium.

SUMMARY

A short, standardized form was devised for the serial testing of the cognitive mental state in patients on a neurogeriatric ward, as well as for consecutive admission to a hospital. It was found to be quick, easy to use, and acceptable to patients and testers.

When given to 69 patients with dementia, depression with cognitive impairment, and depression (Sample A), the test proved to be valid and reliable. It was able to separate the three diagnostic groups, it reflected clinical cognitive change, it did not change in patients thought to be cognitively stable, and it was correlated with the WAIS scores. Standardization of the test by administration to 63 normal elderly subjects and 137 patients (Sample B) indicated that the score of 20 or less was found essentially only in patients with dementia, delerium, schizophrenia or affective disorder and not in normal elderly people or in patients with a primary diagnosis of neurosis and personality disorder. The Mini-Mental Status was useful in quantitatively estimating the severity of cognitive impairment, in serially documenting cognitive change, and in teaching residents a method of cognitive assessment.

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APPENDIX

Patient.....

Examiner .....

Date .....

"MINI-MENTAL STATE"

Maximum Score	Score	
		ORIENTATION
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we: (state) (county) (town) (hospital) (floor).
		REGISTRATION
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he learns all 3. Count trials and record.
		Trials

ATTENTION AND CALCULATION

5 ( ) Serial 7's. 1 point for each correct. Stop after 5 answers. Alternatively spell "world" backwards.

RECALL

3 ( ) Ask for the 3 objects repeated above. Give 1 point for each correct.

LANGUAGE

9 ( ) Name a pencil, and watch (2 points)
Repeat the following "No ifs, ands or buts." (1 point)
Follow a 3-stage command:
"Take a paper in your right hand, fold it in half, and put it on the floor" (3 points)
Read and obey the following:
CLOSE YOUR EYES (1 point)
Write a sentence (1 point)
Copy design (1 point)

_____ Total score

ASSESS level of consciousness along a continuum_____
Alert Drowsy Stupor Coma

INSTRUCTIONS FOR ADMINISTRATION OF MINI-MENTAL STATE EXAMINATION

ORIENTATION

(1) Ask for the date. Then ask specifically for parts omitted, e.g., "Can you also tell me what season it is?" One point for each correct.

(2) Ask in turn "Can you tell me the name of this hospital?" (town, county, etc.). One point for each correct.

REGISTRATION

Ask the patient if you may test his memory. Then say the names of 3 unrelated objects, clearly and slowly, about one second for each. After you have said all 3, ask him to repeat them. This first repetition determines his score (0–3) but keep saying them until he can repeat all 3, up to 6 trials. If he does not eventually learn all 3, recall cannot be meaningfully tested.

ATTENTION AND CALCULATION

Ask the patient to begin with 100 and count backwards by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.

If the patient cannot or will not perform this task, ask him to spell the word "world" backwards. The score is the number of letters in correct order. E.g. dlrow = 5, dlorw = 3.

RECALL

Ask the patient if he can recall the 3 words you previously asked him to remember. Score 0–3.

LANGUAGE

Naming: Show the patient a wrist watch and ask him what it is. Repeat for pencil. Score 0–2.

Repetition: Ask the patient to repeat the sentence after you. Allow only one trial. Score 0 or 1.

3-*Stage command:* Give the patient a piece of plain blank paper and repeat the command. Score 1 point for each part correctly executed.

Reading: On a blank piece of paper print the sentence "Close your eyes", in letters large enough for the patient to see clearly. Ask him to read it and do what it says. Score 1 point only if he actually closes his eyes.

Writing: Give the patient a blank piece of paper and ask him to write a sentence for you. Do not dictate a sentence, it is to be written spontaneously. It must contain a subject and verb and be sensible. Correct grammar and punctuation are not necessary.

Copying: On a clean piece of paper, draw intersecting pentagons, each side about 1 in., and ask him to copy it exactly as it is. All 10 angles must be present and 2 must intersect to score 1 point. Tremor and rotation are ignored.

Estimate the patient's level of sensorium along a continuum, from alert on the left to coma on the right.

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PET imaging of amyloid deposition in patients with mild cognitive impairment

Anton Forsberg [a], Henry Engler [c], Ove Almkvist [a,b,g], Gunnar Blomquist [d], Göran Hagman [b], Anders Wall [e], Anna Ringheim [e], Bengt Långström [e,f], Agneta Nordberg [a,b,*]

[a] *Karolinska Institute, Department of Neurobiology, Care Sciences and Society, Stockholm, Sweden*
[b] *Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden*
[c] *Department of Nuclear Medicine, Uppsala University Hospital, Uppsala, Sweden*
[d] *Department of Oncology, Radiology and Clinical Immunology, Uppsala University, Uppsala, Sweden*
[e] *Uppsala Imanet AB, Imanet, GE Healthcare, Sweden*
[f] *Department of Biochemistry and Organic Chemistry, Uppsala University, Uppsala, Sweden*
[g] *Department of Psychology, Stockholm University, Stockholm, Sweden*

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Abstract

It is of great clinical value to identify subjects at a high risk of developing AD. We previously found that the amyloid positron emission tomography (PET) tracer PIB showed a robust difference in retention in the brain between AD patients and healthy controls (HC). Twenty-one patients diagnosed with MCI (mean age 63.3 ± 7.8 (S.D.) years) underwent PET studies with ^{11}C-PIB, and ^{18}F-fluoro-deoxy-glucose (FDG) to measure cerebral glucose metabolism, as well as assessment of cognitive function and CSF sampling. Reference group data from 27 AD patients and 6 healthy controls, respectively, were used for comparison. The mean cortical PIB retention for the MCI patients was intermediate compared to HC and AD. Seven MCI patients that later at clinical follow-up converted to AD (8.1 ± 6.0 (S.D.) months) showed significant higher PIB retention compared to non-converting MCI patients and HC, respectively ($ps < 0.01$). The PIB retention in MCI converters was comparable to AD patients ($p > 0.01$). Correlations were observed in the MCI patients between PIB retention and CSF $A\beta_{1\text{-}42}$, total Tau and episodic memory, respectively.
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Keywords: Mild cognitive impairment; Converters; Amyloid; PET; PIB; FDG; CSF biomarkers

1. Introduction

Mild cognitive impairment (MCI) represents a transitional phase between normal ageing and dementia disorders, especially Alzheimer's disease (AD). Patients with MCI have an increased risk of developing AD (Petersen et al., 1999). At present there is great interest in finding diagnostic tools for detection of an increased risk of developing AD. The diagnostic accuracy of current and commonly used MCI criteria is low to moderate (Visser et al., 2005). Both structural and functional neuroimaging have shown promising results in improving MCI diagnosis. Results suggest that changes in glucose metabolism, measured by means of [^{18}F]-2-deoxy-d-glucose (FDG) positron emission tomography (PET), might have a predictive value in the detection of MCI patients at a high risk of developing AD (Arnaiz et al., 2001; Chetelat et al., 2003; Drzezga et al., 2003). Similarly, magnetic resonance imaging (MRI) used in the assessment of brain atrophy and deterioration in the hippocampus, and entorhinal and temporal neocortical volumes, has been used to discriminate MCI patients at a risk of developing AD (Chetelat and Baron, 2003; Kordower et al., 2001). Cerebrospinal fluid (CSF) $A\beta_{1\text{-}42}$ and Tau have been studied as potential biomarkers in MCI. They have shown prognostic value in discriminating

* Corresponding author at: Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Molecular Neuropharmacology, Karolinska University Hospital Huddinge, Novum 5th Floor, S-141 86 Stockholm, Sweden. Tel.: +46 8 58585467; fax: +46 8 58585470.
E-mail address: Agneta.K.Nordberg@ki.se (A. Nordberg).

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MCI patients that will develop AD (Blennow and Hampel, 2003; Buerger et al., 2005; Hansson et al., 2006; Herukka et al., 2005). Longitudinal studies involving MRI and CSF measurements might provide synergistic and improved sensitivity and specificity in prognostic studies of conversion from MCI to AD (de Leon et al., 2006). Recently, various PET ligands used in amyloid imaging *in vivo* have been developed (Klunk et al., 2001; Shoghi-Jadid et al., 2002; Verhoeff et al., 2004). Promising results have been obtained with *N*-methyl [^{11}C] 2-(4′-methylaminophenyl)-6-hydroxy-benzothiazole (PIB), which was found to discriminate successfully between AD patients and age-matched healthy controls (Klunk et al., 2004). Since then several studies have been performed studying AD patients with PIB-PET. We have evaluated the longitudinal changes of PIB retention and found PIB showing quite stable PIB binding in AD patients despite progression in cerebral glucose metabolism and cognition (Engler et al., 2006). The use of voxel-based methods for studying amyloid depositions has also been implemented complementing earlier region of interest based analysis (Kemppainen et al., 2006; Ziolko et al., 2006). One recent study showed an interaction between the PIB binding and the rate of grey matter atrophy (Archer et al., 2006). The link between PIB binding, glucose metabolism and cognitive status has been studied previously (Edison et al., 2006; Engler et al., 2006; Klunk et al., 2004). Amyloid imaging in healthy elderly subjects using PIB showed high PIB in 4 out of 41 non-demented subjects (Mintun et al., 2006). Recently, Small et al. using the amyloid ligand FDDNP presented a study of MCI patients that showed intermediate levels of binding compared to healthy volunteers and AD patients (Small et al., 2006). The separation of healthy versus demented subjects measured with FDDNP seems to be somewhat lower than with PIB (Small et al., 2006), although future studies comparing these tracers would be advisable.

The aim of this study was to measure (by PET) PIB retention in the brains of MCI patients and analyse its relationship with cerebral glucose metabolism, cognitive function and CSF biomarkers and conversion to AD.

2. Methods

2.1. MCI patients

Twenty-one MCI patients (mean age 63.3 ± 7.8 (S.D.) years) were recruited from the Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. The patients had been referred from the primary care centres in the community for investigation of suspected dementia development. All patients were examined at the clinic according to the same comprehensive procedure, which included physical examination, evaluation of neurological and psychiatric status, blood (including apolipoprotein E (ApoE) genotyping), serum and urine analysis, electroencephalography (EEG), MRI, single photon computed tomography (SPECT), cerebrospinal fluid (CSF) analysis, mini-mental-state examination (MMSE) and neuropsychological assessment performed by an experienced neuropsychologist. All subjects lived independently in the community and a majority of the subjects below 65 years of age had still a professional job. In most cases a close informant was interviewed in order to obtain information about the functional status. The diagnosis for MCI followed clinical criteria defined by Petersen et al. (Petersen et al., 1999; Winblad et al., 2004). The criteria were used during a consensus meeting where a clinically experienced geriatrician, neurologist, neuropsychologist and nurse met to discuss the outcome of the assessments of the patient and make the established diagnosis. For the diagnosis of MCI the patients met the following criteria: memory complaint, preferable corroborated by a close informant, objective memory impairment, normal general cognitive function, intact daily living, not fulfilling the DSM-IV criteria for dementia (American Psychiatric Association, 1994). All patients enrolled in the study gave written consent to participate. The Ethics Committees of the Karolinska Institute, Stockholm and Uppsala University, Uppsala, and the Isotope Committee at the Uppsala Academic Hospital, Uppsala, Sweden, approved the study.

After the PET studies were performed the MCI patients have been clinically followed includig neuropsychological examination. Some MCI patients have experienced cognitive decline and after clinical examinations have been considered to fulfil the diagnosis of AD. The analysis of MCI converters and non-converters will be described below.

2.2. Alzheimer patients and healthy subjects

As reference group's data from 27 AD patients (13 males and 14 females; mean age 66.2 ± 9.2 (S.D.) (range 51–80) years; MMSE 22.4 ± 5.2 (S.D.); 17/27 ApoE ε4 carriers) and 6 healthy controls (HCs) 67.3 ± 8.8 (S.D.) (range 57–77) were utilized for comparison. The AD patients were recruited from the Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. They had underwent a comprehensive clinical examination including medical history, neurological and psychiatric examination, electroencephalography, computed tomography or magnetic resonance imaging, single photon emission computed tomography scan, cerebrospinal fluid analysis, blood analysis including ApoE genotyping and neuropsychological testing. All fulfilled the diagnosis of probable AD according to the criteria of the National Institute of Neurological and Communication Disorders, Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). The HCs were spouses to AD patients and were evaluated with neuropsychological and clinical assessments that assured their status as healthy controls.

2.3. Neuropsychological assessments

The neuropsychological tests that routinely are used in the assessment of the patients with memory problems at the Department of Geriatric Medicine and used in the present study covered seven domains, namely: (1) intelligence (global cognitive function) (MMSE), (2) language (vocabulary, similarities, FAS word fluency), (3) spatial (reasoning, block design, Rey Osterrieth copy), (4) immediate memory (digit span, Corsi Block span), (5) episodic memory (RAVL learning, RAVL retention, Rey Osterrieth retention), (6) attention/cognitive speed (digit symbol, Trail making test A), (7) executive function (Trail making test B). Twelve out of 21 MCI patients showed neuropsychological test results that were below −1.5 S.D. in episodic memory, four patients showed poor memory compared to what would be expected due to age and education but the test results were not below −1.5 S.D. in any test. Five MCI patients showed test results below −1.5 S.D. in some test(s) but not in memory. According to these results 12 out of 21 MCI patients were considered as amnestic MCI.

The time between neuropsychological tests and PET scans was 3.1 ± 2.8 (S.D.) months. For comparison with the PET data mini-mental-state examination (MMSE) (Folstein et al., 1975) was used as a measurements of global cognitive status and three tests of episodic memory were used: Rey Auditory Verbal Learning and Retention as well as Rey Osterrieth retention (Lezak, 1995). *Z*-scores were generated for each episodic memory test, based on the raw scores, by comparing the data to a reference data set, comprised of reference material in a data base used at Karolinska University Hospital Huddinge, Stockholm (Bergman et al., 2007). The mean *Z*-score of the three episodic memory tests was then calculated and used for statistical analysis. MMSE data was available for all 21 MCI patients and all 27 AD patients. A mean *Z*-score of episodic memory performance was available for all 21 MCI patients.

2.4. Cerebrospinal fluid measurements

Cerebrospinal fluid was obtained by lumbar puncture from 18 of the 21 MCI patients (2 patients preferred to abstain from CSF sampling and in one MCI subject lumbar puncture was contraindicated due to anti-coagulant treatment). The lumbar puncture was performed in non-fasting subjects normally between 8 and 11 a.m. Ten milliliter was collected where the first 0.5 ml was discarded and the rest of the sample centrifuged at 1500 × *g* (3000–4000 rpm) at +4 °C for 10 min. The CSF samples were frozen and stored at −80 °C in portions of 1 ml until analyses were performed. Measurement of total Tau (tTau) was performed using a sandwich enzyme-linked immunosorbent assay (ELISA) (Blennow et al., 1995). Phosphorylated Tau (pTau; P-Thr181) was assayed by sandwich ELISA, with monoclonal antibody (MAb) HT7 as capturing antibody and biotinylated MAb AT270 as detection antibody (Vanmechelen et al., 2000). Amyloid-$\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$) was analysed using a sandwich ELISA specific for $A\beta_{1\text{-}42}$, as described in detail elsewhere (Andreasen et al., 1999). For the MCI patients, CSF $A\beta_{1\text{-}42}$ values were obtained from 16 subjects, pTau values from 15 subjects and tTau values from 18 subjects. Based on comparison with clinical reference values used in assessment of dementia at Karolinska University Hospital Huddinge, the levels of CSF analyses are considered pathological at the following thresholds: $A\beta_{1\text{-}42} < 450$ pg/ml, tTau > 400 pg/ml and pTau > 60 pg/ml.

2.5. Positron emission tomography (PET)

The patients underwent two PET examinations, which were normally performed at the same day. The PET examinations with PIB and FDG were performed at Uppsala PET centre/Uppsala Imanet AB in Uppsala, Sweden. Production of FDG and PIB was carried out according to good manufacturing standards at Uppsala Imanet, and the synthesis of PIB was performed using a method previously described (Klunk et al., 2004; Mathis et al., 2003). The PIB and FDG examinations were performed using Siemens ECAT EXACT HR+ scanners (CTI PET-systems Inc.), with an axial field of view of 155 mm, providing 63 contiguous 2.46 mm slices with a 5.6 mm transaxial and a 5.4 mm axial resolution. The patients were scanned after fasting for 4 h under resting conditions in a dimmed room. The orbito-meatal line was used to centre the heads of the subjects, and the data were acquired in three-dimensional mode. The tracer doses of PIB and FDG, and the scanner protocol for transmissions, emissions and reconstructions has been described in detail previously (Klunk et al., 2004).

The set of regions of interest (ROIs) used in statistical analysis has previously been described in detail (Engler et al., 2003; Klunk et al., 2004). Based on previous results in AD patients (Engler et al., 2006; Klunk et al., 2004) the following areas were included in the analysis: the frontal, parietal and temporal cortices, posterior cingulum, subcortical white matter. The reference region for calculating the late scan ratio of the PIB data was drawn as follows. An early summation image was created. This image gave a good anatomical representation of the cortical areas due to the fact that the early frames show the flow component of the tracer. On top of the early summation image a late summation image was placed showing the non-specific binding in whiter matter. The reference region was then drawn in the cortical area outside the whiter matter seen in the late summation image.

A computerized reorientation procedure was used to align consecutive PET data for accurate intra-individual comparisons (Andersson and Thurfjell, 1997). For each patient the PIB images were realigned to the respective FDG image, using the FDG images as templates.

For the FDG examinations, parametric maps of cerebral glucose metabolism (CMRglc) were generated by means of the Patlak method using the time course of the tracer from arterialized-venous plasma samples as an input function (Patlak et al., 1983). The frames from 20 to 60 min and

Table 1
Demographic and clinical data of the 21 MCI patients as a total group and divided into MCI converters and non-converters

	MCI total	MCI converters	MCI non-converters
N	21	7	14
Age (years)	63.3 ± 7.8	63.4 ± 7.9	62.6 ± 8.4
Gender M/F	8/13	1/6	7/7
Education (years)	12.7 ± 3.8	13.0 ± 3.7	12.0 ± 4.2
APOE ε4 carriers	14	6	8
MMSE	28.2 ± 1.4	27.0 ± 1.3**	28.9 ± 0.9
EpMem	−0.60 ± 0.92	−1.52 ± 0.48***	−0.13 ± 0.72
$A\beta_{1\text{-}42}$ (pg/ml)	551 ± 180	447 ± 56*	614 ± 201
tTau (pg/ml)	382 ± 200	488 ± 183	329 ± 193
pTau (pg/ml)	65 ± 31	76 ± 32	58 ± 29

Data shown as mean ± S.D.; MMSE, mini-mental-state examination; EpMem, episodic memory (mean *Z*-score); $A\beta_{1\text{-}42}$, amyloid-$\beta_{1\text{-}42}$; tTau, total Tau protein; pTau, phosphorylated Tau protein. Significant difference between MCI converters and MCI non-converters (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$), Student's *t*-test, two-tailed, unequal variance.

a lumped constant of 0.418 were used to generate the parametric maps of CMRglc. To account for global differences between patients the CMRglc data was normalized to the pons (ROI/ref). The data on glucose metabolism will be referred to as rCMRglc. No data on glucose metabolism was available for one of the patients as a result of technical problems.

For PIB the mean uptake values of the ROIs obtained in a late time interval (40–60 min) were normalized to the corresponding uptake in a reference region (ROI/ref). These late reference ratio data on PIB retention will be referred to as late scan ratio. The choice of method was based on previous results indicating that the late scan reference ratio renders stable and reliable data (Lopresti et al., 2005). The cerebellar cortex was chosen as reference region because of its previously reported lack of Congo red- and thioflavin-S-positive plaques (Mirra et al., 1994; Yamaguchi et al., 1989).

2.6. Statistical analysis

The statistical analysis used to compare the MCI patients with the reference groups (healthy controls and AD patients) were performed by using two-sample, unequal variance, two-tailed Student's *t*-tests. Based on the sub-division of converted MCI patients and non-converted MCI patients the groups were compared using two-sample, unequal variance, two-tailed Student's *t*-tests. The data was controlled for multiple comparisons using Bonferroni correction yielding a significance level of 0.01 (0.05/5 (number of regions analysed)).

The analysis of correlation between PIB retention, CSF data, rCMRglc, MMSE, *Z*-score of episodic memory, was conducted using Spearman rank order correlation coefficient *R*. The correlations between PIB-PET data and CSF data was corrected for multiple comparisons using Bonferroni correction yielding a significance level of 0.0042 (0.05/12 (number of correlations performed)). No statistical corrections for multiple comparisons were performed for additional correlation analysis due to the explorative nature of the study. This implies some caution when evaluating these results.

3. Results

3.1. MCI patients

The demographic information regarding the MCI patients is seen in Table 1. During clinical follow-up of the MCI patients after the performed PET scans seven of the MCI patients converted to AD after 8.1 ± 6.0 months (S.D.) after their respective PET scans. The diagnosis of AD was based on comprehensive clinical examination as mentioned in Section 2 and according to the criteria of NINCDS-ADRDA (McKhann et al., 1984). These seven MCI patients will below be considered as MCI converters and the remaining 14 MCI patients will be considered as MCI non-converters. It is important to observe that the seven MCI converters did not fulfil the criteria for AD when they underwent the PET studies. As shown in Table 1 there was no significant difference in age between the MCI converters compared to non-converters. There were a higher proportion of ApoE ε4 carriers in the MCI converter group (85%) compared to the non-converter MCI group (57%). The MMSE test score was significant lower in converters compared to non-converters. The MCI converters showed impaired cognitive function compared to MCI non-converters, which reached statistical significance for the mean *Z*-score of episodic memory ($p < 0.001$) (Table 1).

Mean levels of CSF $A\beta_{1\text{-}42}$, tTau and pTau in the MCI patients are shown in Table 1. As regards $A\beta_{1\text{-}42}$ and tTau no difference from normal was observed in the total MCI group, while the mean level of pTau was above the pathological threshold in total MCI group. The MCI group showed significantly higher levels of $A\beta_{1\text{-}42}$ and significantly lower level of tTau compared to AD ($ps < 0.01$). Three MCI patients showed pathological levels of $A\beta_{1\text{-}42}$ and seven showed increased tTau and six pathological pTau values, respectively. The MCI converters showed significantly lower levels of CSF $A\beta_{1\text{-}42}$ compared with the MCI non-converters group ($p < 0.05$) (Table 1). Within the group of seven MCI patients that converted to AD, three subjects had pathological levels of $A\beta_{1\text{-}42}$ and four showed pathological levels of tTau and pTau

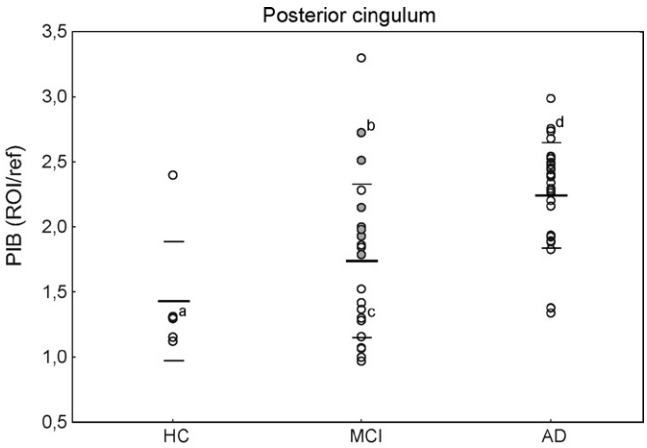

Fig. 1. PIB retention (ROI/ref) in posterior cingulum in MCI patients compared with healthy controls (HCs) ($n=6$) and AD patients ($n=27$). Long horizontal lines indicate mean, short horizontal lines indicate standard deviation (S.D.). Filled circles indicate MCI patients that later after the PET scans converted to AD. The small letters indicate the patients shown in Fig. 2: a, HC; b, MCI converter; c, MCI non-converter; d, AD. One healthy control 77 years of age with normal cognitive function had high PIB retention as earlier reported at baseline and 2 year follow-up studies (Klunk et al., 2004; Engler et al., 2006).

(data was available for six of the MCI subjects that converted to AD).

3.2. PIB retention

The individual data of PIB retention in the posterior cingulum for the MCI patients AD patients and healthy controls are presented in Fig. 1. The mean value for the MCI patients is between the corresponding PIB retention for the HC and AD groups. The PIB retention data for the seven MCI patients that later have converted to AD are all above the mean value (filled circles). The MCI patient in Fig. 1 with highest PIB retention is still a MCI patient after 25 months follow-up but has strong hereditary dispostion for dementia. Example of images from one MCI converter and one MCI non-converter is shown in Fig. 2, together with 1 healthy control and one AD patient. The mean values and statistical analysis between the groups are shown in Table 2. Statistical analysis revealed significantly lower PIB retention in the MCI patients in the frontal, parietal and temporal cortices and the posterior cingulum compared with that in the AD group ($p<0.01$). The total MCI group showed no significant difference compared to the HCs ($p>0.01$). Analysis of PIB retention in the subgroup MCI converters revealed high retention in cortical brain regions in all seven subjects. Compared with the HC group, the MCI converters showed significantly higher PIB retention in the frontal, parietal and temporal cortices ($p<0.01$). There were no significant difference between the MCI converters and the AD patients in any region ($p>0.01$). The MCI converters revealed significantly higher PIB retention in the posterior cingulum ($p<0.01$) compared with the non-converters. There was no significant difference between HC and MCI non-converters ($p>0.01$) in any cortical brain region. The MCI non-converters had significantly lower PIB retention in cortical brain regions compared to the AD group ($p<0.01$).

3.3. Cerebral glucose metabolism

The results from statistical analysis of rCMRglc are shown in Table 3. There was no significant difference in rCMRglc between MCI patients and healthy controls in any cortical brain region ($p>0.01$). The MCI patients, in comparison to

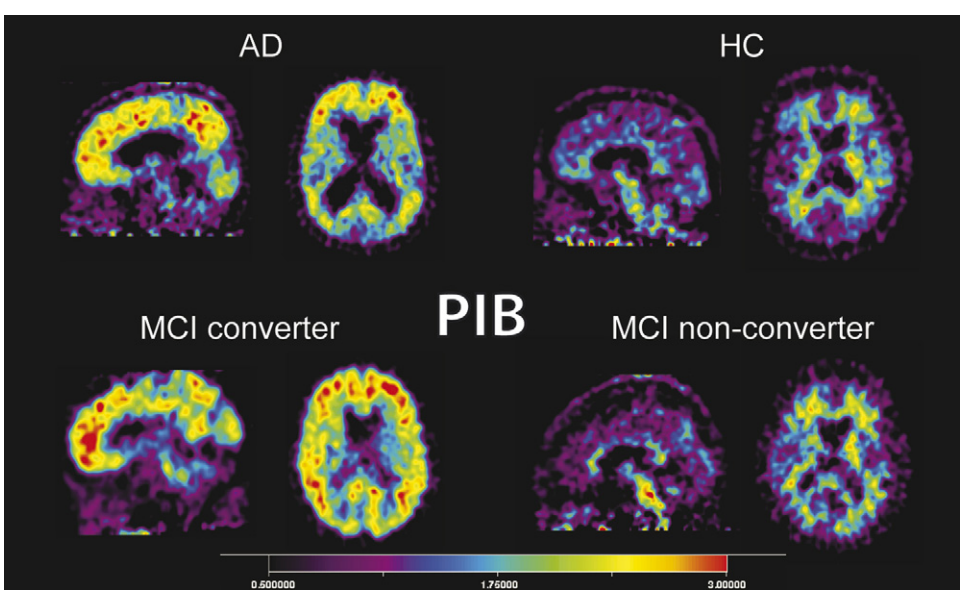

Fig. 2. PIB retention in one MCI converter, one MCI non-converter, one AD patient, and one healthy control. The PET scans show PIB retention at a sagittal and longitudinal section at the level of the basal ganglia. Red indicates high, yellow medium and blue low PIB retention. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 2
PIB retention in AD patients, MCI patients and the two subgroups MCI non-converters (MCI-nc) and MCI converter (MCI-c) and healthy controls (HC)

	Fr ctx	Par ctx	Tmp ctx	Cing post	WhM
AD	2.3 ± 0.5	2.2 ± 0.4	1.8 ± 0.3	2.2 ± 0.4	1.8 ± 0.2
MCI	1.6 ± 0.6*	1.7 ± 0.5*	1.5 ± 0.3*	1.7 ± 0.6*	1.8 ± 0.3
MCI-c	2.0 ± 0.4#	2.0 ± 0.4#	1.6 ± 0.2#	2.2 ± 0.3¥	1.8 ± 0.3
MCI-nc	1.4 ± 0.5*	1.6 ± 0.6*	1.4 ± 0.3*	1.5 ± 0.6*	1.8 ± 0.3
HC	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.1	1.4 ± 0.5	1.9 ± 0.1

Fr, frontal; Par, parietal; Tmp, temporal; Cing post, posterior cingulum; WhM, subcortical white matter.
* Statistical significance between MCI and MCI non-converters compared to AD patients ($p < 0.01$).
# Statistical significance between MCI converters compared to healthy controls ($p < 0.01$).
¥ Statistical significance between MCI converters compared to MCI non-converters ($p < 0.01$). Analysis performed with Student's *t*-test, two-tailed, unequal variance and corrected for multiple comparisons with Bonferroni correction.

Table 3
rCMRglc values in AD patients, MCI patients and the two subgroups MCI non-converters (MCI-nc)and MCI converters (MCI-c) and healthy controls (HC)

	Fr ctx	Par ctx	Tmp ctx	Cing post	WhM
AD	1.4 ± 0.2	1.1 ± 0.2	1.1 ± 0.1	1.1 ± 0.2	0.8 ± 0.2
MCI	1.7 ± 0.2*	1.7 ± 0.3*	1.3 ± 0.2*	1.7 ± 0.3*	0.9 ± 0.2
MCI-c	1.6 ± 0.3	1.5 ± 0.5	1.2 ± 0.2	1.5 ± 0.5	0.9 ± 0.2
MCI-nc	1.8 ± 0.2*	1.7 ± 0.2*	1.3 ± 0.1*	1.7 ± 0.2*	0.9 ± 0.2
HC	1.5 ± 0.3	1.5 ± 03	1.2 ± 0.3	1.5 ± 0.3	0.8 ± 0.1

Fr, frontal; Par, parietal; Tmp, temporal; Cing post, posterior cingulum; WhM, subcortical white matter. Values are normalized to the pons (ROI/ref)
* Statistical significance between MCI and MCI non-converters compared to AD patients ($p < 0.01$, corrected for multiple comparisons with Bonferroni correction), Student's *t*-test, two-tailed, unequal variance.

AD patients, showed significantly higher rCMRglc in the cortical brain areas studied ($p < 0.01$). Neither the MCI converters nor the MCI non-converters did show any significant difference in rCMRglc compared to the healthy controls. The MCI non-converters showed significantly higher rCMRglc in the cortical areas compared to the AD patients ($p < 0.01$), while the MCI converters did not show any significant difference compared to AD ($p > 0.01$).

3.4. Correlation analysis

Significant correlations were observed between CSF $A\beta_{1\text{-}42}$ versus PIB retention in the frontal cortex and posterior cingulum (Table 4) ($p < 0.0042$, corrected for multiple comparisons). Correlations were also observed between cortical PIB retention versus tTau (Table 4), but they did not survive threshold after correction for multiple comparisons. Correlations between PIB retention in the posterior cingulum and CSF biomarkers are presented in Fig. 3A–C.

A significant negative correlation was observed between mean *Z*-score of episodic memory and PIB retention in the posterior cingulum ($p = 0.043$), frontal cortex ($p = 0.034$) and temporal cortex ($p = 0.0064$) (not corrected for multiple comparisons). Correlations between episodic memory and PIB retention in the posterior cingulum is presented in Fig. 3D. There were no significant correlations between glucose metabolism and PIB retention in any of the brain regions analysed (data not shown; $p > 0.05$), and no correlation between mean *Z*-score of episodic memory and glucose metabolism in any of the brain regions analysed (data not shown; $ps > 0.05$).

4. Discussion

MCI is considered as a transitional stage between normal aging and dementia, especially early AD. There are problems and limitations of the clinical diagnosis of MCI. In this study we describe the measurement of PIB retention by means of PET imaging in a group of MCI patients from an academic medical centre where the subjects were recruited among clinical patients referred to the geriatric

Table 4
Correlation between PIB vs. $A\beta_{1\text{-}42}$, tTau and pTau in MCI patients showing Spearman rank order correlation *R* $A\beta_{1\text{-}42}$: $n = 16$; tTau: $n = 18$; pTau: $n = 15$)

ROI	PIB vs. $A\beta_{1\text{-}42}$	PIB vs. tTau	PIB vs. pTau
Fr ctx	−0.74*	0.64#	0.52
Par ctx	−0.64#	0.61#	0.52
Tmp ctx	−0.66#	0.51	0.48
Cing post	−0.70*	0.52	0.48

n, number of subjects; ROI, region of interest; rCMRglc, relative cerebral metabolic rate of glucose; $A\beta_{1\text{-}42}$, amyloid-$A\beta_{1\text{-}42}$; tTau, total Tau protein; pTau, phosphorylated Tau protein; Fr, frontal; Par, parietal; Tmp, temporal; Cing post, posterior cingulum; Statistical significance indicated as.
* $p < 0.0042$, corrected for multiple comparisons with Bonferroni correction.
# $p < 0.01$, not corrected for multiple comparisons.

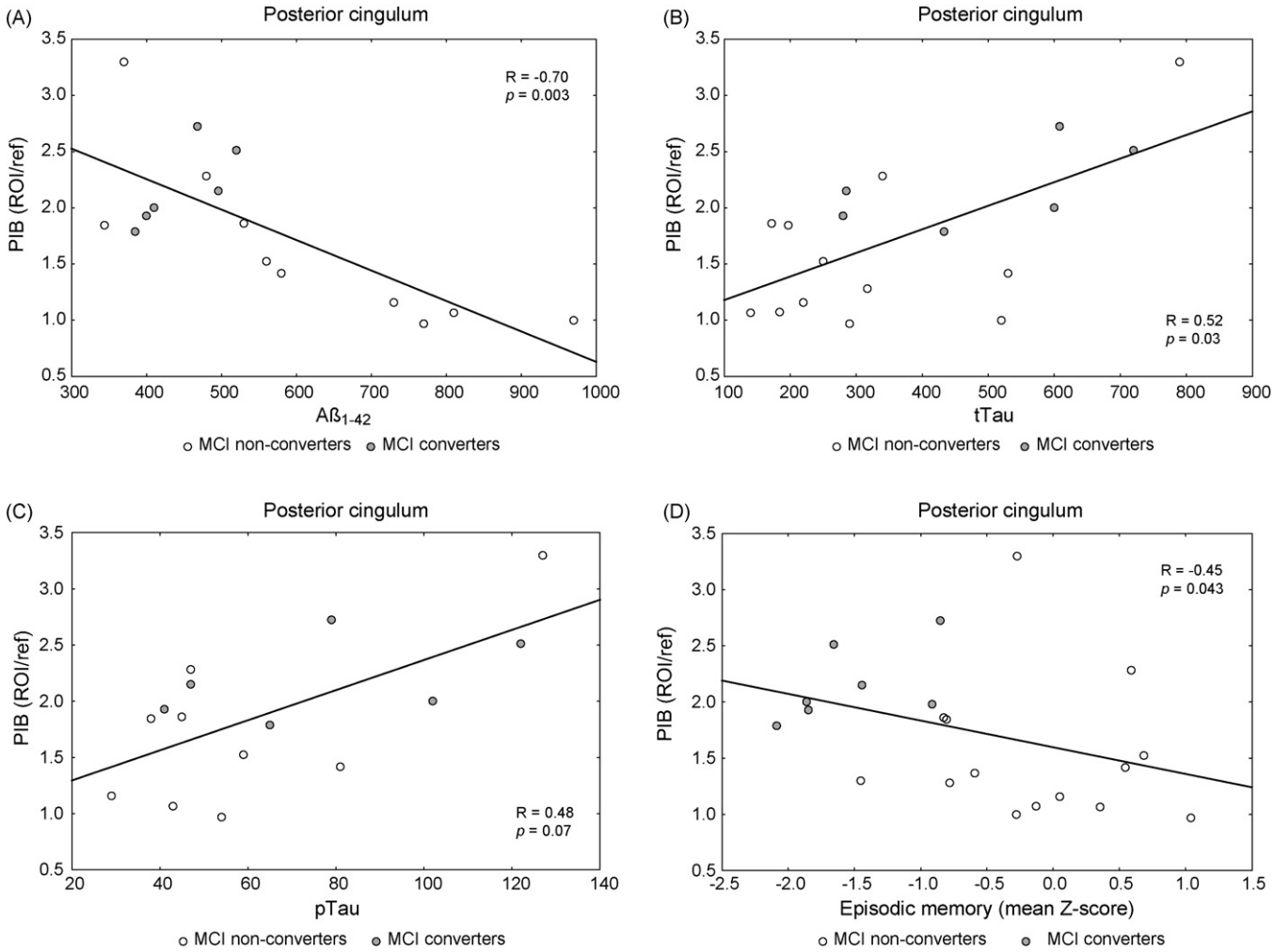

Fig. 3. (A–D) Correlation between PIB retention in posterior cingulum and $A\beta_{1-42}$ (A), respectively, total Tau (tTau) (B), phosphorylated Tau (pTau) (C) and episodic memory (mean *Z*-score (D). MCI patients who converted to AD are indicated with filled circles, non-converted MCI patients are indicated as open circles. Pathological CSF levels of $A\beta_{1-42}$ is <450 pg/ml, tTau is >400 pg/ml, and pTau is >60 pg/ml. *R* = Spearman rank order correlation *R*.

department by primary care physicians in the Stockholm area. It is known that MCI may have a multitude of causes, including AD and other forms of dementia as well as depression and various physical disorders. Since MCI is a common syndrome there is a great need to establish methods for predicting progression to AD (Galvin et al., 2005; Morris et al., 2001; Petersen, 2004; Storandt et al., 2002). This is of special interest when new treatment strategies are established where a prerequisite for successful treatment will be early detection of the disease. The MCI patients in this study were fairly young (mean age 63.3 ± 7.8) compared with those in an earlier report from our clinic where, in which 133 subjects (mean age 69.5 ± 5.8) from Karolinska University Hospital Huddinge were compared with 170 subjects (mean age 78.5 ± 8.4) from the Mayo Clinic (Arnaiz et al., 2004). The global cognitive function was in the very mild range.

The results in the present study show higher mean PIB retention among the MCI patients than in age-matched healthy controls, but lower mean PIB retention than in AD patients. Seven of the 21 MCI patients converted at later clinical follow-ups to AD during 2–16 months after their respective PET scan (8.1 ± 6.0 S.D. months). These seven converting MCI patients differed as a group significantly from the non-converts with respect to higher proportion of ApoE $\varepsilon 4$ carriers, impairment in episodic memory, lower CSF $A\beta_{1-42}$ and higher PIB retention. It is quite apparent from what is presented in Fig. 1 that MCI patients can show high or low PIB retention as also recently reported (Lopresti et al., 2005). In the present study 11 out of 21 the MCI patients showed high retention in the frontal, parietal, and temporal cortices, comparable to data in a previous study on AD patients (Klunk et al., 2004). Nine of the MCI patients with high PIB retention were considered of amnestic type (Winblad et al., 2004). Three of the MCI patients with low PIB retention compared to HC were considered of amnestic type. The seven MCI patients with high PIB retention who converted to AD at follow-up retention were all MCI of amnestic type. Since the neuropathological feature of AD is probably present very early (Morris et al., 2001) the high PIB retention in a subgroup

underline the heterogeneity and difficulty in an accurate diagnosis but highlights also the possibility to discriminate early by amyloid imaging.

Heterogeneity in changes of cerebral glucose metabolism has been suggested in MCI patients (Anchisi et al., 2005). However, in this study we did not detect generally a decreased glucose metabolism in cortical brain areas as earlier reported in MCI patients (Anchisi et al., 2005; Chetelat and Baron, 2003; Drzezga et al., 2003). Nevertheless, in some individual MCI patients, decreased rCMRglc was found in areas, such as the parietal and temporal cortices. More interestingly is that higher cerebral glucose metabolism in the MCI group compared to AD patients and controls might be a sign for possible ongoing compensatory mechanisms. There might be deterioration of rCMRglc at an early stage in the progression to AD although the amyloid deposition is probably an earlier event in the AD pathology than changes in cerebral glucose metabolism. The negative correlation between rCMRglc and PIB retention that we earlier observed in patients with mild AD (Klunk et al., 2004) was not present in the MCI group. This finding suggests that there is a difference in the time courses of amyloid deposition and deterioration of rCMRglc in MCI. The observation is supported by the results of our recent study, in which AD patients were rescanned with PIB and FDG after 2 years. The retention of PIB was found to be unchanged at 2-year follow-up while rCMRglc and cognition had deteriorated (Engler et al., 2006).

A relatively large inter-individual variation was revealed in cognitive function between the MCI patients where the seven patients that later converted to AD showed a decrease in episodic memory as MCI patients. We also observed a negative correlation between episodic memory and PIB in the MCI patients in contrast to the lack of correlation between global cognitive function and PIB retention. These results were not corrected for multiple comparisons due to the exploratory nature of the study implicating caution in interpreting the results. The strongest correlation was found between episodic memory and PIB retention in temporal cortex, a part of the brain known to be involved in memory processes ($R = -0.58$; $p = 0.006$). The lack of correlation between rCMRglc and the analysed cognitive tests are somewhat surprising due to the fact that several studies show decrease in glucose metabolism already in MCI patients (Chetelat et al., 2003; Drzezga et al., 2003). One plausible explanation is the heterogeneity of the MCI group.

Cerebrospinal fluid biomarkers, such as $A\beta_{1\text{-}42}$, tTau and pTau might be useful when identifying MCI patients at risk of developing AD (Blennow and Hampel, 2003; Buerger et al., 2005; Herukka et al., 2005). In a recent 4-year follow-up study it was shown that a combination of $A\beta_{1\text{-}42}$ and tTau yielded a sensitivity of 95% and a specificity of 83% in detecting MCI patients that developed AD (Hansson et al., 2006). Interestingly, we detected significant correlations between CSF $A\beta_{1\text{-}42}$ and tTau versus PIB retention in the brain for the 18 patients in which CSF was available. It can be observed from Fig. 3A that 11 MCI patients showed high PIB retention (1 S.D. above the mean for HC) but only 5 of these patients showed pathological levels of $A\beta_{1\text{-}42}$, 7 showed pathological levels of tTau and 6 showed pathological levels of pTau. All seven of the MCI patients that converted to AD showed high PIB retention and from the CSF data (available from six of the patients) pathological levels of $A\beta_{1\text{-}42}$ was observed in three patients and pathological levels of pTau in four patients. It thus seems as if PIB imaging might be more effective than CSF biomarkers in the discrimination of prodromal AD patients. A larger study of MCI patients with PIB scans and CSF measurements is needed. An inverse relationship between PIB retention and $A\beta_{1\text{-}42}$ in humans was recently suggested by Fagan et al. (2006), while they found no correlation between PIB retention versus tTau or pTau (Fagan et al., 2006). A possible explanation for the lack of correlation might be the low number of AD patients (Fagan et al., 2006). Although our findings in the present study with PIB are promising, further studies are needed to evaluate the predictive value of PIB-PET studies in a larger population of MCI patients.

In this study we demonstrate that PIB retention in MCI patients is intermediate between healthy controls and AD patients. There are MCI patients with high or low PIB retention. The seven MCI patients that later, at follow-up, converted to AD all showed significant high levels of amyloid in the brain compared to MCI non-converters and healthy controls. Interestingly in this clinical material of MCI patients there is a subgroup of patients with PIB retention in the range of healthy controls. A significant correlation was observed between PIB retention and CSF $A\beta_{1\text{-}42}$, tTau and episodic memory, respectively. Amyloid neuroimaging might be a promising diagnostic tool for detection of subjects at risk of developing AD, as well as for evaluating new anti-amyloid therapy.

Conflicts of interest

A.W., A.R., B.L. are employed by Uppsala Imanet GE HealthCare, Uppsala, Sweden. The dementia program within Imanet which this manuscript is a part of has been driven since the start as an academic program and the employees have no financial benefit of the work. None of the other authors have any conflict of interest.

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A New Clinical Scale for the Staging of Dementia

CHARLES P. HUGHES, LEONARD BERG, WARREN L. DANZIGER, LAWRENCE A. COBEN and RONALD L. MARTIN

Summary: Accurate clinical staging of dementia in older subjects has not previously been achieved despite the use of such methods as psychometric testing, behavioural rating, and various combinations of simpler psychometric and behavioural evaluations. The Clinical Dementia Rating (CRD), a global rating device, was developed for a prospective study of mild senile dementia—Alzheimer type (SDAT). Reliability, validity, and correlational data are discussed. The CDR was found to distinguish unambiguously among older subjects with a wide range of cognitive function, from healthy to severely impaired.

By far the commonest cause of progressive intellectual deficit in older persons is senile dementia—Alzheimer type (SDAT) (Wells, 1978). Determining the presence of the disorder and its severity is central to any clinical study of SDAT. Even though the severity of the pathologic lesions at autopsy may be an indicator of the clinical status (Blessed *et al*, 1968), investigation and potential treatments require that this assessment be made during life.

Clinical staging in dementia has been approached variously. Performance has been scored on established, often lengthy psychometric tests (Birren, 1964; Botwinick, 1978), but Piercy (1959) summarized the problems of using formal psychometric tests to reflect stages of intellectual impairment. Particularly difficult is the selection of cut off scores to group subjects reliably. His suggestion that these tests be used to evaluate subjects already grouped by other means has largely been followed.

Others have used behavioural rating scales (Salzman *et al*, 1972) in which the subject is observed and scored on several activities and abilities. Composed of 18 behavioural rating subscales, the Sandoz Clinical Assessment Scale—Geriatric (Shader *et al*, 1974) was used to separate subjects with dementia and depression from healthy controls. While the groups were separable statistically, only a few items seemed useful. The lack of a standardized method of administration hampers its reproducibility, a problem common to other such scales (Hersch *et al*, 1978).

In view of the difficulty in testing many demented subjects with formal psychometric batteries, some authors have turned to simplified psychometric tests in which the examiner may be flexible in order to obtain the subject's best performance (Roth and Hopkins, 1953; Shapiro *et al*, 1956; Kahn *et al*, 1960; Hemsi *et al*, 1968; Coblentz *et al*, 1973; Pfeiffer, 1975; Folstein *et al*, 1975; Copeland *et al*, 1976; Fishback, 1977; Hare, 1978; Hersch, 1979; Carlen *et al*, 1981). Kahn *et al* (1960) and Pfeiffer (1975) used just ten short questions to measure orientation and memory. Other assessments, such as the Mattis scale (Coblentz *et al*, 1973; Hersch, 1979), are more complex and may require an hour to administer. Even the simplest of these tests is reasonably accurate in separating large groups of subjects into those with and without cognitive impairment.

The simplified psychometric scales pose two problems. They presuppose a certain background of information in all subjects, and they fail to separate the more severe grades of dementia. These problems suggest that a useful 'rating' of dementia can only be 'global', one which assesses both behavioural and psychometric data.

An early global rating was the Crichton Geriatric Behavioural Rating Scale (Robinson, 1961). While not well suited to a study of cognitive loss (containing only two relevant measures out of 11), it was an attempt to specify levels of global function. Roberts and Caird (1976) reported good correlation between the Crichton and their own dementia rating scale, which divided subjects into four groups (normal, mild, moderate, and severe impairment) with descriptive sentences for each.

Early in our prospective study of patients with mild SDAT and healthy controls it was appreciated that a global measure of dementia must be used for comparison with other variables: psychometric tests, electroencephalography, event-related potentials, and quantitative computed tomography (CT). We devised a Clinical Dementia Rating (CDR) which resembles that of Roberts and Caird but offers more detail. The

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CDR has been used extensively by the Washington University Memory and Aging Project in this prospective study and in other work (Hughes and Gado, 1981).

Methods

Subjects ranged in age from 65 to 80. There were 58 healthy controls (CDR 0), 43 subjects with mild dementia (CDR 1) and 16 subjects with questionable dementia (CDR 0.5). All were living in the community; none were in hospital or resident in nursing homes or other institutions. Only a few subjects were referred by other physicians in response to letters sent to the medical community. The majority of the impaired subjects were recruited when their families responded to newspaper, television and radio discussions of the research program. Healthy control control subjects responded to the same public announcements or were among those who had already volunteered for other studies at our university. Control subjects were matched with the impaired subjects for age, sex and social position (Hollingshead, 1957).

The criteria for the diagnosis of SDAT were global and gradual intellectual deterioration for 6 months or longer, exclusion of reversible dementias and other medical disorders (including medication) that cause mental impairment, exclusion of other psychiatric disorders (including alcohol abuse, major depression, 'pseudodementia') and exclusion of other neurologic diseases, such as parkinsonism, Huntington's disease, communicating hydrocephalus, multi-infarct dementia (Rosen *et al*, 1980), stroke and seizure disorders. Other reasons for exclusion were severe loss of vision or hearing, insulin dependent diabetes mellitus, malignancy and other serious medical illnesses. We eliminated 489 impaired subjects in the search for our study population of 117.

Eighteen additional subjects with moderate dementia (CDR 2) and 3 subjects with severe dementia (CDR 3), who are not enrolled in the longitudinal study, were studied to illustrate the full range of the CDR, but statistical analyses include only CDR 0, 0.5 and 1.

The interviews were conducted as out-patients at the Department of Neurology and required about 90 minutes. Collateral source (usually the spouse or child) and subject were interviewed separately. All initial interviews were evaluated by the interviewer and were also recorded on videotape for rating by an independent reviewer. The interviews and videotape reviews were done by the same group of three neurologists and one psychiatrist. Information on the subject's family history, social, educational and cultural background, medical and psychiatric history was gathered in a standardized structured interview devised by us, the Initial Subject Protocol (ISP). In addition to giving a history of the illness, the collateral source is asked to rate the subject on a number of items (memory items and problem solving abilities) on a scale from 1 (as good as in the best of the subject's recent years) to 9 (the worst possible function the collateral source can conceptualize). The subject's ability to dress and care for self is graded by the collateral source as normal or impaired to various degrees. Then the subject is given tasks in memory, orientation, abstraction, calculation, judgment and problem solving. These are rated from 0 (good performance) to 3 or 4 (worst performance) according to defined scoring standards.

The ISP includes previously described methods to rate subjects with dementia. The Dementia Scale (DS) of Blessed *et al* (1968) is a behavioural checklist derived exclusively from questions asked of the collateral source and is the one scale in the literature which has been compared with neuropathologic findings. This scale has a perfect score of 0 and a worst score of 28. The Short Portable Mental Status Questionnaire (SPMSQ) of Pfeiffer (1975), composed of just ten questions, has the advantage of having been standardized on older adult out-patient populations. Scores on this test range from 0 (normal) to 10 (severe dementia). The Face-Hand Test (FHT) (Fink *et al*, 1952; Kahn *et al*, 1960; Zarit *et al*, 1978) is included as a performance measure unrelated to the intellectual background of the subject. It is scored from 0 (normal) to 16 (severe impairment). Although the DS, SPMSQ and FHT results influence the global CDR, neither these older tests nor any other portion of the ISP determine the CDR directly by numerical scoring.

Other questions are asked of both the collateral source and subject in order to provide sufficient information for rating the subject in each of the six cognitive and behavioural categories that form the basis for the CDR: memory (M), orientation (O), judgment and problem solving (JPS), community affairs (CA), home and hobbies (HH), and personal care (PC). The rater must consider the subject's function only in relation to cognitive ability and to the subject's past performance, not to that of the general population..

Also in the subject interview are verbal tasks taken from the Boston Diagnostic Aphasia Evaluation (Goodglass and Kaplan, 1972). Portions of both the collateral source and subject interview are devoted to evaluating the subject for depression (Hamilton, 1967; Feighner *et al*, 1972).

The CDR is depicted in Table I. Subjects are assigned a rating of healthy (CDR 0), mild (CDR 1), moderate (CDR 2), or severe dementia (CDR 3). A rating of questionable dementia (CDR 0.5) is included

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TABLE I

Clinical dementia rating (CDR)

	Healthy CDR 0	Questionable dementia CDR 0.5	Mild dementia CDR 1	Moderate dementia CDR 2	Severe dementia CDR 3
Memory	No memory loss or slight inconstant forgetfulness	Mild consistent forgetfulness; partial recollection of events; 'benign' forgetfulness	Moderate memory loss, more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented		Some difficulty with time relationships; oriented for place and person at examination but may have geographic disorientation	Usually disoriented in time, often to place	Orientation to person only
Judgment + problem solving	Solves every day problems well; judgment good in relation to past performance	Only doubtful impairment in solving problems, similarities, differences	Moderate difficulty in handling complex problems; social judgment usually maintained	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Independent function at usual level in job, shopping, business and financial affairs, volunteer and social groups	Only doubtful or mild impairment, if any, in these activities	Unable to function independently at these activities though may still be engaged in some; may still appear normal to casual inspection	No pretense of independent function outside home	
Home + hobbies	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests well maintained or only slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly sustained	No significant function in home outside of own room
Personal care	Fully capable of self care		Needs occasional prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; often incontinent

Score as 0.5, 1, 2, 3 only if impairment is due to cognitive loss.

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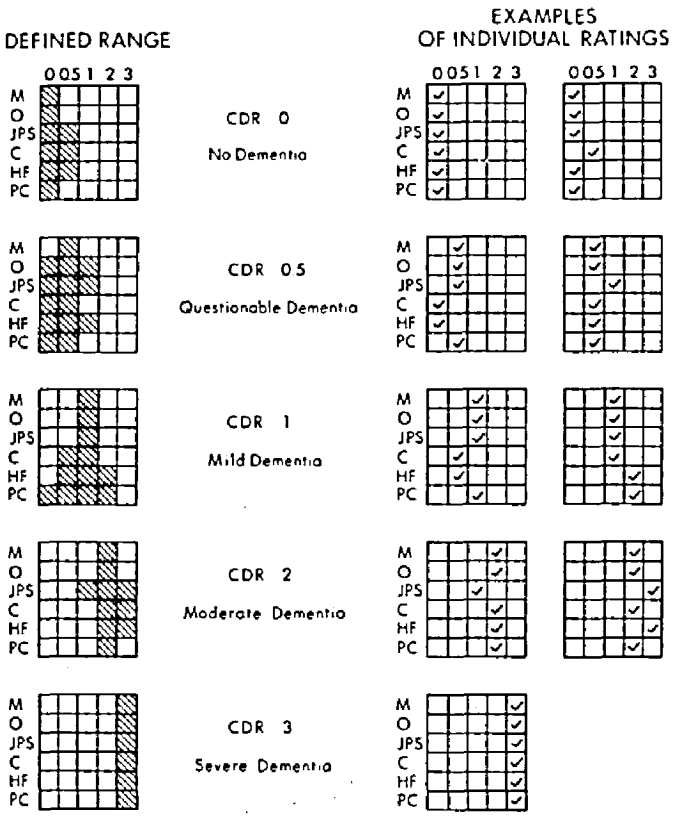

FIG 1.—The assigning of the CDR. Shaded areas indicate defined range within which scores of individual subjects must fall to be assigned a given CDR.

M = Memory; O = Orientation; JPS = Judgment and problem solving; CA = Community affairs; HH = Home functions; PC = Personal care.

Instructions for assigning the CDR are as follows:

Use all information and make the best judgment. Score each category (M, O, JPS, CA, HH, PC) as independently as possible. Mark in only one box, rating each according to subject's cognitive function. For determining the CDR, memory is considered the primary category; all others are secondary. If at least three secondary categories are given the same numerical score as memory, then CDR = M. If three or more secondary categories are given a score greater or less than the memory score, CDR = score of majority of secondary categories, unless three secondary categories are scored on one side of M and two secondary categories are scored on the other side of M. In this last circumstance, CDR = M.

When M = 0.5, CDR = 1 if at least three of certain others (O, JPS, CA, HH) are scored 1 or greater (PC not influential here). If M = 0.5, CDR cannot be 0; CDR can only be 0.5 or 1. If M = 0, CDR = 0 unless there is slight impairment in two or more secondary categories, in which case CDR = 0.5.

for subjects who are neither clearly demented nor healthy. For subjects in this stage the complaints of the family centre on memory impairment. While frequently evident, the forgetfulness does not interfere significantly with the subject's life. The subject often remembers later what has been temporarily forgotten. Many in this group have syndromes compatible with the 'benign senescent forgetfulness' of Kral (1962) while others probably have normal cognitive function but may be mildly depressed or excessively concerned over minor forgetfulness. Still others are probably in a very early stage of SDAT.

Although an effort has been made to provide unambiguous descriptions of the typical performance, some subjects do not have the same degree of impairment in each category. Fig 1 illustrates ranges of individual functional ratings within each CDR stage. To the right are given examples of subjects with CDR 0, 0.5, 1, 2, 3.

Data from the ISP were entered into a computer. Appropriate scores were tested by Pearson and Spearman rank correlation coefficients. Since the results with the two coefficients were essentially the same, only the Pearson measures are given.

Results

In a previous pilot study of 35 similar subjects, inter-rater reliability was good (r = 0.89). In the present longitudinal study of subjects with CDR 0, 0.5, 1, only six of 123 were eliminated because the interviewer and reviewer disagreed in assigning the CDR.

Table II includes data on 138 subjects whose cognitive function was staged by the CDR. SPMSQ scores vary appropriately among groups of healthy controls and milder stages of SDAT but do not separate the more severe stages (CDR 2, 3) from each other. Similarly FHT scores do not differ sufficiently between CDR 2 and CDR 3 to be useful but do show appropriate changes in the milder stages. DS results are much the same, showing little difference among the milder stages of dementia.

In Table III are shown the correlations among the various tests both with each other and with the CDR. All correlations are highly significant ($P < 0.0001$) but the DS and the SPMSQ show the strongest relationships with the CDR. (Data in Tables III and IV refer only to subjects with CDR 0, 0.5 and 1).

Table IV lists other ISP items, singly and in combination, together with their correlations among CDR groups. Among items in the collateral source interview, only the report on the subject's ability to dress himself and on urinary incontinence did not correlate significantly with the CDR. All items of the subject

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TABLE II
The CDR and other dementia assessments

CDR		0	0.5	1	2	3
N		58	16	43	18	3
Age		71.7±4.1	71.4±4.0	71.4±5.0	70.5	73.3
SPMSQ[1]	Mean±SD Range	0.4±0.6 (0–2)	1.8±1.7 (0–5)	5.7±2.2 (1–10)	8.4	8.7
FHT[2]	Mean±SD Range	0.8±2.0 (0–11)	2.5±4.2 (0–15)	7.3±6.4 (0–16)	14.3	16.0
DS[3]	Mean±SD Range	0.2±0.7 (0.0–4.5)	3.1±2.0 (0.5–7.0)	5.1±3.1 (1.0–15.5)	8.2	10.3

[1] Short portable mental status questionnaire (Pfeiffer, 1975).
[2] Administered and scored according to Zarit *et al* (1978).
[3] Dementia score of Blessed *et al* (1968).

TABLE III
Correlations among the CDR and other dementia assessments

	CDR	DS	SPMSQ	FHT
CDR	1.00			
DS	0.74[1]	1.00		
SPMSQ	0.84	0.61	1.00	
FHT	0.57	0.45	0.62	1.00

[1] All of these values significant ($P \leq .0001$).

performance selected for statistical review correlated well with the final CDR rating.

Ninety subjects have been assessed a second time, 6 to 9 months after the first interview. The second assessment was performed independently by raters who were unfamiliar with the subject's original CDR. Table V shows the change over time in CDR ratings for these 90 subjects. All healthy subjects (CDR 0) remained so. Some with mild dementia (CDR 1) remained at the same stage, while others progressed to more severe stages. None was reclassified as CDR 0 or CDR 0.5. One subject deteriorated within 9 months from CDR 1 to CDR 3 and at autopsy had severe SDAT. Of the subjects rated as 'questionable' (CDR

TABLE IV
Correlations among components of the ISP and the CDR

Collateral source information		Subject performance	
Subject ability	CDR	Subject ability	CDR
1. Memory for recent events	0.85*	1. Recall of 3 objects	0.76*
2. Memory for events of years ago	0.57*	2. Recall of recent personal events	0.66*
3. Memory for current news events	0.83*	3. Recall of job	0.42*
4. Ability to handle problem situations	0.86*	4. Recall of schooling	0.36*
5. Ability to maintain intellectual interests	0.70*	5. Insight into examination	0.71*
6. Ability to maintain home activities	0.74*	6. Ability to abstract	0.66*
7. Ability to dress self	0.10	7. Ability to calculate	0.70*
8. Urinary or fecal incontinence	0.24	8. Judgment	0.67*
9. Memory (#1+#2+#3)	0.87*	9. Memory (#1+#2+#3+#4)	0.80*
10. Functional activity (#4+#5+#6)	0.85*	10. Other cognitive (#6+#7+#8)	0.74*

* All of these values significant ($P < .0001$).

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TABLE V
Changes in CDR over time

Subjects initially classified		CDR assigned to these subjects 6–9 months later				
CDR	N	0	0.5	1	2	3
0	50	50	0	0	0	0
0.5	14	1	9	4	0	0
1	26	0	0	19	6	1

0.5), a few progressed to definite dementia, one was later rated healthy, and most were unchanged. This heterogeneity of the CDR 0.5 group was to be expected.

Discussion

The staging of clinical dementia in older subjects by the CDR has shown good inter-rater reliability. This result suggests that the descriptions of the six cognitive and behavioural categories have similar meaning to different clinicians trained in the use of the method. The fact that the CDR shows strong correlations with previously devised dementia ratings (DS, SPMSQ, FHT) suggests that these scales all measure similar qualities. While DS, SPMSQ, and FHT distinguish moderate or severe dementia from normal subjects and are easier to administer, it has not been possible with any of these simple tests, nor with the more elaborate scales mentioned above, to separate subjects reliably into the various stages of dementia used in the CDR. The strong correlations of the CDR with each of the simpler tests and the strong inter-rater correlations for the CDR attest to its reliability in staging dementia.

The correlations between the CDR and items from the collateral source (Table IV) were as expected. Only the subject abilities to dress and to remain continent of urine were not highly correlated with the CDR, since the subjects (CDR = 0, 0.5, 1) had only mild dementia or were healthy controls. Factors 9 and 10 of the collateral source information (Table IV) correlate particularly well with the final CDR. They represent ratings of the subject memory and abilities to handle everyday problem situations, household duties and hobbies.

From the subject interview portion of the ISP, factors 9 and 10 (Table IV) are correlated with the CDR at a slightly higher level than any of the individual items alone. Since scoring on items in the ISP did not lead automatically to a particular CDR, the various correlations are indications of the effect of the various items on the global rating.

The validity of the CDR is both a more important issue and a more difficult problem. No physiologic, anatomic, biochemical, psychometric or neuropathologic test is available with which to validate such a scale. Even a complete neuropathologic study cannot distinguish between subjects who are normal and those who exhibit a mild degree of dementia. Only severe SDAT can be identified by this means (Blessed *et al*, 1968).

The only reasonable validation of a clinical method of staging SDAT lies in the natural history of the dementia, followed by a careful neuropathologic examination if the subject dies with a CDR of 2 or 3. That study will require further years, but at 6 to 9 months after entry into the longitudinal study, the original CDR has accurately predicted the subsequent rating (Table V).

The usefulness of the Clinical Dementia Rating is based on several factors. It is a global rating which allows the clinician to consider many characteristics of a given patient. It can be used by neurologists, psychiatrists, psychologists, and others experienced in assessing cognitive function of older persons. Guidelines are furnished for combining the separate assignments in the six behavioural and cognitive categories into a global CDR. These guidelines have helped achieve a high inter-rater reliability. Finally, the CDR focuses on cognitive function, not on disability arising from other medical, social or emotional problems.

For these reasons, the CDR should be most useful when dementia is being studied and global assessment of cognitive function is required in older persons. It will be applicable to a wide range of mild through more severe stages of dementia and to subjects who are neither clearly normal nor clearly demented.

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Complete copies of the Initial Subject Protocol will be furnished on request.

*Charles P. Hughes, M.D., *Associate Professor of Neurology*,
Leonard Berg, M.D., *Professor of Clinical Neurology*,
Warren Danziger, Ph.D., *Research Assistant of Neurology*,
Lawrence A. Coben, M.D., *Associate Professor of Neurology*,
Department of Neurology and Neurological Surgery (Neurology), Washington University School of Medicine, 660 S. Euclid Avenue, St Louis, Missouri 63110, USA

Ronald L. Martin, M.D., *Assistant Professor of Psychiatry*,
Department of Psychiatry, Washington University School of Medicine

* Reprint requests.

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Post-mortem correlates of *in vivo* PiB-PET amyloid imaging in a typical case of Alzheimer's disease

Milos D. Ikonomovic,[1,2] William E. Klunk,[2] Eric E. Abrahamson,[1] Chester A. Mathis,[3] Julie C. Price,[3] Nicholas D. Tsopelas,[2] Brian J. Lopresti,[3] Scott Ziolko,[3] Wenzhu Bi,[3] William R. Paljug,[1] Manik L. Debnath,[2] Caroline E. Hope,[1] Barbara A. Isanski,[1] Ronald L. Hamilton[4] and Steven T. DeKosky[1,2]

[1]Department of Neurology, [2]Department of Psychiatry, [3]Department of Radiology and [4]Department of Neuropathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15213, USA

Correspondence to: Steven T. DeKosky, MD, Department of Neurology, 3471 Fifth Avenue, Suite 811, Pittsburgh, PA 15213, USA
E-mail: dekoskyst@upmc.edu

The positron emission tomography (PET) radiotracer Pittsburgh Compound-B (PiB) binds with high affinity to β-pleated sheet aggregates of the amyloid-β (Aβ) peptide *in vitro*. The *in vivo* retention of PiB in brains of people with Alzheimer's disease shows a regional distribution that is very similar to distribution of Aβ deposits observed post-mortem. However, the basis for regional variations in PiB binding *in vivo*, and the extent to which it binds to different types of Aβ-containing plaques and tau-containing neurofibrillary tangles (NFT), has not been thoroughly investigated. The present study examined 28 clinically diagnosed and autopsy-confirmed Alzheimer's disease subjects, including one Alzheimer's disease subject who had undergone PiB-PET imaging 10 months prior to death, to evaluate region- and substrate-specific binding of the highly fluorescent PiB derivative 6-CN-PiB. These data were then correlated with region-matched Aβ plaque load and peptide levels, [^{3}H]PiB binding *in vitro*, and *in vivo* PET retention levels. We found that in Alzheimer's disease brain tissue sections, the preponderance of 6-CN-PiB binding is in plaques immunoreactive to either Aβ42 or Aβ40, and to vascular Aβ deposits. 6-CN-PiB labelling was most robust in compact/cored plaques in the prefrontal and temporal cortices. While diffuse plaques, including those in caudate nucleus and presubiculum, were less prominently labelled, amorphous Aβ plaques in the cerebellum were not detectable with 6-CN-PiB. Only a small subset of NFT were 6-CN-PiB positive; these resembled extracellular 'ghost' NFT. In Alzheimer's disease brain tissue homogenates, there was a direct correlation between [^{3}H]PiB binding and insoluble Aβ peptide levels. In the Alzheimer's disease subject who underwent PiB-PET prior to death, *in vivo* PiB retention levels correlated directly with region-matched post-mortem measures of [^{3}H]PiB binding, insoluble Aβ peptide levels, 6-CN-PiB- and Aβ plaque load, but not with measures of NFT. These results demonstrate, in a typical Alzheimer's disease brain, that PiB binding is highly selective for insoluble (fibrillar) Aβ deposits, and not for neurofibrillary pathology. The strong direct correlation of *in vivo* PiB retention with region-matched quantitative analyses of Aβ plaques in the same subject supports the validity of PiB-PET imaging as a method for *in vivo* evaluation of Aβ plaque burden.

Keywords: Pittsburgh Compound-B; PiB; amyloid imaging; plaques; PET imaging

Abbreviations: Aβ = amyloid-β peptide; AC-PC = the plane of anterior comissure-posterior comissure; BA = Brodmann area; CAA = cerebral amyloid angiopathy; DVR = Logan distribution volume ratio; ELISA = enzyme linked immunoadsorbant assay; ERC = entorhinal cortex; FA = formic acid; IHC = immunohistochemistry; NFT = neurofibrillary tangles; PiB = Pittsburgh Compound-B; ROI = region-of-interest; Thio-S = thioflavin-S; VOI = volume-of-interest

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Introduction

Clinically symptomatic Alzheimer's disease can be diagnosed with high accuracy at academic centres (Lopez *et al.*, 2000*a*, *b*), but diagnosis in the community is less accurate (Pearl, 1997). Non-Alzheimer's disease dementia cases are not infrequently misdiagnosed as Alzheimer's disease (Mayeux *et al.*, 1998), and an emerging issue is the accurate prediction of conversion of patients with mild

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cognitive impairment (MCI) to Alzheimer's disease (Gauthier *et al.*, 2006). For optimal treatment, it is also critical to identify hallmark Alzheimer's disease pathology as early as possible. This pathology includes β-pleated sheet protein aggregates of amyloid-β (Aβ) peptides in senile plaques (SP) and hyperphosphorylated tau protein in neurofibrillary tangles (NFT) (Khachaturian, 1985; Mirra *et al.*, 1991; Consensus, 1998). The development of anti-amyloid therapies (Nicoll *et al.*, 2006) further emphasizes the need for a technology to assess treatment efficacy in individual patients. Thus sensitive *in vivo* markers of Alzheimer's disease brain lesions are needed (Consensus, 1998; Klunk, 1998; Growdon, 1999; Morris *et al.*, 2005; Thal *et al.*, 2006).

Positron emission tomography (PET) imaging of amyloid deposits (Klunk *et al.*, 2004; Verhoeff *et al.*, 2004; Small *et al.*, 2006) employs blood–brain barrier penetrant amyloid-binding compounds such as the thioflavin-T derivative Pittsburgh Compound-B (PiB) (Klunk *et al.*, 2001, 2004; Mathis *et al.*, 2002, 2004, 2005). Compared to age-matched, cognitively intact controls, Alzheimer's disease patients have 2- to 3-fold greater PiB retention on PET scans in brain areas known to have high amounts of fibrillar (i.e. Congo red and thioflavin-S labelled) Aβ plaques in Alzheimer's disease, such as frontal cortex and temporal lobe (Klunk *et al.*, 2004; Price *et al.*, 2005). Conversely, brain areas relatively unaffected by fibrillar Aβ pathology, such as the cerebellum, do not have increased PiB retention in Alzheimer's disease subjects. In agreement with these observations *in vivo*, studies of post-mortem Alzheimer's disease brain homogenates show that PiB binds preferentially to Aβ fibrils (Klunk *et al.*, 2003*a*), suggesting that PiB imaging could serve as a tool for monitoring changes in Aβ pathology in Alzheimer's disease. However, the evidence of a direct correlation between *in vivo* PiB-PET retention levels and Aβ plaques in the same subject is lacking. A recent study of a subject diagnosed with dementia with Lewy bodies, who at autopsy manifested severe vascular Aβ40 peptide-containing amyloid and infrequent SP, demonstrated that vascular amyloidosis can contribute significantly to PiB-PET signal (Bacskai *et al.*, 2007), as did a study of cerebral amyloid angiopathy (CAA) (Johnson *et al.*, 2007), while Lewy bodies themselves contributed little if at all to overall PiB-PET signal (Fodero-Tavoletti *et al.*, 2007). An *in vitro* study, comparing PiB autoradiography signal with Aβ/amyloid immuno/histology in adjacent autopsy tissue sections, reported a close correspondence of PiB signal with vascular amyloid and Aβ plaques in Alzheimer's disease, and with NFT in a non-Alzheimer's disease case (Lockhart *et al.*, 2007). However, the degree to which PiB binding to Aβ plaques compared to NFT contributes to *in vivo* recorded PiB retention signal, and the basis for region-specific differences in PiB retention levels in Alzheimer's disease brains *in vivo*, remains to be fully established.

In the present study we addressed these issues by examining the binding substrates of the highly fluorescent PiB derivative 6-CN-PiB in Alzheimer's disease post-mortem tissues collected from brain regions known to differentially accumulate neuritic and diffuse Aβ plaques and NFT, and to display differential PiB-PET retention levels *in vivo* (Klunk *et al.*, 2004). The physical, pharmacodynamic and pharmacokinetic properties of 6-CN-PiB are very similar to PiB (Mathis *et al.*, 2003), but the bright fluorescence of 6-CN-PiB greatly facilitates histochemical studies compared to the more weakly fluorescent parent compound, PiB. These combined histological/immunohistochemical analyses in brain tissue sections were supplemented by quantitative biochemical analyses of [^{3}H]PiB binding and Aβ peptide levels in brain tissue homogenates. We also examined the brain of an Alzheimer's disease subject who underwent PiB-PET imaging 10 months prior to death, to determine the relationship of ante-mortem PiB retention levels (determined by PET) to quantitative measures of 6-CN-PiB and Aβ labelled plaque load, neurofibrillary pathology, [^{3}H]PiB-binding levels and soluble and insoluble Aβ40 and Aβ42 peptide levels assessed post-mortem in the same brain regions of this subject. The results of these studies provide new insight into the basis for region-specific patterns of PiB binding *in vivo*, an understanding of which is critical for future evaluation of PiB-PET imaging during the course of Alzheimer's disease, and in the evaluation of effects of anti-amyloid therapies.

Methods

Clinical and neuropathological information: autopsy series

Brain tissues were obtained post-mortem from 27 dementia patients enrolled in the University of Pittsburgh Alzheimer's Disease Research Center (ADRC). Clinical diagnosis of Alzheimer's disease dementia utilized standard criteria (McKhann *et al.*, 1984). Mean Mini Mental Examination Score (MMSE) was 11 ± 8, mean age was 76 ± 11 years and mean duration of disease was 7 ± 4 years. Neuropathological diagnosis of 'definite Alzheimer's disease' was made by the established criteria (Mirra *et al.*, 1991; Consensus, 1998). Fifteen subjects had no other types of brain pathology besides occasional old infarcts; 11 had concomitant α-synuclein-immunoreactive neocortical Lewy bodies (Lewy body variant of Alzheimer's disease), and one subject had concomitant Parkinson's disease. Superior frontal and medial temporal cortices, parahippocampal gyrus, striatum and cerebellum were dissected at autopsy, immersed in cold 4% paraformaldehyde for 48 h, cryoprotected in sucrose and sectioned at 40 microns on a freezing sliding microtome. Tissue sections were collected serially in a cryoprotectant solution and stored at −20°C. Fresh-frozen tissue samples of frontal and occipital cortex grey matter were obtained from six of these Alzheimer's disease brains and were frozen at −80°C until analysis.

Clinical and neuropathological information: case study

A 64-year-old female with severe Alzheimer's disease (MMSE = 1 at the time of PiB-PET and MR imaging) was followed clinically in the University of Pittsburgh ADRC for 1 year. Dementia symptoms were first recorded 8 years prior to her death. Her apolipoprotein-E genotype was 3/4. The patient's mother, maternal aunt and uncle all had onset of Alzheimer's disease in their 80s. Her cognitive decline was described by family members as gradually progressive but more rapid in the 18 months prior to her death. At autopsy, the brain weighed 1070 g and upon gross examination was unremarkable except for cortical and hippocampal atrophy and minimal atherosclerosis of the circle of Willis. Multiple brain regions were sampled from the right hemisphere and flash frozen (unfixed) on dry ice for biochemical analyses; the left hemisphere was immersed in 10% formalin for histology.

PiB-PET and MRI scans and image analyses: case study

The subject underwent PiB-PET and MR imaging 10 months prior to death. Before the PET imaging session, a spoiled gradient recalled MR scan was obtained for anatomical region-of-interest (ROI) definition. MRI/PET image co-registration was performed using automated methods as previously described (Price *et al.*, 2005). PET scanning also was performed as previously described (Lopresti *et al.*, 2005); data were acquired using a Siemens/CTI ECAT HR+ scanner (3-dimensional mode, 63 image planes, 15.2 cm axial field of view) following the injection of ~555 MBq of high-specific activity (>21.4 GBq/μmol) PiB. PET emission data were acquired over 60 min (31 frames: 4 × 15 s, 8 × 30 s, 9 × 60 s, 2 × 180 s, 8 × 300 s), corrected for attenuation scatter, and radioactive decay, and reconstructed using filtered back-projection. The reconstructed image resolution was ~6-mm full width at half maximum in the transverse and axial planes. PiB retention levels were determined by the Logan distribution volume ratio (DVR), with the cerebellum as reference region, and were adjusted for partial volume effects (see below) (Lopresti *et al.*, 2005). Logan graphical analyses (Logan *et al.*, 1996) were performed for 35–60 min (5 points) intervals using input functions derived from cerebellar tissue radioactivity to yield the DVR as the outcome measure (Lammertsma and Hume, 1996). The DVR is a unitless value related directly to the free binding-site pool (B_{max}) and the ligand dissociation constant (K_d) (Mintun *et al.*, 1984), and is a measure of region-specific PiB retention (Lopresti *et al.*, 2005).

In vivo–in vitro correlation analyses: case study

From the left (formalin fixed) hemisphere, a 1-cm thick axial tissue slab was dissected by making a cut along the AC-PC plane (i.e. along a plane through the anterior and posterior commissures), and a second cut parallel and 1 cm dorsal to the AC-PC plane. This plane of section allowed for sampling from multiple cortical and subcortical regions known to be differentially affected with Aβ and NFT pathology, and also allowed for precise sampling of a matching clinical imaging plane. From this 1-cm thick axial tissue slab, 25 tissue cubes were chosen to sample the entire cortical ribbon and most of the subcortical nuclei present at this brain level (see Figs 4 and 5). All tissue cubes were ~1 × 1 cm except cube #25 (hippocampus: 0.5 × 0.5 cm) and cube #19 (occipital pole: polygon) that were adjusted to fit their respective anatomical boundaries in this axial plane of section. The 25 tissue cubes were dissected, cryoprotected (as described subsequently) and sectioned serially at 40 μm. Alternate sections were then divided into two sets. Selected tissue sections from one set were processed for histochemical staining with 6-CN-PiB, thioflavin-S (Thio-S) and X-34 compounds, and for immunohistochemistry (IHC) with anti-Aβ and anti-tau antibodies as described below (Fig. 4). All of the alternate tissue sections from each cube were combined and homogenized for the [^{3}H]PiB-binding assay (see below).

Co-registered MRI and PiB-PET images of the left hemisphere were oriented along the axial AC-PC plane. Guided by anatomical landmarks on the ventral surface (i.e. the AC-PC plane) of the tissue slab, the 25 ROIs were drawn in the AC-PC plane of the MRI. Except for the slight adjustments necessary due to post-mortem collapse of the ventricles, all ROIs on the MRI scan matched the tissue cubes taken from the autopsy tissue slab (Fig. 5). These ROIs were then copied onto three additional MRI planes superior to the AC-PC plane for a total of four adjacent 0.24-cm planes, to produce 25 volumes-of-interest (VOIs). The VOIs were all 1 × 1 × 1 cm except VOI #25 (caudal portion of the hippocampus; 0.5 × 0.5 × 1 cm) and the polygonal VOI #19 (occipital pole). To minimize inclusion of CSF space in the hippocampal VOI, ROI #25 was moved slightly from plane to plane. The entire set of 25 VOIs was then transferred from the MRI scan onto the co-registered PiB-PET scan (Fig. 5).

Histochemically assessed 6-CN-PiB plaque load was calculated as percent area, and biochemical [^{3}H]PiB binding and ELISA Aβ levels were calculated as picomoles per gram of tissue wet weight. Both of these post-mortem measures inherently corrected for (i.e. exclude) any partial volume effects by focusing only on tissue and excluding any contribution from CSF spaces. Therefore, the *in vivo* PiB-PET DVR values also were adjusted for partial volume effects by the use of a 2-component MRI-based partial-volume correction to adjust for the dilutional effect of expanded cerebrospinal fluid spaces (Meltzer *et al.*, 1999; Lopresti *et al.*, 2005). Because the placement of six of the VOI (i.e. 10–13, 15 and 24) resulted in <70% tissue in the VOI, and this could result in artefactually high corrected DVR values, only those VOI with >70% tissue ($n = 19$) were included in our analyses.

From the right hemisphere, fresh (unfixed) tissue samples were dissected from 14 regions: superior (BA9) and middle (BA46) frontal cortex, frontal pole (BA10), occipital cortex (BA18), superior (BA41), middle (BA22) and inferior (BA21) temporal cortex, inferior parietal cortex (BA40), cingulate gyrus (BA31), caudate nucleus, subiculum/entorhinal cortex, Ammon's horn, subcortical white matter and cerebellum. It should be noted that these frozen tissue samples from right hemisphere did not correspond exactly to the 25 tissue cubes dissected from the formalin-fixed (left hemisphere) slab at the AC-PC level, but were contained within the standard VOI set routinely sampled in our *in vivo* PiB-PET studies (Price *et al.*, 2005). Frozen tissue samples were homogenized (150 mg/ml) in a tissue homogenization buffer [250 mM sucrose, 20 mM Tris base and protease inhibitors (Sigma #8340 protease inhibitor cocktail; 10 μl per millilitre buffer)] using a glass vessel and piston-type Teflon pestle. An aliquot of the 150 mg/ml homogenate was used for the Aβ ELISA; another aliquot was diluted to 10 mg tissue/ml with phosphate-buffered saline (PBS, pH 7.4) for the [^{3}H]PiB-binding assay (see below). For correlation analyses of these post-mortem biochemical assays and *in vivo* PiB-PET retention levels, these 14 areas were mapped

Table 1 Summary of histofluorescent markers and antisera used for histological and immunohistochemical analyses

Histofluorescent cmpd	Affinity	Concentration	Source (Reference)
6-CN-PiB	β-pleated sheet	10 μM	Dr W.E. Klunk (Mathis *et al.*, 2003)
Thioflavin S	β-pleated sheet	0.05%	Sigma (Guntern *et al.*, 1992)
X-34	β-pleated sheet	100 μM	Dr W.E. Klunk (Ikonomovic *et al.*, 2006)
Antisera (Host)	**Epitope**	**Dilution**	
b6E10 (mouse)	Aβ aa3–10	1:3000	Signet (Kim *et al.*, 1990)
AT8 (mouse)	Ser-202 (P) of tau	1:10,000	Signet (Mercken *et al.*, 1992)
Aβ40 (rabbit)	Ala-40; $A\beta_{1-40}$	1:1000	Chemicon (Kamal *et al.*, 2001)
Aβ42 (rabbit)	Ala-42; $A\beta_{1-42}$	1:1000	Chemicon (Kamal *et al.*, 2001)
K9JA (rabbit)	Repeat domain of tau	1:10,000	Dako (Thies *et al.*, 2007)
10D5 (mouse)	Aβ aa3–6	1:3000	Elan (Hyman *et al.*, 1992)

b = biotinylated.

onto corresponding VOIs drawn on the MR image (performed on the same day as the PiB-PET study) of the same hemisphere. VOIs were then transferred to the corresponding PiB-PET image for calculation of the DVR values (as described earlier), and the values correlated with the results of Aβ ELISA and [^{3}H]PiB-binding analyses (as below).

6-CN-PiB, X-34 and Thio-S histofluorescence

Tissue sections were slide mounted and processed for attenuation of lipofuscin autofluorescence (Guntern *et al.*, 1992). 6-CN-PiB was used at concentrations of 100 nM, 1 μM, 10 μM and 100 μM. The 10-μM concentration (Table 1) provided the optimal signal to noise ratio, and was used for the regional and double labelling analyses in both the autopsy series tissues and in sections from the 25 tissue cubes from the PiB-PET case. Sections were incubated in 6-CN-PiB for 45 minutes, dipped three times in phosphate buffer (PB; 0.1 M), followed by a 1-min differentiation in a solution containing 132.9 mM NaCl, 8.7 mM K_2HPO_4 and 1.5 mM KH_2PO_4 (pH 7.4), and coverslipped with Fluoromount (Electron Microscopy Services, Hatfield, PA). Tissue sections were also processed for Thio-S or X-34, a fluorescent derivative of Congo red, as previously described [Table 1; (Ikonomovic *et al.*, 2006)].

Immunohistochemistry

IHC was performed on free-floating tissue sections as previously described (Ikonomovic *et al.*, 2006). The 4% paraformaldehyde fixed tissue sections from ADRC Alzheimer's disease autopsy series were washed in PB, incubated in 70% formic acid (FA) and washed in PB. Endogenous peroxidase activity was inhibited by 0.3% H_2O_2 in 0.1 M Tris-buffered saline containing 0.25% Triton X-100 (TBST) for 45 min. Sections were then rinsed in TBST and incubated in 3% normal serum in TBST for 30 min followed by two 10-min rinses in 1% normal serum in TBST. Sections were then incubated overnight at 4°C in polyclonal $A\beta_{x-40}$ and $A\beta_{x-42}$ antisera, or the monoclonal 6E10 ($A\beta_{1-16}$) antibody (Table 1). Additional primary antibodies included anti-Aβ 10D5, pan-tau and phospho-tau AT8 (Table 1), used as described earlier except for omission of the FA incubation step. After washing in 1% normal serum in TBST, sections were incubated for 1 h in the species-appropriate biotinylated IgG (Vector Laboratories, Burlingame, CA; in 1% normal serum in TBST), except for the biotinylated 6E10. The sections were washed in TBST and processed with the avidin-biotin Elite kit (Vector Labs) in TBST for 1 h at room temperature. After washing repeatedly in imidazole acetate buffer (IAB), they were exposed to a solution containing 0.05% 3′,3-diaminobenzidine tetra-hydrochloride (DAB)/0.0015% H_2O_2 for 4 min, washed in IAB, mounted on gelatinized slides, dehydrated in alcohols, cleared in xylene and coverslipped with Permount (Fischer). The PiB-PET autopsy case sections were processed identically, with b6E10 and AT8 (Table 1) IHC performed following a 30-min incubation in 95% FA.

Dual IHC and histochemistry

To detect neuritic plaques, 6-CN-PiB labelled tissue sections were imaged, photobleached and then counterstained with either X-34 or Thio-S, to determine the extent of 6-CN-PiB labelling of neuritic plaques (containing X-34 or Thio-S labelled dystrophic neurites) and neurofibrillary tangles (labelled with either X-34 or Thio-S). The validity of this procedure was confirmed in an additional set of tissue sections that were either double immunolabelled with a monoclonal antibody to detect Aβ (10D5) and a polyclonal antiserum to detect tau (Table 1), or single-labelled with tau, and then counterstained with 6-CN-PiB. Tau IHC was performed as above, except that alkaline phosphatase-conjugated secondary antibodies and the Vector Blue substrate were used, and sections were pre-treated with levamisole (Vector) to prevent endogenous phosphatase activity. This procedure distinguished neuritic (10D5-immunoreactive plaques with tau-immunoreactive dystrophic neurites) and non-neuritic (10D5-immunoreactive plaques lacking tau- immunoreactive neurites) plaques. 6-CN-PiB counterstaining of IHC-processed sections followed removal of the chromogen using the tissue autofluorescence quenching procedure (Guntern *et al.*, 1992).

In vitro [^{3}H]PiB-binding assay

Formalin-fixed tissue samples were homogenized with a Polytron tissue homogenizer (PT 10/35, Brinkman Instruments Inc., Westbury, NY) at room temperature for 30 s at setting 6 in PBS (137 mM NaCl, 3 mM KCl, 10 mM sodium phosphate; pH 7.0) at a concentration of 10 mg brain/ml. Fresh-frozen tissue homogenates were diluted from 150 mg/ml in tissue homogenization buffer (see above) to 10 mg/ml with PBS and then re-homogenized with the PT 10/35 as described earlier. The homogenates were aliquoted and frozen at −80°C until used (within 2 months)

for binding assays. No significant changes in binding characteristics were observed in samples assayed repeatedly over this time period. Unlabelled PiB was dissolved in DMSO at 400 μM (to yield <1% DMSO in the final assay). This stock solution was diluted with PBS to achieve the desired concentration in the final assay. For determination of [^{3}H]PiB binding in homogenates of Alzheimer's disease brains, 1 nM [^{3}H]PiB (American Radiolabeled Chemicals, St. Louis, MO; specific activity 72.4 Ci/mmol) was incubated with 100 μg tissue in 1 ml PBS. Non-specific binding was defined as the number of counts remaining in the presence of 1 μM unlabelled PiB. The binding mixtures were filtered through a Whatman GF/B glass filter using a Brandel M-24R cell harvester (Gaithersburg, MD) and rapidly washed five times with 3 ml PBS. The filters were counted in Cytoscint-ES after thorough vortexing and resting overnight. Results were corrected for non-specific, non-displaceable binding in the presence of 1 μM PiB and expressed as picomoles [^{3}H]PiB bound per gram of wet tissue weight in the homogenate. Linearity of [^{3}H]PiB binding was confirmed using 1 nM [^{3}H]PiB and 20–500 μg/ml of the Alzheimer's disease brain homogenate with the highest level of [^{3}H]PiB binding. Linearity with respect to [^{3}H]PiB was confirmed using 100 μg tissue/ml and 1 to 6 nM [^{3}H]PiB. The amount of [^{3}H]PiB bound by this method has been shown to correlate highly with the total number of PiB-binding sites (i.e. the B_{max}; $r = 0.99$) (Klunk *et al.*, 2005) and, importantly, mimics the low nanomolar concentrations of radioactive PiB achieved in human brain during a PET study.

For synthetic Aβ fibril-binding studies, $A\beta_{1-40}$ or $A\beta_{1-42}$ (Bachem Biosciences, King of Prussia, PA) were aggregated as previously described (Klunk *et al.*, 2001). Binding studies were performed with slight modifications of a procedure previously described in detail (Klunk *et al.*, 2003*a*). The K_d and B_{max} values for [^{3}H]PiB binding to Aβ fibrils were determined using increasing concentrations of [^{3}H]PiB between 0.2 and 1 nM and, to achieve total PiB concentrations from 1 to 1000 nM, a constant 1-nM concentration of [^{3}H]PiB plus additional unlabelled PiB. The labelled and unlabelled PiB were prepared in 950 μl PBS. Binding was initiated by addition of 50 μl of a 4 μM suspension of Aβ fibrils in PBS (in triplicate) and the samples were incubated at 22°C for 60 min. Filtration was performed as described earlier for brain homogenates except that the filters were washed only three times with 3 ml PBS before counting.

Aβ enzyme linked immunoadsorbant assay (ELISA)

$A\beta_{1-40}$ and $A\beta_{1-42}$ peptides were quantified in both soluble (diethylamine, DEA) and insoluble (FA extracted) Aβ fractions following a published protocol (DeKosky *et al.*, 2007). The soluble fraction was prepared by homogenizing the tissue in 0.4% DEA in 100 mM NaCl, centrifuging at 135 000 *g* at 4°C for 1 h and neutralizing the supernatant with 0.5 M Tris–Cl. The insoluble fraction was prepared by homogenizing the pellet in 70% FA for 1 min, then centrifuging at 109 000 *g* at 4°C for 1 h. The supernatant was then neutralized with 1 M Tris, 0.5 M sodium phosphate. Both soluble and insoluble fractions were assayed using a fluorescent-based ELISA (Biosource; Camarillo, CA) with a capture antibody specific for the NH_2-terminus of Aβ (amino acids 1–16), and detection antibodies specific for Aβ peptides Aβ40 and Aβ42. Values were determined from standard curves using synthetic $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides (Biosource) and were expressed as picomoles per milligram wet brain tissue. 'Total' Aβ levels refer to the sum of $A\beta_{1-40}$ and $A\beta_{1-42}$ values.

Plaque load analysis

Plaque load was determined by calculating the percent area labelled either immunohistochemically ($A\beta_{x-40}$, $A\beta_{x-42}$, 6E10) or histofluorescently (6-CN-PiB) in tissue sections. For the ADRC autopsy series brain tissue, nine randomly chosen areas were imaged on three sections for each brain region examined from each case. For correlation of *in vivo* PiB (PET) DVR levels with region-matched post-mortem quantitation of 6-CN-PiB histofluorescence and Aβ and phosphotau IHC, a 1000 by 750 μm field of the greatest plaque or NFT frequency was imaged in two sections chosen randomly from each of the 25 tissue cubes; plaque load was determined from the percent area occupied by Aβ-immunoreactive or 6-CN-PiB positive plaques, while the AT8 (phosphotau) immunoreactive 'load' represented percent area occupied by all AT8-immunoreactive structures (including NFTs, neuropil threads and other neuritic elements) in the field. An independent check of the representative nature of the two sections chosen randomly for each histological analysis was made by determining the total Aβ plaque load by 6E10 IHC in three additional sections chosen randomly from each of the 25 tissue cubes; these data correlated strongly with the original dataset. Microscope settings were held constant throughout the sampling. Images were then converted to binary using the public domain NIH Image program (available at: http://rsb.info.nih.gov/nih-image/). A predetermined threshold value was held constant throughout the analysis. Percent area values were obtained by dividing area labelled by total area sampled.

Statistical analysis

Correlation analyses were performed using Spearman rank order correlation. Statistical significance was set at 0.05 (two-sided).

Results

Characterization of 6-CN-PiB histofluorescence in Alzheimer's disease brain tissue from autopsy cases

6-CN-PiB binds primarily to Aβ plaques in Alzheimer's disease cortex

At concentrations of 1–10 μM, 6-CN-PiB fluorescent signal was detected almost exclusively in amyloid plaques and (when present) large, amyloid-laden blood vessels (Fig. 1A). The morphology of 6-CN-PiB labelled plaques was diverse, both within and between brain regions examined (see Table 2 for region-specific plaque terminology). In the neocortex, entorhinal cortex (ERC) and hippocampus, 6-CN-PiB robustly labelled compact/cored plaques, while diffuse/amorphous plaques were less prominently labelled (Fig. 1). No differences in the type of 6-CN-PiB labelled structures were observed at higher concentrations (e.g. 100 μM). At 100 nM, the lowest concentration tested, the overall intensity of 6-CN-PiB fluorescence was considerably reduced, and diffuse/amorphous plaques in the cortical and hippocampal regions were difficult to discern while

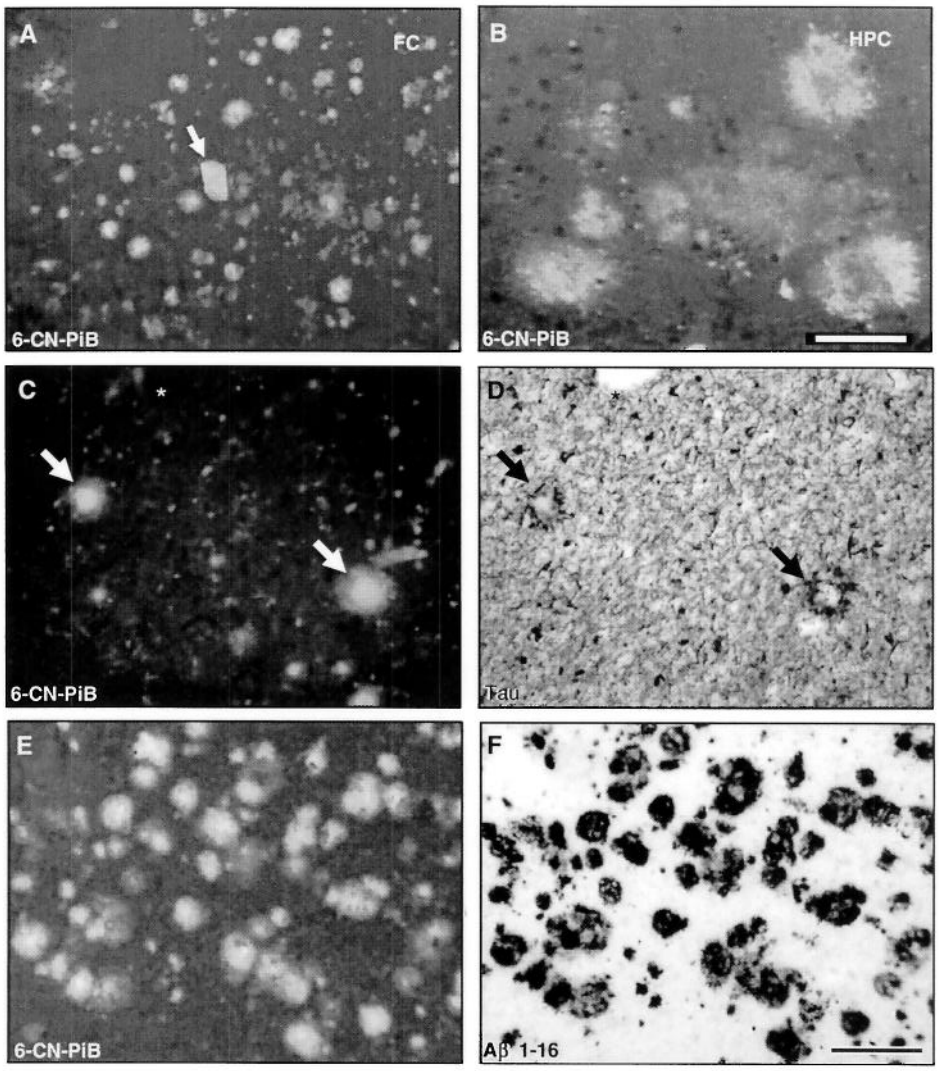

Fig. 1 Regional variations in 6-CN-PiB fluorescence signal in Alzheimer's disease brain tissue. In the frontal cortex (FC), 6-CN-PiB histofluorescence is seen in numerous compact/cored and diffuse plaques, and in an isolated large blood vessel with amyloid angiopathy (**A**, arrow). Amorphous diffuse plaques in the hippocampus (HPC; **B**) are 6-CN-PiB positive, but have lower fluorescence intensity compared to cored/compact 6-CN-PiB labelled plaques. 6-CN-PiB histofluorescence is prominent in cores of neuritic plaques identified by the presence of tau-immunoreactive dystrophic neurites (**C** and **D**; double labelling of the same Alzheimer's disease frontal cortex tissue section with tau IHC; asterisk denotes a tissue landmark, matched plaques are marked by arrows). 6-CN-PiB and Aβ immunoreactivity co-localize in plaques in an Alzheimer's disease frontal cortex (**E**, **F**; tissue section double labelled for 6-CN-PiB histofluorescence and Aβ immuhistochemistry with 10D5 antibody). Both markers are seen exclusively in amyloid plaques. Scale bar = 175 μm (**A**), 100 μm (**B–F**).

compact/cored plaques and vascular deposits were still detectable. 6-CN-PiB was not detectable in dystrophic neurites and neuropil threads (see below). Double-labelling experiments, combining 6-CN-PiB with tau IHC to reveal the presence or absence of dystrophic neurites in plaques, demonstrated that 6-CN-PiB labelled plaques both with (neuritic) and without (non-neuritic) tau-positive dystrophic neurites (Fig. 1).

No 6-CN-PiB labelling was detected in brain areas that were free of Aβ plaques as determined by Aβ IHC. There was an apparent one-to-one co-localization between 6-CN-PiB fluorescent plaques and Aβ immunoreactive plaques in cortical regions (Fig. 1), resulting in a direct correlation between plaque loads determined using these two markers ($r = 0.56$, $P = 0.009$). 6-CN-PiB labelled both Aβ42- and Aβ40-immunoreactive plaques (Supplementary Fig, 1A–D). Compact/cored Aβ40- and Aβ42-immunoreactive plaques were most intensely labelled, while diffuse/amorphous Aβ42 deposits were more lightly labelled. Plaque load analysis (by percent area; see Supplementary Fig. 1E) demonstrated a direct correlation between cortical plaque loads determined with 6-CN-PiB and with antibodies to either Aβ42 ($r = 0.82$, $P = 0.0002$) or Aβ40 ($r = 0.58$, $P = 0.011$).

6-CN-PiB labelling was not detectable in plaque-containing Alzheimer's disease tissue sections pre-treated

Table 2 6-CN-PiB (10 μM) labeling intensity in different plaque types and amyloid-containing structures in 4% paraformaldehyde fixed, 40 μM thick tissue sections

Plaque type	6-CN-PiB intensity	X-34 intensity
Compact/cored (NC, PhG, Crbl)		
Neuritic	++++	++++
Non-neuritic	++++	++++
Diffuse		
Amorphous (NC, PhG)	++	++
Cloud-like (Str)	++	++
Fleecy (Crbl)	0	++
Non-plaque amyloid	**6-CN-PiB intensity**	**X-34 intensity**
Vascular	++++	++++
Neurofibrillary tangles iNFT	+[a]	++++
Neurofibrillary tangles eNFT	+++	++++
Neuropil threads	0	++++
Dystrophic neurites	0	++++

0 = no 6-CN-PiB fluorescence signal; + = very light fluorescence barely above backgrounds; ++ = light fluorescence; +++ = moderate fluorescence; ++++ = intense fluorescence. NC = neocortex; PhG = parahippocampal gyrus; Str = striatum; Crbl = cerebellum; iNFT = intracellular NFT; eNFT = extracellular NFT.
[a]Only a small proportion of tangles per section detected in entorhinal cortex and subiculum.

with formic acid, which disrupts β-pleated sheets (Kitamoto *et al.*, 1987), and conversely, treating 6-CN-PiB processed tissue with formic acid abolished 6-CN-PiB labelling. The pattern of 6-CN-PiB plaque labelling matched that observed using two other amyloidal-binding compounds, Thio-S and X-34 (see Fig. 3); the latter two compounds' labelling of plaques was comparable, except that X-34 was more sensitive in detecting diffuse plaques.

6-CN-PiB is not detectable in cerebellar diffuse plaques

Similar to the pattern of 6-CN-PiB labelling of diffuse plaques in cortical and hippocampal regions, 6-CN-PiB labelling was detected in diffuse cloud-like plaques in the striatum (Fig. 2A); these plaques matched the pattern of Aβ-immunoreactive and X-34 histofluorescent diffuse plaques in this region (data not shown). In the cerebellum, however, 6-CN-PiB fluorescence was not detectable in diffuse plaques, although in adjacent tissue sections there were abundant diffuse Aβ-immunoreactive and X-34-positive plaques in the cerebellar cortical molecular layer (Fig. 2B–D). The only types of cerebellar structures detectable with 6-CN-PiB were large blood vessels (when present) and small to medium size compact plaques in the Purkinje cell layer. These structures also showed X-34 fluorescence signal (Fig. 2D inset).

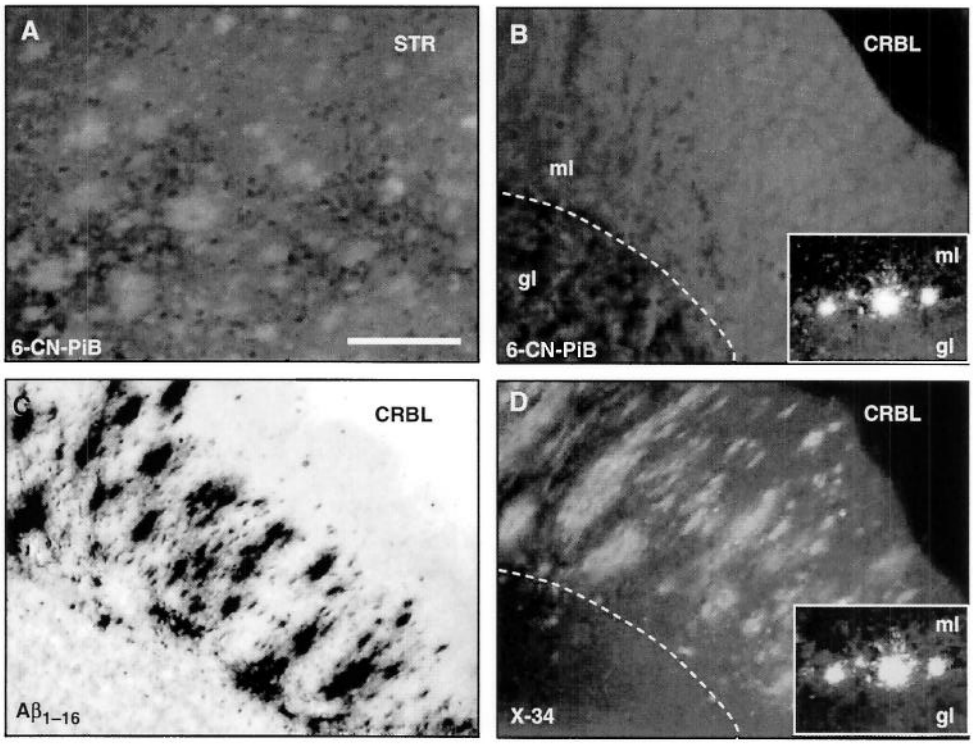

Fig. 2 6-CN-PiB histofluorescence is detectable in cloud-like diffuse plaques in the caudate nucleus of the striatum (STR; **A**). In the cerebellum (CRBL), 6-CN-PiB labelling is not appreciably above background levels (**B**), although the adjacent tissue sections processed for Aβ IHC (**C**, 10D5 antibody) and X-34 (**D**) show fleecy diffuse plaques in the molecular layer (ml) of cerebellar cortex (dotted line in **B** and **D** approximates the Purkinje cell layer). In the Purkinje cell layer, some isolated small compact plaques are detectable with both 6-CN-PiB and X-34 (inserts in **B** and **D**; gl, granular layer). Scale bar = 150 μm (**A–D**), 75 μm (Inset).

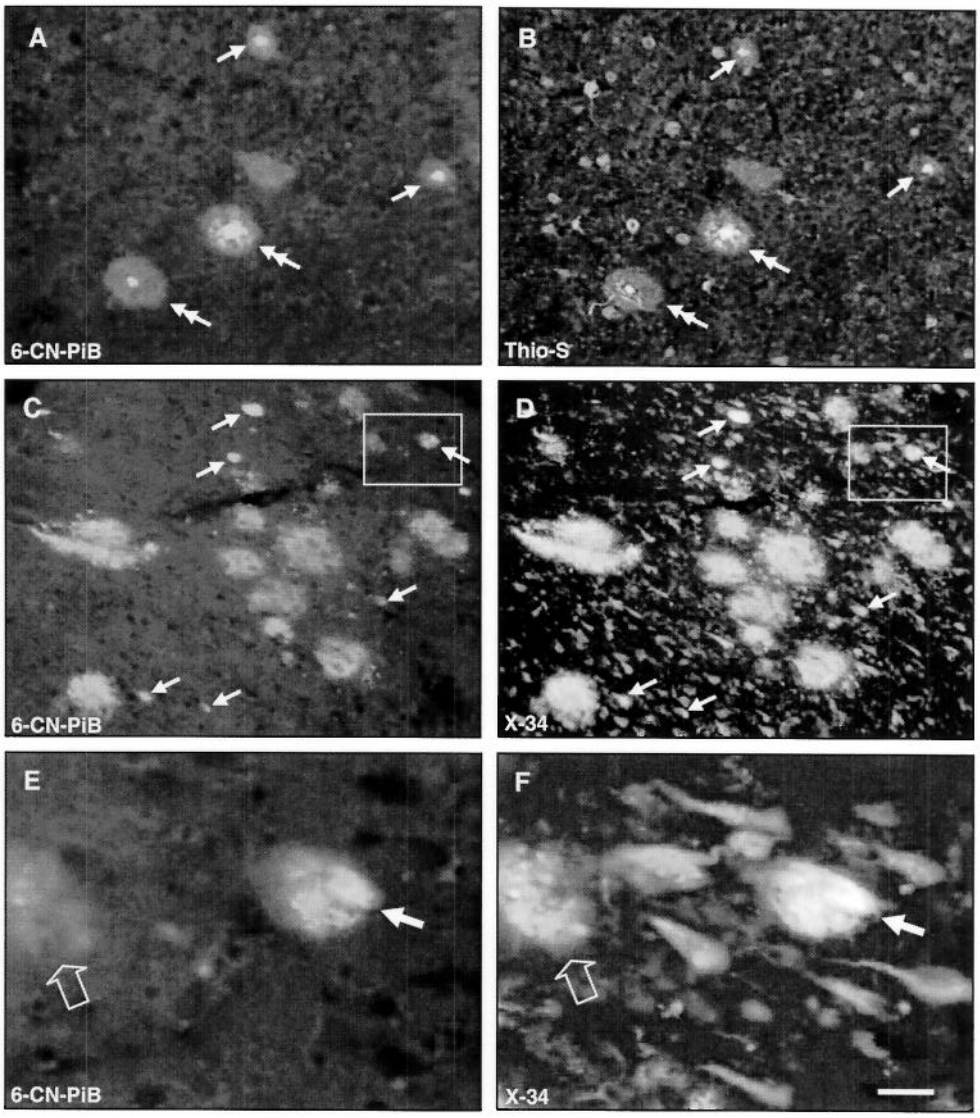

Fig. 3 Co-localization of 6-CN-PiB (**A, C, E**) with Thio-S (**B**) and X-34 (**D, F**) in plaques, but not in NFT in Alzheimer's disease temporal cortex (**A, B**), and hippocampus (**C–F**). Large cored plaques (double arrows) and small burnt out plaques (arrows) are labelled with both 6-CN-PiB and Thio-S in the temporal cortex, but Thio-S also labels numerous NFT that are not detectable with 6-CN-PiB (**A, B**). There is a good co-localization of 6-CN-PiB and X-34 in plaques in the hippocampus (**C, D**). X-34 also labels an array of neurofibrillary pathology in the hippocampus (**D**); only small numbers of these structures are detectable with 6-CN-PiB (**C**, arrows). **E** and **F** represent boxed areas in **C** and **D**, respectively, and illustrate a structure labelled with both 6-CN-PiB and X-34 (small arrow) that resembles an extracellular NFT with distinct bundles of longitudinally oriented fibrils that are loosely dispersed in the neuropil. A small diffuse plaque is also double labelled (empty arrow), while the rest of the X-34 positive NFT in the field are not detectable with 6-CN-PiB. Scale bar = 75 μm (**A–D**), 25 μm (**E, F**).

6-CN-PiB binding is absent from dystrophic neurites, neuropil threads and the majority of neurofibrillary tangles

6-CN-PiB was not detected in neocortical NFT, or in the vast majority of NFTs in the ERC and subiculum/CA1 that were detectable with tau IHC and Thio-S or X-34 histology in the same tissue sections (Fig. 3). In the ERC and subiculum/CA1, occasional 6-CN-PiB labelled NFT had a distinct morphology of extracellular 'tombstone' tangles (eNFT), enlarged NFT-like structures consisting of longitudinally oriented bundles of fibrils (Fig. 3C–F). In the ERC layer II cell islands, there were abundant NFT intensely labelled by X-34, while 6-CN-PiB labelling of these NFT was sparse. The same pattern of almost exclusive labelling of plaques in the ERC was also observed with BTA-1 (PiB) histochemistry (see Supplementary Fig. 2). In the hippocampus of one subject with large numbers of tau-immunoreactive and X-34 labelled intracellular NFT, but no Aβ plaques, there was no detectable 6-CN-PiB labelling (see Supplementary Fig. 3). 6-CN-PiB did not label neuritic elements such as tau-immunoreactive

dystrophic neurites and neuropil threads, all of which were detectable with X-34.

Direct correlation between quantitative [^{3}H]PiB binding and Aβ peptide (ELISA) levels in homogenates of Alzheimer's disease brain tissue from autopsy cases

In agreement with the 6-CN-PiB labelling of both Aβ40 and Aβ42 immunoreactive plaques in Alzheimer's disease brain tissue as described earlier, [^{3}H]PiB bound equally well to synthetic Aβ fibrils formed *in vitro* from either $A\beta_{1-40}$ or $A\beta_{1-42}$ peptides. The high-affinity K_d for [^{3}H]PiB binding was 0.90 nM for $A\beta_{1-40}$ and 0.95 nM for $A\beta_{1-42}$ (Supplementary Fig. 4A). The B_{max} values of the high-affinity sites were 0.42 pmol [^{3}H]PiB/nmol $A\beta_{1-40}$ and 0.46 pmol [^{3}H]PiB/nmol $A\beta_{1-42}$. This stoichiometry was similar to that previously reported (Klunk *et al.*, 2005). The low-affinity components had K_d values of 70–145 nM and thus represent binding that would not be relevant *in vivo* where [^{11}C]PiB concentrations are on the order of 1 nM or less (Klunk *et al.*, 2005). Using 1 nM [^{3}H]PiB, there was a direct correlation between *in vitro* [^{3}H]PiB binding and total (i.e. combined $A\beta_{1-40}$ and $A\beta_{1-42}$) insoluble Aβ in post-mortem frozen tissue homogenates of frontal and occipital cortices from six Alzheimer's disease subjects ($r = 0.95$, $P < 0.0001$, Supplementary Fig. 4B). There was no significant correlation of [^{3}H]PiB binding with soluble Aβ peptides.

Direct correlation of *in vivo* PiB-PET retention levels with region-matched post-mortem quantitations of PiB binding, plaque load and Aβ peptide levels

Regional correlations of ante-mortem PiB retention (DVR) levels and post-mortem analyses of PiB binding and Alzheimer's disease pathology in the same individual were possible because one Alzheimer's disease subject underwent *in vivo* PiB-PET, and a brain autopsy was performed 10 months later. In this case, the final neuropathological diagnosis by CERAD criteria (Mirra *et al.*, 1991) was 'definite Alzheimer's disease', and the Braak stage (Braak and Braak, 1991*b*) was V/VI. No cortical or brainstem Lewy bodies (assessed by α-synuclein IHC) were present. There was only minimal cortical gliosis, and no infarcts in subcortical or cortical structures. Immunohistochemical analyses demonstrated frequent Aβ immunoreactive plaques and mild amyloid angiopathy. Bielschowsky staining revealed frequent SP and NFT in all neocortical areas; this was confirmed with IHC using the anti-phosphotau antibody clone AT8.

Post-mortem measures of 6-CN-PiB and Aβ plaque loads, AT8-immunoreactive neurofibrillary load and [^{3}H]PiB binding were quantified in tissue sections cut from the 25 tissue cubes in a 1-cm thick tissue slab from the formalin-fixed left hemisphere. The final analysis included values from 19 tissue cubes (the MRI VOI of six of the 25 tissue cubes contained <70% tissue and were excluded, see Methods section); these values were correlated with the PiB-PET DVR values from the 19 corresponding VOIs on the ante-mortem PET scans at the same axial level of the same hemisphere in this person, after correction for any partial volume effects (see Methods section). At this brain level, the highest values for 6-CN-PiB plaque load were observed in the frontal and temporal cortices, and in the basal ganglia. The lowest 6-CN-PiB plaque load levels were in the tail of the hippocampus, internal capsule and lateral occipital cortex (Fig. 4). This distribution of 6-CN-PiB plaque load values was similar to the distribution of PiB DVR values in the same brain regions on the matching ante-mortem PiB-PET scan (Fig. 5). Figure 4 illustrates the pattern of 6-CN-PiB labelling and the extent of X-34 labelled amyloid pathology, 6E10 immunoreactive Aβ plaques and AT8 immunoreactive neurofibrillary pathology, in adjacent tissue sections from three tissue cubes representative of brain areas with either high-plaque/high-NFT density (cube #16, frontal cortex), high plaque/low NFT (cube #1, striatum) or low-plaque/high-NFT density (cube #25, hippocampus). 6-CN-PiB labelling corresponded well with Aβ plaques revealed by 6E10 IHC, but not with NFT density as revealed by AT8 IHC (Fig. 4). The overall X-34 labelling load, which reveals all β-sheet deposits including Aβ plaques and neurofibrillary pathology (NFT, DN and NT) (Ikonomovic *et al.*, 2006), did not correspond as well to 6-CN-PiB labelling as did 6E10 IHC for Aβ alone. However, after restricting the analysis to include only X-34 labelled plaques, there was a good correlation between 6-CN-PiB and X-34 plaque load. There was a direct correlation ($r = 0.81$, $P < 0.0001$) of 6-CN-PiB fluorescent plaque load determined post-mortem with *in vivo* PiB retention (Figs 5 and 6A). A similar direct correlation was found between *in vivo* PiB DVR values and Aβ immunoreactive plaque load (Fig. 6B). In contrast, there was no correlation between *in vivo* PiB DVR values and the neurofibrillary pathology load as revealed by AT8 IHC (Fig. 6C).

Aβ peptide levels could not be quantified by ELISA in the formalin-fixed tissue homogenate. However, specific, displaceable [^{3}H]PiB binding could be detected in this formalin-fixed tissue. There was a strong significant correlation ($r = 0.82$, $P < 0.0001$) between [^{3}H]PiB binding to homogenates of post-mortem formalin-fixed tissue and PiB DVR values from ante-mortem PET scans (Fig. 6D). In a separate validation study of six Alzheimer's disease brains from our autopsy series, we examined [^{3}H]PiB binding in tissues bisected from frontal and occipital cortical samples; half of each sample was formalin-fixed for three days (to reproduce the effects of formalin-fixation on the autopsied brain in the PiB-PET Alzheimer's disease case study) and the other half was fresh frozen. Although there was a good correlation between [^{3}H]PiB binding to the formalin-fixed

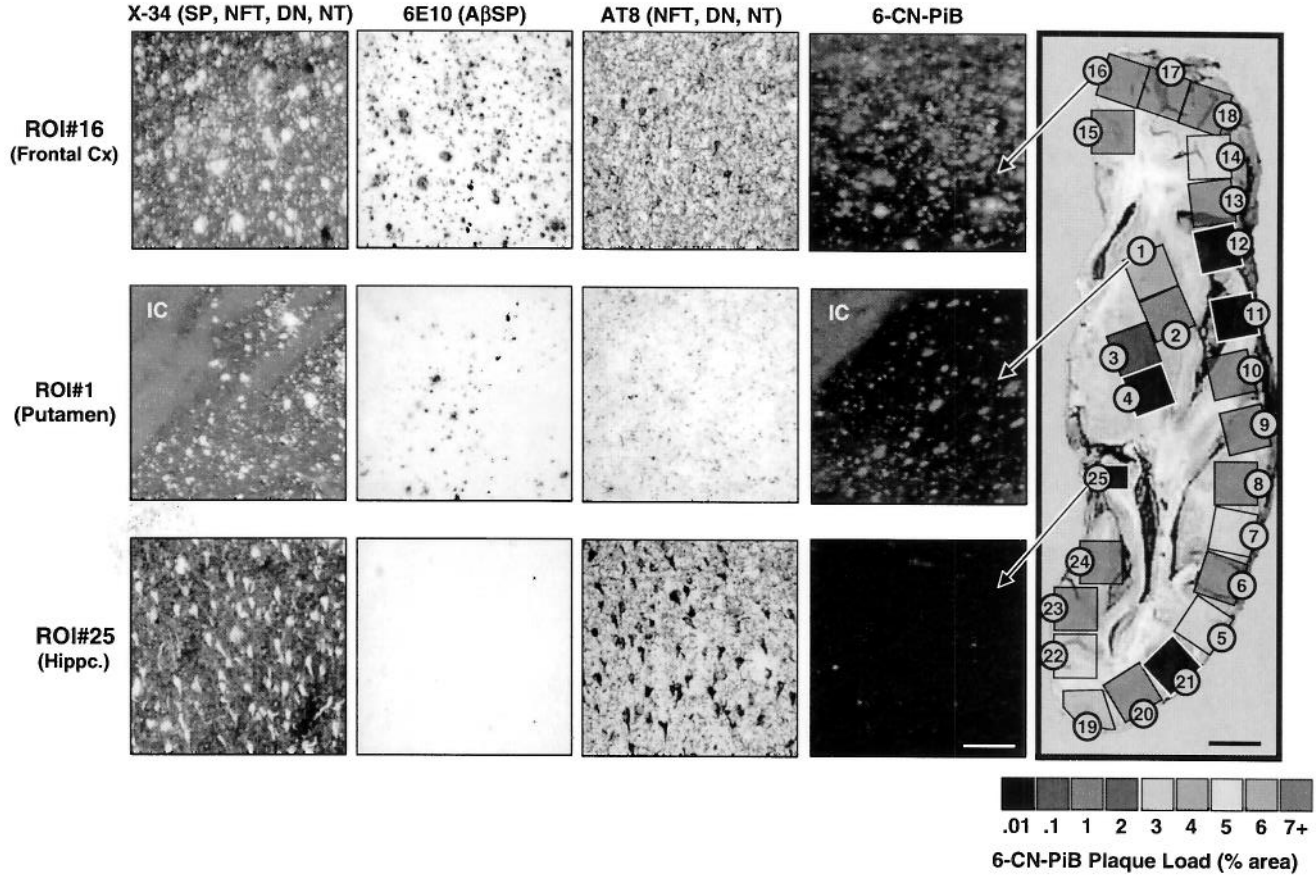

Fig. 4 6-CN-PiB plaque load (% area) values, quantified in each of the 25 tissue cubes dissected from an axial post-mortem tissue block, are pseudo-colour-coded on a rainbow scale from black/purple (low% area) to red (high% area). Images of 6-CN-PiB and X-34 histofluorescence, and 6EI0 and AT8 IHC, were obtained in adjacent tissue sections from tissue cube #16 (frontal cortex), tissue cube #1 (striatum) and tissue cube #25 (hippocampus), and are each representative of an area with highest concentrations of labelled elements. In all tissue cubes, 6-CN-PiB exclusively labels plaques, matching the distribution of 6EI0 immunoreactive and X-34 labelled plaques, but not AT8 immunoreactive or X-34 labelled NFT, DN and NT. Abbreviations: IC = internal capsule (low background fluorescence in the white matter tracts); NFT = neurofibrillary tangles; DN = dystrophic neurites; NT = neuropil threads; Hippc = hippocampus; Cx = cortex. Scale bar = 150 μm for tissue cube #16 and #1, 75 μm for tissue cube #25 and 1 cm for tissue slab.

and frozen samples ($r = 0.66$; $P = 0.038$), the binding of [^{3}H]PiB to the formalin-fixed samples was only $43 \pm 24\%$ of that observed in the corresponding frozen tissue samples. Therefore, we also measured [^{3}H]PiB binding in fresh-frozen tissue samples from 14 brain regions dissected from the contralateral (frozen) hemisphere of the PiB-PET-scanned Alzheimer's disease case. Although the co-localization of the VOI used to determine the *in vivo* DVR value and the frozen tissue used to measure [^{3}H]PiB binding could not be performed as exactly as it could on the formalin-fixed tissue, there also was a strong correlation of [^{3}H]PiB binding with *in vivo* PiB retention DVR levels in the frozen tissue ($r = 0.64$, $P = 0.013$, Fig. 6E).

In the same 14 fresh-frozen tissue samples from the right hemisphere, we next quantified Aβ40 and Aβ42 peptide levels for correlations with region-matched *in vivo* PiB retention DVR values and *in vitro* [^{3}H]PiB binding. There was a strong correlation of *in vivo* PiB retention levels with tissue levels of total (i.e. Aβ40 + Aβ42) insoluble Aβ ($r = 0.73$, $P < 0.0028$, Fig. 6F). As observed in frozen frontal and occipital cortex tissue homogenates from six Alzheimer's disease subjects in our autopsy series (Supplementary Fig. 4B), in the 14 frozen tissue homogenates from the PiB-PET scanned Alzheimer's disease case there was a strong correlation of *in vitro* [^{3}H]PiB binding with total (i.e. Aβ40 + Aβ42) insoluble Aβ ($r = 0.85$, $P = 0.0001$, Supplementary Fig. 5A). These biochemical results were supported by a strong correlation between histological 6-CN-PiB plaque load and 6E10 immunoreactive Aβ plaque load in the tissue cubes dissected from the formalin fixed hemisphere ($r = 0.86$; $P < 0.0001$; Supplementary Fig. 5B).

Discussion

We have defined the histological and biochemical specificity of PiB binding across different regions of Alzheimer's disease brain, and demonstrated a direct correlation

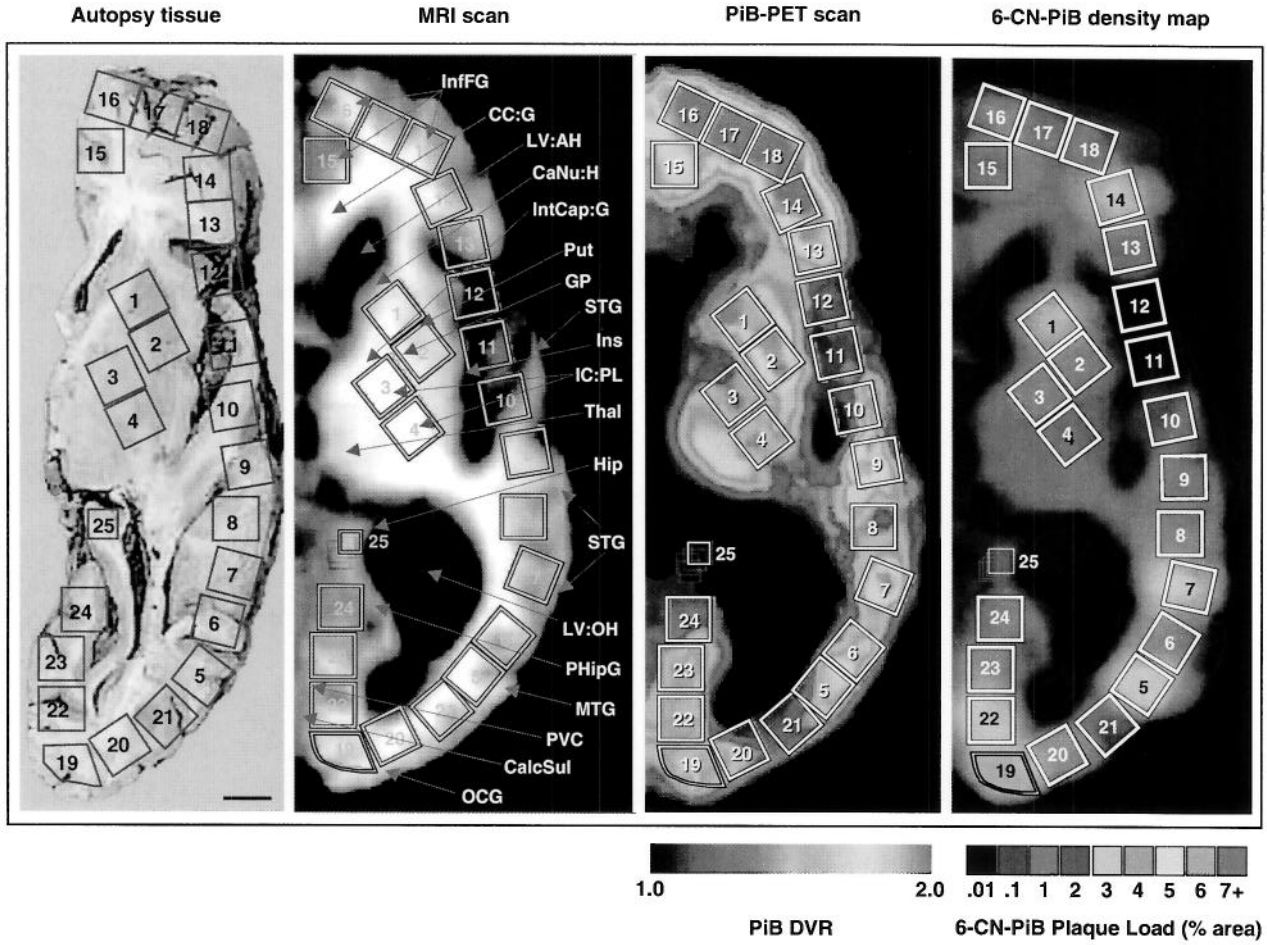

Fig. 5 Correlation between ante-mortem PiB-PET retention levels and a post-mortem VOI-matched 6-CN-PiB plaque density map as a 'virtual PiB scan' of the same subject. The face of the autopsy tissue block is at the level of the anterior and posterior commisures. On the autopsy tissue (left) each of the 25 blue squares represents the face of a tissue cube that was dissected from this 1-cm formalin-fixed slab. ROIs corresponding to these 25 tissue cubes were drawn on the corresponding four 0.24-cm slices of this same patient's MRI scan (second from the left; taken at the time of the PiB scan 10 months before death). These same ROIs were then transferred to the co-registered PiB-PET scan (third from left) for quantification of the *in vivo* PiB retention. Some tissue distortion post-mortem is evident, due to the collapse of the ventricles. On the 6-CN-PiB density map (right), the data from the post-mortem regional 6-CN-PiB plaque load analysis (see Fig. 4) were digitally blurred to create the 'virtual PiB scan', shown overlying the contour of the MRI scan for ROI comparison purposes. This post-mortem 6-CN-PiB plaque density map closely reflects the distribution of PiB retention levels in the PiB-PET scan recorded ante-mortem in the same person. Abbreviations: InfFG = inferior frontal gyrus; CC:G = corpus callosum: genu; LV:AH = lateral ventricle: anterior horn; CaNu:H = caudate nucleus: head; IntCap:G = internal capsule: genu; Put = putamen; GP = globus pallidus; STG = superior temporal gyrus; Ins = insular cortex; IC:PL = internal capsule: posterior limb; Thal = thalamus; Hip = hippocampus; STG = superior temporal gyrus; LV:OH = lateral ventricle: occipital horn; PHipG = parahippocampal gyrus; MTG = medial temporal gyrus; PVC = primary visual cortex; CalcSul = calcarine sulcus; OCG = occipital gyrus. Scale bar = 1 cm.

between Aβ containing amyloid plaques and *in vivo* PiB retention measured by PET imaging. The highly fluorescent PiB analogue, 6-CN-PiB, almost exclusively labelled Aβ-containing structures including compact/cored, diffuse, neuritic and non-neuritic Aβ plaques. 6-CN-PiB also labelled vascular amyloid, as previously reported (Bacskai *et al.*, 2007; Lockhart *et al.*, 2007), but fluorescence signal was not detected in neuropil threads or dystrophic neurites, and only sporadically in a subset of NFT; these were primarily of extracellular 'ghost' tangle (eNFT) morphology. Our study of an Alzheimer's disease subject who underwent post-mortem neuropathological examination 10 months after *in vivo* PiB-PET imaging, demonstrated that *in vivo* PiB retention correlated directly with region-matched post-mortem quantification of 6-CN-PiB and Aβ plaque load, PiB binding and Aβ peptide levels, but not NFT or other neurofibrillary pathology. Although the PiB-PET study and autopsy were separated by 10 months, Engler *et al.* (2006) have shown that PiB-PET DVR values do not change appreciably over 2 years in patients with Alzheimer's disease.

The close co-localization of 6-CN-PiB labelling with Aβ40 and Aβ42 immunoreactive plaques, and the *in vitro* binding of [^{3}H]PiB to synthetic fibrils made from either

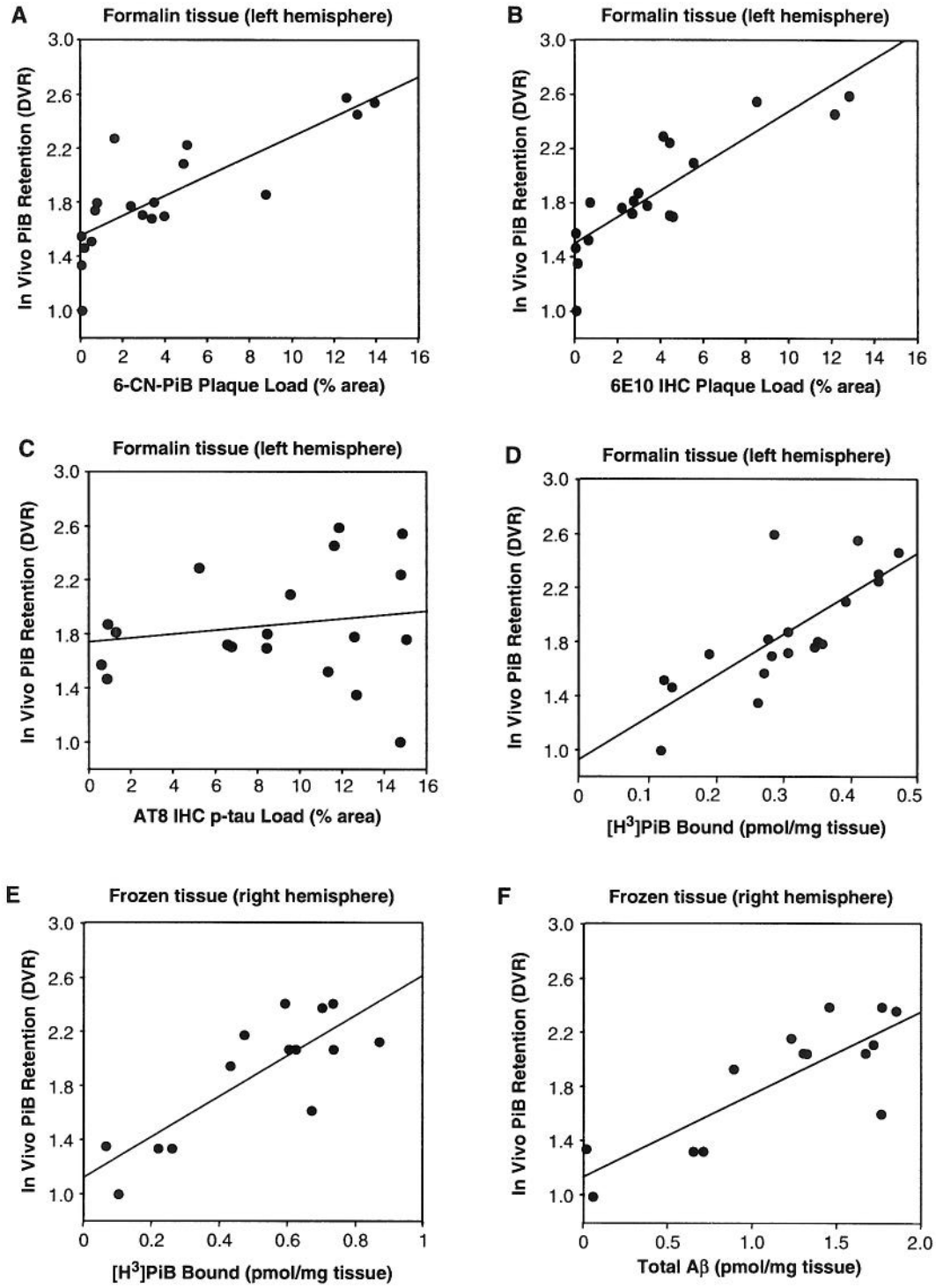

Fig. 6 Correlations of the *in vivo* PiB DVR values from the 19 VOIs (six of the 25 VOIs had <70% tissue and were not included in the analysis, see Methods section) on the PET scan with post-mortem quantifications of 6-CN-PiB (**A**) or Aβ (**B**) plaque load, neurofibrillary load (**C**) and [^{3}H]PiB binding (**D**) in the corresponding 19 tissue cubes from the formalin fixed left hemisphere. *In vivo* PiB-PET retention (DVR) levels correlate directly with regional post-mortem quantitations of 6-CN-PiB (**A**) and 6E10 (**B**) plaque loads as well as *in vitro* PiB binding (**D**), but not with AT8 neurofibrillary load (**C**) in formalin-fixed tissue from the left hemisphere. In fresh-frozen tissue from the right hemisphere of the same Alzheimer's disease subject, there is a significant correlation of both *in vitro* PiB binding (**E**) and total insoluble Aβ ($A\beta_{1-40} + A\beta_{1-42}$) peptide levels (**F**) with *in vivo* PiB-PET retention (DVR) levels.

$A\beta_{1-40}$ or $A\beta_{1-42}$, indicate that PiB binds similarly to these two forms of Aβ, once they have adopted a β-sheet fibrillar structure. Aβ42-containing plaques and Aβ42 peptide levels are much more abundant in Alzheimer's disease brain (Iwatsubo *et al.*, 1994; Naslund *et al.*, 2000), and therefore likely drive the correlation between PiB and total Aβ peptide (Aβ42 and Aβ40 combined) levels as determined in our ELISA assays. Thus, the majority of *in vivo* PiB retention on PET scans in Alzheimer's disease reflects aggregated Aβ42 deposits. We did not explore the effect of the Aβ N-terminal heterogeneity on PiB binding, but a recent paper examining PiB binding to brain tissue from transgenic mouse models of amyloid deposition suggested that the form of Aβ starting with cyclized glutamate in the 3-position [i.e. pyroglutamate or N3(pE) form] is a major contributor to PiB binding (Maeda *et al.*, 2007). This is of interest given the previously reported findings that the N3(pE) form of Aβ comprises 25–50% of total Aβ (Harigaya *et al.*, 2000; Russo *et al.*, 2002).

The requirement that Aβ be in fibrillar form for PiB binding was verified both by the demonstration that formic acid pre-treatment of tissue sections (which disrupts the β-sheet fibrillar structure) abolished 6-CN-PiB binding to plaques and vascular amyloid, and by the direct correlation of *in vitro* PiB binding with insoluble (formic acid extracted) Aβ which forms amyloid plaques, but not with soluble Aβ. The intensity of 6-CN-PiB plaque labelling reflected the density of Aβ immunoreactive fibrils in plaques, from lightly labelled diffuse plaques to intensely fluorescent compact/cored plaques.

The only region that lacked the close correlation between 6-CN-PiB fluorescence labelling and Aβ immunoreactivity in plaques was the cerebellum. The rare, small compact plaques in the Purkinje and granular layers, and infrequent CAA were labelled by 6-CN-PiB. However, fleecy appearing diffuse plaques in the molecular layer (the vast majority of Aβ immunoreactive and X-34 positive plaques in the cerebellum) were not detectable with 6-CN-PiB. This is consistent with the observation that *in vivo* PiB retention levels in Alzheimer's disease brain are consistently lowest in the cerebellum, and further justifies using the cerebellum as a reference region when quantifying regional *in vivo* PiB retention levels (Lopresti *et al.*, 2005).

The binding of PiB to diffuse plaques in the striatum and other regions examined, but not in the cerebellum, is likely due to the unique secondary structure and amino acid composition of cerebellar diffuse Aβ aggregates (Lalowski *et al.*, 1996). Furthermore, unlike the occasional small compact plaques that were 6-CN-PiB positive, cerebellar diffuse plaques contain few amyloid fibrils characteristic of plaque cores (Verga *et al.*, 1989). The intense 6-CN-PiB labelling of all compact cored plaques, the weaker labelling of diffuse cortical, striatal and hippocampal plaques, and the complete absence of labelling in cerebellar fleecy amyloid may be due to higher amyloid fibril density in the compact cored plaques. 6-CN-PiB did not label dystrophic neurites, indicating that plaque-associated neuritic elements do not likely contribute to overall PiB signal, despite the robust labelling of these structures with other amyloid-binding compounds such as X-34. Because PiB can detect diffuse plaques in addition to cored and neuritic plaques, PiB-PET imaging may be useful for detection of early amyloid deposition. PiB-PET is able to track Aβ deposition across the spectrum of normal aging to advanced Alzheimer's disease (Forsberg *et al.*, 2007; Kemppainen *et al.*, 2007; Rowe *et al.*, 2007), and further histological studies will need to be performed to assess the relative contributions of different plaque types across this spectrum. Compact Aβ plaques are likely associated with increased presence of reactive glial cells. It will be important to examine correlations of PiB binding with microglial and astrocytic activation, as well as additional cellular and molecular alterations, in future studies.

In contrast to the strong correlation between 6-CN-PiB staining and Aβ plaques, 6-CN-PiB did not bind at detectable levels to significant numbers of NFT, even in the ERC layer II cell islands where tau-immunoreactive and X-34 fluorescent NFT were abundant. This is consistent with the previously reported observation in elderly healthy control brain of a lack of [^{3}H]PiB binding to homogenates of transentorhinal cortex (Klunk *et al.*, 2003*b*), a brain area that is the first to show NFT pathology (Braak and Braak, 1991*a*). These observations differ somewhat from those of Lockhart *et al.* (2007), who reported overlap between NFT-labelling and PiB autoradiography in the ERC. The finding by Lockhart *et al.* could be the result of long autoradiography exposure time (7 weeks) wherein even the weakest signal can be amplified, or it could be due to misidentification of structures due to the low resolution of film autoradiography, as well as comparison of different tissue sections (as opposed to multiple labelling on single tissue section). In the present study, we did observe weak PiB labelling of a relatively small subset of NFT, mostly extracellular NFT detectable in the ERC layer II and subiculum/CA1, while the majority of intracellular NFT were not detectable. This pattern was confirmed by additional histological experiments using another fluorescent PiB derivative, BTA-1 (see Supplementary Fig. 2). In the ERC lamina II, the bulk of NFT were BTA-1 negative, while small-diameter plaques were BTA-1 positive. This distinction would not have been detected by the autoradiographic approach used by Lockhart *et al.* (2007). Furthermore, in the Lockhart *et al.* study (Lockhart *et al.*, 2007), some N-terminus Aβ truncated diffuse Aβ plaques in the ERC could have gone undetected by the N-terminus Aβ IHC and thioflavin-S histochemistry. Since select NFT, and particularly extracellular NFT, contain epitopes recognized by Aβ antibodies (Masters *et al.*, 1985; Grundke-Iqbal *et al.*, 1989; Hyman *et al.*, 1989; Spillantini *et al.*, 1990; Tabaton *et al.*, 1991; Perry *et al.*, 1993), we must also consider the possibility that the NFT labelled by 6-CN-PiB and BTA-1 represent NFT-associated Aβ peptides that fibrilized once

the NFT became extracellular (Grundke-Iqbal *et al.*, 1989). Thus, even the occasional labelling of extracellular NFT observed in this study may be due to the presence of Aβ fibrils, rather than the presence of high-affinity binding sites on tau-formed amyloid (Lockhart *et al.*, 2007). Alternatively, extracellular proteolysis of tau in extracellular NFT may expose the protease-resistant core of PHF, or change its structure (Mena *et al.*, 1995, 1996) making it accessible to PiB. Regardless, the binding of PiB to a subset of NFT produces weak signal relative to that generated by PiB-bound Aβ plaques, and does not likely contribute significantly to tracer uptake and PiB-PET signal *in vivo*. This is supported by the fact that *in vivo* PiB-PET imaging studies consistently demonstrated very little signal in mesial temporal lobe, despite the high NFT load detected both histologically and immunohistochemically in this region (see Figs 4 and 5). It should also be noted that the presence of the cell membrane is not likely the determining factor for PiB labelling differences between intracellular and extracellular NFT because: (i) the cell membrane is not likely to be intact in the histological sections; and (ii) PiB has to cross several membranes which comprise the blood–brain barrier in order to access either plaques or NFT *in vivo*.

In this study, the strong labelling of CAA (when present) by 6-CN-PiB was of similar intensity to compact plaques, but the frequency of CAA in the typical Alzheimer's disease brains we examined was much lower than that of plaques. Thus in most Alzheimer's disease subjects, PiB binding to CAA contributes relatively little to the total *in vivo* signal, which appears to be driven primarily by Aβ-containing amyloid plaques. In subjects with amyloid angiopathy (Johnson *et al.*, 2007) CAA could be a major contribution to the *in vivo* PiB signal. However, CAA pathology has an occipital predilection, resulting in a greater occipital-to-global PiB ratio compared to Alzheimer's disease patients (Johnson *et al.*, 2007). This underscores the need to interpret the PiB-PET imaging relative to the known occurrence of neuropathological lesions in the brain areas under investigation.

Until recently, it was not possible to establish a direct relationship between PiB retention *in vivo* and Aβ pathology in the same subject. In a case of pathologically confirmed dementia with Lewy bodies and severe CAA (Bacskai *et al.*, 2007), ante-mortem PiB retention levels correlated with post-mortem biochemical measures of Aβ and PiB binding in three brain regions. PiB binding in this case was primarily associated with vascular Aβ deposits due to the CAA, while Aβ plaques were scarce. This made it difficult to directly correlate *in vivo* PiB retention with Aβ plaque deposits in that case, and no correlation was attempted with histological or immunohistochemical Aβ load. Nevertheless, the results of that study suggested a correlation between *in vivo* PiB measures with Aβ amyloid load, and thus are in accord with the present study, which clearly demonstrates that *in vivo* PiB retention in a pathologically typical Alzheimer's disease patient is related directly to the amount of insoluble Aβ peptides, including Aβ plaques.

Our results underscore the validity of using PiB-PET scanning not only to detect and follow the progression of Aβ-containing fibrillar amyloid deposits in clinically defined subject populations, but also to assess effectiveness of therapies aimed at clearing these potentially toxic deposits from the brain.

Supplementary material

Supplementary material is available at *Brain* online.

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SPECT perfusion imaging in the diagnosis of Alzheimer's disease

A clinical-pathologic study

W. Jagust, MD; R. Thisted, PhD; M.D. Devous, Sr., PhD; R. Van Heertum, MD; H. Mayberg, MD; K. Jobst, MD; A.D. Smith, DPhil; and N. Borys, MD

Article abstract—*Objective:* Numerous studies have suggested that temporoparietal hypoperfusion seen on brain imaging with SPECT may be useful in diagnosing AD during life. However, these studies have often been limited by lack of pathologic validation and unrepresentative samples. The authors performed this study to determine whether SPECT imaging provides diagnostically useful information in addition to that obtained from a clinical examination. *Methods:* Clinical data and SPECT images were collected prospectively, and patients were followed to autopsy. Clinical history, pathologic findings, and SPECT images were each evaluated by raters blind to other features, and clinical and SPECT diagnoses were compared with pathologic diagnoses. The study population consisted of 70 patients with dementia, followed to autopsy; 14 controls followed to autopsy; and 71 controls (no autopsy performed). The primary outcome was the likelihood of a pathologic diagnosis of AD given a positive clinical diagnosis, a positive SPECT diagnosis, and both. *Results:* When all participants (patients and controls) were included in the analysis, the clinical diagnosis of "probable" AD was associated with an 84% likelihood of pathologic AD. A positive SPECT scan raised the likelihood of AD to 92%, whereas a negative SPECT scan lowered the likelihood to 70%. SPECT was more useful when the clinical diagnosis was "possible" AD, with the likelihood of 67% without SPECT, 84% with a positive SPECT, and 52% with a negative SPECT. Similar results were found when only patients with dementia were included in the analysis. *Conclusions:* In the evaluation of dementia, SPECT imaging can provide clinically useful information indicating the presence of AD in addition to the information that is obtained from clinical evaluation.

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Despite intense efforts aimed at developing laboratory markers for specific dementing illnesses, establishing the cause of dementia during life remains a clinical process. Because clinical diagnostic criteria for AD[1] generally perform with high positive predictive value relative to the current pathologic "gold standard" in research settings,[2] laboratory diagnostic tests need to meet a relatively high standard to be accepted. Functional brain imaging using SPECT to evaluate cerebral perfusion is a laboratory investigation that has been proposed as useful in the diagnosis of dementia. Although many studies have found

From the Department of Neurology (Dr. Jagust), University of California, Davis; Departments of Health Studies and Statistics (Dr. Thisted), University of Chicago, IL; Department of Radiology (Dr. Devous), University of Texas Southwestern Medical Center, Dallas; Department of Radiology (Dr. Van Heertum), Columbia University, New York; Rotman Research Institute (Dr. Mayberg), University of Toronto, Ontario, Canada; Oxford Project to Investigate Memory in Aging (OPTIMA) (Drs. Jobst and Smith), Department of Pharmacology, University of Oxford, UK; and Cytogen Corporation (Dr. Borys), Princeton, NJ.

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Address correspondence and reprint requests to Dr. William Jagust, Department of Neurology, University of California Davis Medical Center, 4860 Y Street, Suite 3700, Sacramento, CA 95817.

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that the pattern of temporal and parietal hypoperfusion has high sensitivity, specificity, and positive and negative predictive value for discriminating patients with AD from healthy older subjects,[3-5] most studies have suffered to varying extent from lack of pathologic validation or highly selected and screened patients, limiting the validity and generalizability of the findings.

In 1988, the Oxford Project to Investigate Memory and Aging (OPTIMA) began a longitudinal prospective study, enrolling a cohort of patients with dementia who underwent clinical evaluation, SPECT perfusion imaging, annual reevaluation, and, ultimately, autopsy. The results of applying a specific set of SPECT diagnostic criteria were originally reported in the first 105 cases to come to postmortem.[6] We now report the results of an independent, blinded evaluation of SPECT imaging that includes some of this cohort of subjects with dementia, all of whom had neuropathologic verification of the cause of dementia, in addition to a group of control subjects, some of whom also had neuropathologic evaluation at autopsy. The study was designed to determine the accuracy of the premortem diagnosis of AD using SPECT perfusion imaging, and also to determine the additional benefit, over and above a clinical evaluation, that SPECT may confer.

Methods. *Patient selection.* A total of 158 subjects meeting inclusion and exclusion criteria were imaged with SPECT during the time period of this project. Although recruitment for the OPTIMA study began in 1988, in November 1992 SPECT instrumentation was upgraded. Because of the superior quality of SPECT images obtained after this upgrade, and to ensure comparability of scans and high quality of images, only subjects who were scanned on this instrument were included in this study. Subjects were included in this series if they were scanned on this instrument between November 1992 and the conclusion of the project in 1996 and also had pathologic postmortem examination of the brain. For the purposes of this study, initial evaluation was taken as the time of the first SPECT scan on this scanner.

Patients were referred to the study from both community and institutional settings by health care practitioners who were aware of the ongoing research project. Referrals were obtained from a host of different medical specialists (geriatric psychiatrists, neurologists, general practitioners, and geriatricians), along with community organizations, social service agencies, and local advertisements. Subjects were included if they had documented cognitive loss as determined using the Cambridge Mental Disorders of the Elderly Examination (CAMDEX),[7] had a reliable informant, could tolerate small doses of benzodiazepines for sedation (if necessary), and were willing to participate in all aspects of the longitudinal study. Exclusionary criteria included only the presence of very late stage dementia. Specific dementia diagnoses were neither inclusion nor exclusion criteria, nor were specific psychiatric diagnoses (e.g., depression). Subjects were permitted to take any additional medications at the time of enrollment or during the study, including those that might have CNS effects. At the time of the study, cholinergic therapy was generally unavailable in the United Kingdom and was not used in any of the subjects enrolled in this series. All medication use was recorded.

Control subjects were volunteers from the community, including spouses of patients with dementia and those recruited through advertisement or word of mouth. Identical exclusion and inclusion criteria were applied to the control subjects, except that they had no evidence of cognitive dysfunction or memory complaints. Procedures for obtaining informed consent from both patients and controls were approved by both the Central Oxford Research and Psychiatric Sector Research Ethics Committees.

Clinical evaluation and follow-up. At the time of enrollment, all patients and controls underwent an extensive evaluation that included the CAMDEX, history and physical examination, routine blood tests, lumbar puncture, and CT and SPECT brain imaging. At the conclusion of the evaluation, a clinical diagnosis was established and patients were enrolled for follow-up. The evaluation was repeated annually, unless a patient died, withdrew from the study, or was too ill to undergo the evaluations. Autopsy consent was often requested in life and reconfirmed at death using a carefully constructed protocol as previously reported.[8]

SPECT imaging. SPECT imaging was performed using single-headed rotating scanner (General Electric 400XCT) and the perfusion radiotracer ^{99m}Tc exametazime (Ceretec, Amersham International, Amersham, UK). Each subject was prepared with a 22-gauge IV catheter, and 500 MBq was injected IV, followed by a 5-mL saline flush while the subject sat in a quiet waiting area with subdued light. SPECT imaging began approximately 30 minutes following tracer injection. Data were acquired as 64 images over 360°, with each image having an acquisition time of 20 seconds and a 64 × 64 matrix. At the time of the studies, patients and controls with behavioral difficulties or anxiety were rarely given low doses of diazepam after the uptake period of the tracer.

Neuropathology. Within 24 to 48 hours of death, the brain was removed and suspended in buffered neutral formalin for at least 6 weeks. Histologic sections were taken from the frontal, temporal, and parietal neocortex, hippocampus, cerebellum, midbrain, and pons. The sections were stained with hematoxylin and eosin, congo red, Luxol fast blue, and cresyl violet, and with methenamine silver and Cross's modification of the Palmgren stain to demonstrate argyrophilic plaques and neurofibrillary tangles. Neuropathologic reports were prepared describing the density and distribution of neurofibrillary tangles and neuritic plaques. Specific neuropathologic criteria included those described by Khachaturian[9] and those proposed by the Consortium to Establish a Registry for AD (CERAD).[10] Other causes of dementia were diagnosed according to standard neuropathologic criteria available at the time.

Clinical, pathologic, and imaging interpretation. To ensure that clinical and imaging diagnoses were arrived at independently, separate raters evaluated both aspects of the study. A single individual (W.J.J.) reviewed all clinical protocols, which consisted of clinical history, physical examination, and cognitive tests, and arrived at a clinical diagnosis using standard criteria for probable or possible AD.[1] Other diagnostic choices included multi-infarct de-

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Table 1 *Subject characteristics*

Group	n	Age, y, mean (SD)	Sex, M/F	MMSE score, mean (SD)	Time from SPECT to death, mo, mean (SD)
Patients	70	77.1 (8)	35/35	13.2 (8.5)	29.3 (15)
Autopsied controls	14	80.4 (8)	9/5	27.9 (2.0)	22.9 (18.6)
Nonautopsied controls	71	73.3 (11)	28/43	28.8 (1.3)	NA

MMSE = Mini-Mental State Examination; NA = not applicable.

mentia, cerebrovascular disease without dementia, frontotemporal dementia, dementia with Lewy bodies, and Binswanger's syndrome. The clinical diagnostic evaluation was accompanied by a statement of the degree of certainty in the diagnosis, using a four-point scale. This individual was blinded to all imaging and neuropathologic results.

The same individual reviewed the neuropathologic report at a different time, blinded to all clinical and imaging data. The neuropathologic report included a description of the gross and microscopic histology and a pathologic diagnosis made by a senior neuropathologist. Although the pathologic diagnosis was thus usually obvious from the report, at times interpretation was required. The diagnostic options were AD, multi-infarct dementia, frontotemporal dementia, stroke, dementia with Lewy bodies, and Binswanger's syndrome. In addition, the rater could grade Alzheimer's pathology as present, but not diagnostic. All data were entered at the time of interpretation using a laptop computer that did not permit alterations after a case was recorded.

Digital data from the SPECT images were transferred to a single laboratory where they were uniformly formatted and processed (University of Texas Southwestern Medical Center, Dallas), and then forwarded to a separate laboratory (Bio Imaging Technologies, Trenton, NJ) where they were interpreted. The data were evaluated for compliance with the imaging protocol and technical adequacy. Images were presented on a video monitor in sagittal, coronal, and axial formats. Ratings were performed independently by three raters (H.M., M.D., and R.V.), each of whom was blind to all clinical and pathologic data and each of whom was experienced in the interpretation of clinical SPECT imaging. Individual scans were presented to each rater in a random order, and all interpretations were recorded directly into a computer that did not permit subsequent alteration of the entry. Coronal, sagittal, and transverse SPECT projection data were displayed at one time. Two high-resolution monitors were used for image display. The reader adjusted image brightness and contrast, magnification and panning, and cine display to personal satisfaction. Readers had the option of evaluating the images in black and white or standard color schemes.

During an initial training session on a separate set of images, readers reached consensus on how to interpret images and judge artifacts and positioning. Raters evaluated each image for a number of different features. First, each image was assessed for technical quality. Next, the images were read as normal or abnormal, and brain regions were independently rated as hyperperfused: normal, mildly, or moderately hypoperfused (a single category), or severely hypoperfused. These ratings were performed for each lobar region, cerebellum, and the subcortical structures in each hemisphere. The last stage of image interpretation included a final diagnosis, for which the choices were AD, multi-infarct dementia, frontotemporal dementia, and ischemia or vascular disease. Multiple diagnoses were permitted. Criteria for the presence of AD were previously agreed on to include either bilateral or asymmetric temporal or parietal lobe hypoperfusion or both. Readers indicated their personal degree of confidence in the diagnosis on a four-point scale.

Statistical analysis. Two different methods were used to assess the utility of SPECT. The primary analysis of interest was the incremental diagnostic value of SPECT after taking clinical diagnosis into account. To do this, clinical diagnosis (obtained by review as described above) and SPECT diagnosis were entered into a multivariate logistic regression model to predict the presence or absence of Alzheimer pathology. Alzheimer pathology was considered present if the neuropathology assessment was "AD" but not present if Alzheimer's changes were graded as present but not diagnostic. SPECT scans were considered positive for AD if at least two reviewers identified AD as the principal diagnosis with a moderate to high confidence. Statistical significance of SPECT diagnosis was assessed using models that first control for the clinical diagnosis. Two separate models were evaluated, one using all subjects and another using only patients with dementia. In the first case, it was assumed that all controls, whether they had been autopsied or not, were free of Alzheimer pathology. This method of analysis permitted the determination of what pathology to expect for individual subjects with specific combinations of imaging and clinical diagnoses drawn from a specified population.

In addition to this logistic regression analysis, a separate analysis evaluated the diagnostic performance of SPECT. In this analysis, sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and positive likelihood ratio were calculated. This analysis, therefore, simply evaluated SPECT as a diagnostic test, so that a "positive SPECT scan" for AD was evaluated in relationship to the presence or absence of AD neuropathology. The identical evaluation was performed for clinical diagnosis, in which case the diagnosis of "probable AD" or "probable or possible AD" was considered as a positive test for AD. This method of analysis permits the comparison of different types of diagnostic tests (clinical or imaging) in different populations.

Analysis of variance and χ^2 tests were used to assess baseline differences between groups for continuous and categorical variables. Two-sided p values are reported.

Results. During the initial image evaluation and quality control process, three studies were deemed technically inadequate, leaving a total of 155 studies for analysis. Of these, 70 were in patients with dementia and 14 were in

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Table 2 *Pathologic diagnoses vs SPECT and clinical diagnoses in 70 demented patients and 85 controls*

Diagnosis	Neuropathology assessment		
	AD absent	AD present	Total
Clinical			
AD Absent	96	3*	99
Probable or possible AD	13†	43	56
Total	109	46	155
SPECT			
AD absent	101	17‡	118
AD present	8§	29	37
Total	109	46	155

* Neuropathologic diagnoses for false negatives were AD + Huntington's, AD + ischemic/vascular disease, and AD only.

† Neuropathologic diagnoses for false positives were nonspecific changes/unknown (3), frontotemporal lobar degeneration (4), ischemia/vascular disease (2), PD (3), and progressive supranuclear palsy (1).

‡ Neuropathologic diagnoses for false negatives were AD (9), AD + cerebrovascular disease (5), AD + Lewy bodies (2), AD + PD (1).

§ Neuropathologic diagnoses for false positives were PD (4), frontotemporal lobar degeneration (2), cerebrovascular disease (1), and normal (1).

control subjects for whom autopsy was performed later. An additional 71 control subjects were studied with SPECT, but autopsy was not performed on them. Demographic characteristics of these subjects, including the time from SPECT imaging to death, are provided in table 1. No significant differences were seen between groups for sex and time from SPECT to death. Patients with dementia and autopsied control patients did not differ in age; however, living controls were younger on average than either of the other two groups ($p = 0.003$).

Of the 70 patients with dementia, 32 (46%) were clinically diagnosed as having probable AD and 24 (34%) were diagnosed as having possible AD. These diagnoses were established solely by review of the clinical information in the protocols. The remaining 14 patients (20%) were given clinical diagnoses of multi-infarct dementia (7), frontotemporal dementia (2), Lewy body (1), and other (4). None of the controls, either living or having had autopsy performed, were clinically diagnosed as having AD or any non-AD dementia. In contrast, 35 patients (50%) were diagnosed by SPECT imaging as showing evidence of AD. SPECT scans from two control subjects (one living and one autopsied) were interpreted as positive for AD.

Table 2 provides measures of true positive, true negative, false-positive, and false-negative findings for clinical diagnosis vs neuropathology and SPECT imaging versus neuropathology. The tables assume that control subjects without autopsies were truly negative for AD pathology. These tables also show the actual pathology when either diagnostic criterion produced a false-negative or false-positive finding. For both techniques, false-negative findings were often related to combined pathology, with AD plus an additional pathologic process. False-positive findings included a number of different pathologic conditions, including PD and frontotemporal dementia.

Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and positive likelihood ratios for clinical and SPECT diagnoses relative to pathology are provided in table 3.

The logistic regression model was fit using clinical diagnosis alone, SPECT diagnosis alone, and the combination of clinical and SPECT diagnoses. The reference groups used for these analyses were subjects who did not have clinical diagnoses of AD (when the clinical diagnosis model was evaluated), or who did not have SPECT diagnoses of AD (when the SPECT diagnosis model was evaluated). These models demonstrated that the clinical diagnosis of probable or possible AD is a highly significant predictor of Alzheimer pathology, increasing the odds of having AD over patients without these diagnoses 172 times for a diagnosis of probable AD and 64 times for possible AD. The SPECT image interpretation of AD alone is also a significant predictor of Alzheimer pathology, increasing the odds of having AD over subjects with a negative SPECT scan by a factor of 22. When SPECT and clinical diagnoses are considered together, a positive SPECT interpretation increases the odds of having AD by an additional factor of five (compared with those with a negative SPECT image), after taking into account any increase in odds associated with the clinical diagnosis. This incremental predictive value of SPECT is significant ($p = 0.018$).

These data are presented clinically in table 4. The clinical diagnosis of probable AD has an 84% likelihood of being associated with AD pathology. In the presence of a negative SPECT scan, this likelihood decreases to 70%, whereas a positive SPECT scan increases the likelihood to 92%. For the clinical diagnosis of possible AD, a similar result was obtained (67% without SPECT, 84% with a positive SPECT, and 52% with a negative SPECT). When this analysis was repeated excluding all control subjects, both the clinical diagnosis of AD, the SPECT diagnosis of AD, and the combined clinical and SPECT diagnoses remained significant predictors of neuropathologic AD.

Because varying delays occurred between SPECT imaging and autopsy, we also evaluated whether the time between the SPECT scan and death was a factor in determining the value of the scan. Positive and negative predictive values for SPECT vs autopsy in patients who died <1 year, between 1 and 2 years, 2 to 3 years, 3 to 4 years, or >4 years after SPECT scanning did not significantly differ.

Discussion. SPECT brain perfusion imaging has been widely reported to differentiate patients with AD from both control subjects and other dementing illnesses in a variety of studies.[5,11-14] A recent review of the data on SPECT imaging in dementia by the American Academy of Neurology Therapeutics and Technology Assessment Subcommittee suggested that SPECT was an established technique for supporting the clinical diagnosis of AD.[15] Dementia practice parameters[16] list SPECT as an optional part of the dementia evaluation. Despite this enthusiasm, the data supporting the clinical utility of SPECT imaging have had several limitations. The first is that the use of clinical diagnoses as opposed to neuropathologic ones as the "gold standard" for SPECT imaging may be inaccurate. Secondly, the true utility

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Table 3 *Sensitivities, specifities predictive values, accuracy, and positive likelihood ratios for clinical- and SPECT-based diagnosis rules, based on different clinical populations*

Population	Sensitivity/specificity	PPV/NPV	Accuracy	LR-Pos
Clinical diagnosis rule				
All subjects				
Probable AD	59/95	84/85	85	12.8
Possible or probable AD	93/88	77/97	90	7.8
SPECT	63/93	78/86	84	8.6
SPECT + probable AD	41/98	90/80	81	22.5
SPECT + possible or probable AD	61/96	88/85	86	16.6
SPECT or possible or probable AD	96/84	72/98	88	6.1
Autopsied subjects only				
Probable AD	59/87	84/63	71	4.5
Possible or probable AD	93/66	77/89	81	2.7
SPECT	63/82	81/65	71	3.4
SPECT + probable AD	41/95	90/57	65	7.8
SPECT + possible or probable AD	61/89	88/65	74	5.8
SPECT or possible or probable AD	96/58	73/92	79	2.3
Patients with dementia only				
Probable AD	60/80	84/53	67	3.0
Possible or probable AD	96/48	77/86	79	1.8
SPECT	64/76	83/54	69	2.7
SPECT + probable AD	42/92	90/47	60	5.3
SPECT + possible or probable AD	62/84	88/55	70	3.9
SPECT or possible or probable AD	98/40	75/91	77	1.6

Sensitivity: true positives/(true positives + false negatives); specificity: true negatives/(true negatives + false positives); PPV: true positives/(true positives + false positives); NPV: true negatives/(true negatives + false negatives); accuracy: (true positives + true negatives)/total; LR-pos: sensitivity/(1-specificity).

PPV = positive predictive value; NPV = negative predictive value; LR-Pos = positive likelihood ratio.

of a test is best evaluated by defining the additional information contributed by the test over and above that obtained in the standard clinical evaluation. When the clinical evaluation is used as the final determination of validity, this is impossible. Finally, another frequent shortcoming of many reports is that the most typical cases of AD are chosen for study, and very clear-cut comparison diagnoses (e.g., normal older subjects) are chosen as controls. Although this improves confidence in the clinical standard of validation, it limits the utility of the results. For example, differentiation of typical AD from healthy older individuals is usually not a clinically useful finding.

This report eliminates many of the shortcomings of prior studies. The use of neuropathologic diagnoses provides the highest standard of validation for a study of this sort. The sample of subjects includes patients with a variety of dementias, and, although not necessarily typical of a general practice, does reflect a broad spectrum of cognitive disorders likely to be referred for a specialized evaluation. Most importantly, the experimental procedure permitted the separate evaluation of clinical and SPECT diagnostic accuracy, allowing the determination of the additional value of SPECT imaging over accuracy of clinical diagnosis.

In this study, the case record reviews resulted in clinical diagnoses that were highly predictive of the presence of AD on pathology. This is consistent with previous reports that clinical criteria are reasonably valid.[17] Clear differences were seen in sensitivity and specificity, depending on whether probable or possible AD was diagnosed, with the inclusion of possible AD raising sensitivity but lowering specificity. Not surprisingly, when only patients with dementia were included, clinical diagnoses were far less specific but not less sensitive, because no control subjects were falsely diagnosed as demented. For the same reason, a similar picture emerged for SPECT diagnoses, with reduction in specificity when only subjects with dementia were evaluated. Interestingly, the sensitivity, specificity, and predictive values of SPECT alone were generally comparable to the clinical diagnosis of probable AD. The addition of possible AD cases clearly increased the sensitivity of clinical diagnoses. However, as has been shown in other autopsy studies[2] this increase in sensitivity when possible AD

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Table 4 *Results of logistic regression models showing the fraction of all subjects who actually have Alzheimer neuropathologic findings for three levels of clinical diagnosis (AD absent, possible AD, and probable AD) without SPECT, with a negative SPECT scan, and with a positive SPECT scan*

	Clinical diagnosis		
Subjects	AD absent	Possible AD	Probable AD
All			
If SPECT not done	0.03	0.67	0.84
SPECT negative for AD	0.02	0.52	0.70
SPECT positive for AD	0.11	0.84	0.92
Demented patients only			
If SPECT not done	0.14	0.67	0.84
SPECT negative for AD	0.10	0.54	0.72
SPECT positive for AD	0.30	0.82	0.91

Results are presented for all subjects (70 demented patients and 85 controls) and for dementia patients only.

cases are included comes at the price of reduced specificity, which is considerable when only the dementia group is included. Finally, it is worth noting that the addition of SPECT imaging to clinical diagnosis resulted in lower overall accuracy than the use of either technique alone. This is because the requirement of both a positive clinical diagnosis and a positive SPECT diagnosis is more stringent than requiring only one positive test, resulting in lower sensitivity. However, requiring two positive diagnostic tests increases specificity so that the positive likelihood ratio increases. The positive likelihood ratio is a useful clinical metric because it provides an index of the incremental value of a test by defining the posttest probability for a given pretest probability. Positive likelihood ratios greater than 10 generate large, usually clinically relevant changes in probability of a diagnosis; values between 5 and 10 generate modest changes in probability; and values below 5 generate relatively small but sometimes useful changes.[18] For these data likelihood ratios depended to a considerable extent on the population sampled, with relatively small to modest effects seen when only patients with dementia were evaluated.

In the clinical situation where diagnoses have imperfect predictive power, SPECT can play a role. Thus, even with the high likelihood of pathologic AD conferred by a clinical diagnosis of probable AD, SPECT significantly improves diagnostic accuracy, with the likelihood of AD pathology increasing by 7 to 8% to a value above 90% if the SPECT scan is positive. The increased probability of AD is twice as great if a SPECT scan is positive when the clinical diagnosis is possible AD. That is, a clinical diagnosis of possible AD with a positive SPECT scan is as likely to be associated with AD pathology as a clinical diagnosis of probable AD alone. These results thus indicate a demonstrable incremental value in both a positive and negative SPECT scan in addition to the clinical diagnosis, and that this incremental value is greater in atypical or uncertain cases.

Another study evaluated the ability of SPECT to predict histopathology in dementia, finding a sensitivity of 86, specificity of 73, positive predictive value of 92, and negative predictive value of 57 for a study of 54 patients with dementia and no controls.[19] These figures are comparable to our results in the dementia-only analysis, although the sensitivity we report is lower. The lower sensitivity could reflect the fact that we did not exclude cases with extensive cerebrovascular disease, and mixed dementia produced a substantial number of false-negative findings in our report. Two other SPECT studies have shown very high correspondence between imaging and pathologic diagnoses,[20,21] but these studies have involved relatively small numbers of highly selected patients.

Although these data clearly demonstrate general clinical utility of SPECT imaging in dementia, a number of questions about the specific situations in which SPECT imaging may be useful remain unanswered. The subjects in this report were moderately to severely demented, as evidenced by a mean Mini-Mental State Examination score of 13. Whether SPECT would have greater or lesser utility in less severe cases is unknown. The degree of clinical uncertainty in the diagnosis might also be expected to influence the clinical utility of SPECT. Although we did not find that SPECT was more useful in situations in which the clinical certainty was low (perhaps because clinical certainty did not relate to the accuracy of the diagnosis), our sample size was small for this analysis. Similarly, specific differential diagnoses might be presumed to be more or less useful. A number of reports have suggested that SPECT is most useful in differentiating AD from frontotemporal dementias[14,22,23] and least useful in differentiating AD from PD and vascular dementia.[5,24] However, the sample of non-Alzheimer dementias was inadequate to evaluate the utility of specific differential diagnoses. Finally, the utility of SPECT in comparison to other diagnostic tests was not evaluated. For example, previous studies have shown that both CT and MRI may provide useful diagnostic information in the evaluation of patients with dementia.[25,26] It is not clear how SPECT performs in relation to clinical diagnosis when CT and MRI are included in the evaluation process.

The correct diagnosis of the cause of dementia is increasingly recognized as important because of better understanding of genetic risks and disease mechanisms. Some potential therapeutic options (e.g., antiamyloid agents, vaccination, or neural transplantation) might be associated with high risks, necessitating accurate diagnoses. The addition of SPECT in this situation could increase the likelihood of a correct diagnosis. Furthermore, the availability of treatment for AD has shifted the strategy for the diagnosis of AD from a traditional approach of ex-

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cluding a host of diseases, to an approach that seeks typical signs and symptoms with confirmatory tests done to support a positive diagnosis in some situations. SPECT perfusion imaging is clearly a technique that may provide other valuable information in addition to the clinical diagnosis.

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SPECT perfusion imaging in the diagnosis of Alzheimer's disease: A clinical-pathologic study
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ORIGINAL ARTICLES

Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B

William E. Klunk, MD, PhD,[1] Henry Engler, MD,[2] Agneta Nordberg, MD, PhD,[3,4] Yanming Wang, PhD,[5] Gunnar Blomqvist, PhD,[2] Daniel P. Holt, BS,[5] Mats Bergström, PhD,[2] Irina Savitcheva, MD,[2] Guo-feng Huang, PhD,[5] Sergio Estrada, PhD,[2] Birgitta Ausén, MSCI,[4] Manik L. Debnath, MS,[1] Julien Barletta, BS,[6] Julie C. Price, PhD,[5] Johan Sandell, PhD,[2] Brian J. Lopresti, BS,[5] Anders Wall, PhD,[2] Pernilla Koivisto, PhD,[2] Gunnar Antoni, PhD,[2] Chester A. Mathis, PhD,[5] and Bengt Långström, PhD[2,6]

This report describes the first human study of a novel amyloid-imaging positron emission tomography (PET) tracer, termed Pittsburgh Compound-B (PIB), in 16 patients with diagnosed mild AD and 9 controls. Compared with controls, AD patients typically showed marked retention of PIB in areas of association cortex known to contain large amounts of amyloid deposits in AD. In the AD patient group, PIB retention was increased most prominently in frontal cortex (1.94-fold, $p = 0.0001$). Large increases also were observed in parietal (1.71-fold, $p = 0.0002$), temporal (1.52-fold, $p = 0.002$), and occipital (1.54-fold, $p = 0.002$) cortex and the striatum (1.76-fold, $p = 0.0001$). PIB retention was equivalent in AD patients and controls in areas known to be relatively unaffected by amyloid deposition (such as subcortical white matter, pons, and cerebellum). Studies in three young (21 years) and six older healthy controls (69.5 ± 11 years) showed low PIB retention in cortical areas and no significant group differences between young and older controls. In cortical areas, PIB retention correlated inversely with cerebral glucose metabolism determined with 18F-fluorodeoxyglucose. This relationship was most robust in the parietal cortex ($r = -0.72$; $p = 0.0001$). The results suggest that PET imaging with the novel tracer, PIB, can provide quantitative information on amyloid deposits in living subjects.

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We and others have worked to develop in vivo amyloid-imaging agents for use with a variety of brain imaging techniques.[1–8] Modification of the amyloid-binding histological dye, thioflavin-T, led to the finding that neutral benzothiazoles bound to amyloid with high affinity and crossed the blood–brain barrier very well.[5] The basic properties of the prototypical benzothiazole amyloid binding agent 2-(4′methylaminophenyl)benzothiazole (termed *BTA-1*) and related derivatives have been described in detail.[8–10] These studies showed that these compounds could bind to amyloid with low nanomolar affinity, enter brain in amounts sufficient for imaging with positron emission tomography (PET), and clear rapidly from normal brain tissue. At the low nanomolar concentrations typically used in PET studies, the binding of BTA-1 to postmortem human brain was shown to be a good indication of Aβ amyloid deposition but did not appear to detect the presence of neurofibrillary tangles.[11] The exact form of the amyloid target of BTA-1 binding have not yet been identified with certainty. In vitro studies[11] suggest that BTA-1 binds to aggregated, fibrillar Aβ deposits such as those found in the cortex and striatum, but not to the amorphous Aβ deposits such as those that predominate in cerebellum. The binding of BTA-1 and related derivatives to oligomeric Aβ has not yet been studied.

A structure-activity study of a series of benzothiazoles suggested that a hydroxylated BTA-1 derivative had brain clearance properties typical of many useful PET radiotracers.[10] Therefore, this hydroxybenzothiazole was chosen as the lead compound for the first human trial of benzothiazole amyloid-imaging agents. For simplicity, the compound, *N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole, was given the Uppsala University PET Centre code of "Pittsburgh Compound-B" or, simply, PIB. Preclinical studies showed that PIB bound to Alzheimer's disease (AD) brain with a K_d of 1 to 2nM, entered the brain rapidly (approximately 7%ID/g 2 minutes after intravenous in-

From the [1]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA; [2]Uppsala University, PET Centre/Uppsala Imanet AB, Uppsala; [3]Neurotec Department, Karolinska Institute, Huddinge University Hospital, Stockholm; [4]Department of Geriatric Medicine, Huddinge University Hospital, Stockholm, Sweden; [5]Department of Radiology, PET Facility, University of Pittsburgh, Pittsburgh, PA; and [6]Department of Organic Chemistry, Uppsala University, Uppsala, Sweden.

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Address correspondence to Dr Mathis, PET Facility, B-938 UPMC Presbyterian, 200 Lothrop Street, Pittsburgh, PA 15213-2582. E-mail: mathisca@upmc.edu

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jection in mice), and cleared rapidly from normal mouse brain (clearance $t_{1/2}$ approximately 8 minutes).[10] Using real-time in vivo multiphoton microscopy, researchers have shown that PIB and other benzothiazole amyloid-imaging agents label individual amyloid plaques in transgenic mouse models of AD within 3 minutes after intravenous injection and clear rapidly from normal brain parenchyma.[8,12] This study describes the first results from PIB PET imaging of 16 mild AD patients and 9 healthy control (HC) subjects.

Subjects and Methods

Preclinical development of the benzothiazole class of compounds and PIB was completed at the University of Pittsburgh,[10] recruitment and evaluation of AD patients subjects and older controls were performed at the Department of Geriatric Medicine, Huddinge University Hospital, and good manufacturing process evaluation of PIB and human PET studies were performed at Uppsala University.

PET-Microdosing Toxicology

The human use of PIB was preceded by a toxicity assessment using the PET-microdosing concept.[13] Toxicological studies included genotoxicity (chromosomal aberration, mouse lymphoma mutagenesis, bacterial reverse mutation assay, and mouse micronucleus assay), single dose toxicity in rats, and cardiopulmonary physiology in the rhesus monkey. No toxic effects of PIB were observed.

Radiotracers

^{18}F-fluorodeoxyglucose (^{18}FDG) and PIB were produced according to the standard good manufacturing process at the Uppsala University PET Centre. PIB, *N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole, was prepared (Fig 1) by the method described previously,[10] with several modifications including the use of NaH as base and dimethyl formamide as the reaction solvent. A solution of PIB consisting of normal saline (2ml), propyleneglycol (2ml), ethanol (0.7ml), and HCl (0.3mM) was filtered (Dynagard ME, 0.22μm), yielding a solution that was sterile and apyrogenic. Addition of 5ml sterile phosphate-buffered saline to the solution adjusted the pH to between 6.0 and 7.0. The radiochemical yield was in the range of 10 to 15% based on [^{11}C]methyl iodide, and the specific radioactivity was on average 25GBq/μmol (range, 6–74) at end of synthesis. Routine quality control of the solutions for human injection consisted of a pH measurement and high-performance liquid chromatography analysis to determine radiochemical and chemical purity. The radiochemical purity was greater than 95%. In addition, the following analyses were performed on selected batches: sterility and endotoxin test, radiochemical and chemical stability test including column recovery determination, and verification of the identity of the radiolabeled compound with liquid chromatography mass spectrometry.

Autoradiography

Fresh-frozen pieces (2 × 2cm) of frontal cortex from postmortem brain of Alzheimer's patients and from age-matched control brain were used for the autoradiographic binding studies. Tissue was obtained from the University of Pittsburgh Alzheimer Disease Research Center Brain Bank and was collected as previously described.[11] Frozen sections (25μm) were preincubated in phosphate-buffered saline, pH 7.0, complemented with 2% bovine serum albumin, for 8 to 10 minutes. Subsequently, the sections were incubated in 10nM PIB, with or without 10μM BTA-1 (unlabeled compound) for 30 minutes, in the same buffer. After that, the slices were washed 2 × 2 minutes in the same buffer with an additional 2 × 2–minute wash step in buffer without bovine serum albumin. Finally, the slides were dried under an air stream, at 37°C, for 8 to 10 minutes, before being exposed to β-sensitive phosphor imager plates (Molecular Dynamics, Sunnyvale, CA) for at least 40 minutes. The exposed plates were scanned in a PhosphorImager, model 400S (Molecular Dynamics) and the obtained digital images were displayed and analyzed by the software ImageQuant 5.1 (Molecular Dynamics).

Human Subjects

HEALTHY VOLUNTEERS. Nine subjects volunteered as HCs for the PIB study and for regional cerebral glucose metabolic rate ($rCMR_{glc}$) by ^{18}FDG. Six older controls (OCs) ranging in age from 59 to 77 years old, and three young controls (YCs) all 21 years old were examined. The three YCs were studied under a separate Human Ethics Committee Protocol, which included an arterial line for the purpose of collecting samples for metabolite analysis and input function determination. Arterial sampling was not included in the initial AD patient protocol but subsequently was obtained from three AD patients and two older controls under a modified protocol (see below). In addition to the arterial sampling, the YC subjects also were included because of the near certainty that these young subjects would represent true plaque-negative controls. None of the HC subjects had a history of a medical or neurological disease or substance abuse, and all scored normally on neuropsychological testing.

ALZHEIMER'S DISEASE PATIENTS. Sixteen AD patients (Tables 1 and 2) ranging in age from 51 to 81 years old were

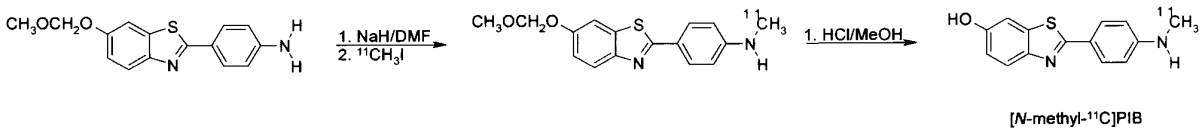

Fig 1. Reaction scheme for the radiochemical synthesis of PIB.

Table 1. Clinical Data of Individual AD Patients

ID[a]	Duration (yr)	MMSE at Diagnosis	Time Since Diagnosis (yr)	MMSE at Study	ChEI	Years Taking ChEI[b]
AD1[c]	4	28	0.5	26	No	0
AD2	6	27[d]	4	25	Yes	3
AD3	2	18	0.2	18	No	0
AD4[e]	**5**	**29**	**4**	**28**	**Yes**	**4**
AD5	6	25	4	22	Yes	4
AD6	7	25	6	21	Yes	4
AD7	5	29	4	18	Yes	4
AD8	1	25	0.3	25	No	0
AD9	3	27	0.3	25	No	0
AD10	4	27	2	25	Yes	2
AD11	5	28	3	27	Yes	2
AD12[e]	**5**	**28**	**3**	**28**	**Yes**	**2**
AD13	4	29	2	27	Yes	2
AD14[e]	**4**	**28**	**2**	**29**	**Yes**	**2**
AD15	4	23[f]	3	27	Yes	3
AD16	4	27	0	27	No	0
Mean	4.3	26.6	2.4	24.9	11 Yes	2.9
SD	1.5	2.9	1.8	3.4	5 No	0.9

[a]AD patient identification code.
[b]Mean treatment time refers to only those receiving ChEI treatment.
[c]AD patient AD1 was not included in standardized uptake value analyses for the reason listed in Results.
[d]The first available MMSE score is from 2 years before the study.
[e]AD4, AD12, and AD14 showed PIB retention typical of that seen in controls.
[f]The first available MMSE score is from 1 year before the study.

AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; ChEI = cholinesterase inhibitor therapy.

Table 2. Group Mean Clinical Data

Parameter	AD	OC	YC
Age (yr)	65.9 ± 10.7	69.0 ± 7.2	21 ± 0
Female	5	3	3
Male	11	3	0
Education (yr)	12.3 ± 3.7	12.7 ± 4.0	n/a[a]
ApoE 3/3	8	nd	nd
ApoE 2/4	1	nd	nd
ApoE 3/4	1	nd	nd
ApoE 4/4	6	nd	nd
CSF Aβ42 <450pg/ml[b]	11 of 16	nd	nd
Mean CSF Aβ42	372 ± 129	nd	nd
CSF tau >400pg/ml[b]	10 of 16	nd	nd
Mean CSF tau	639 ± 283	nd	nd

[a]Because these young volunteers had not yet reached their full educational potential.
[b]Indicates the number of patients with a level outside of the normal range.

AD = Alzheimer's disease; OC = older control; YC = younger control; n/a = not applicable; ApoE = apolipoprotein E; nd = not determined; CSF = cerebrospinal fluid.

recruited at the department of Geriatric Medicine, Huddinge University Hospital, Karolinska Institute. The AD patients had diagnoses of probable AD according to National Institute of Neurological and Communication Disorders Alzheimer's Disease and Related Disorders Association criteria.[14] Before diagnosis, subjects underwent a comprehensive clinical examination including medical history with close informant, neurological and psychiatric examination, routine blood analysis, cerebrospinal fluid analysis for Aβ(1-42) and tau, electrocardiogram, magnetic resonance imaging/computed tomography scans, single-photon emission computed tomography blood flow scans, electroencephalography, apolipoprotein E (ApoE) genotyping, and a comprehensive neuropsychological examination. The degree of dementia, as evaluated by the Mini-Mental State Examination (MMSE), varied from mild to very mild, ranging from 18 to 29. Eleven of the AD patients had been on cholinesterase inhibitor treatment for 2 to 4 years (five rivastigmine and six galantamine). Five recently diagnosed AD patients had never received treatment before the study. There was no significant

difference in age or education level between the AD patients and the OC subjects (see Table 2).

All AD patients and their next of kin and all HC subjects gave informed consent to participate in the study. The study was approved by the Ethics Committee of Uppsala University and Karolinska Institute, Stockholm, the Isotope Committee, Uppsala University Hospital, Uppsala, Sweden, and the Institutional Review Board of the University of Pittsburgh.

Positron Emission Tomography

Patients and healthy volunteers were examined after fasting for at least 6 hours before PET. Electrocardiography, pulse and blood pressure were measured throughout the PIB study. PET was performed in either of two Siemens ECAT HR+ cameras with an axial field of view of 155mm, providing 63 contiguous 2.46mm slices with a 5.6mm transaxial and a 5.4mm axial resolution. The orbitomeatal line was used to center the head of the subjects. The data were acquired in three-dimensional mode. The patients and healthy volunteers were given an intravenous injection of approximately 300MBq of PIB. PET measured the time-dependent uptake of radioactivity in the brain according to a predetermined set of measurements (frames 2×60, 3×120, 4×180, 4×300, and 2×600 seconds) for 1 hour.

Subjects were given 200 to 300MBq of ^{18}FDG intravenously and PET measured the radioactivity in the brain for 5×60, 5×180, 5×300, and 1×600 seconds frames for 55 minutes. The plasma glucose concentration was measured three times, once before and twice after the ^{18}FDG injection. All ^{18}FDG scans of AD patients were obtained within 30 days of the PIB scan.

Attenuation correction was based on a 10-minute windowed transmission scan with rotating ^{68}Ge rod sources before administration of the radioactivity. The emission data were normalized, corrected for random coincidences and dead time, and corrected for scatter using a method by Watson and colleagues.[15] Images were reconstructed with the standard software supplied with the scanner (ECAT 7.1; CTI PET Systems, Knoxville, TN), using Fourier rebinning followed by two-dimensional filtered back-projection applying a 4mm Hanning filter. A computerized reorientation procedure was used to align consecutive PET studies for accurate intra- and interindividual comparisons.[16]

Metabolite Analysis

Arterialized-venous blood samples were obtained from 13 AD patients and 4 OC subjects. Radial artery blood samples were obtained in 2 of the 3 YC subjects, 2 of the 6 OC subjects, and 3 of the 16 AD patients (AD12, AD13, and AD14). Whole-blood samples were centrifuged and an equal volume of acetonitrile was added to the plasma fraction to precipitate the proteins. The supernatant was analyzed by high-performance liquid chromatography. Separation of metabolites and tracer was performed on a Genesis C18 column with a mobile phase consisting of acetonitrile 50mM ammonium formate, pH 3.5 (55:45, vol/vol). The metabolite and tracer fractions were collected and the radioactivity was measured in a well-type scintillation counter.

Regions of Interest

All PET investigations were analyzed using identical standardized regions of interest (ROI) in the brain.[17] Cortical ROI (1×3cm) were placed in the frontal (three slices) and parietal (four slices) cortices. ROI for the striatum were placed at the level with highest uptake. Other cortical ROI were placed in the occipital and cerebellar cortices at the level of highest radioactivity uptake and in the temporal cortices (five coronal slices). Two ROI (1.5cm in diameter) were located in the pons and linked, and the subcortical white matter was defined with a traced ROI at the location of centrum semiovale. The parietal, temporal, frontal, and occipital ROI were linked to form volumes of interest.

Image Quantitation

Arterial plasma data were available for 7 of the 25 subjects, but 2 of the AD patients were among the 3 outliers that did not show PIB retention (see below). Therefore, arterial data were available for only one subject who showed significant PIB accumulation (AD13). This precluded conventional compartmental analysis on the subject group as a whole. Reference tissue modeling using the cerebellum then was explored. The cerebellum was chosen as a reference region because of its previously reported lack of Congo red and thioflavin-S–positive plaques.[18,19] Over the 60-minute time frame that the data were collected, the tissue-to-reference ratio did not plateau over a sufficient number of points to validly apply steady state–based modeling methods (eg, Logan graphical analysis[20,21]). Future studies with extended periods of data acquisition of at least 90 minutes should allow for definitive determination of whether or not steady state–based methods can be applied. Models which assume irreversible binding (eg, Gjedde[22] and Patlak and colleagues[23,24]) also were applied to the data, but difficulties were observed in brain areas with very low accumulation, such as the cortical regions of HC subjects. There was some indication that this may be caused by a small but significant net accumulation of tracer in the cerebellum, perhaps because of nonspecific retention in the white matter which contaminates this reference ROI. Efforts are under way to analyze the data with a modified Patlak method that corrects for this accumulation in the reference region. The details of this analysis will be presented separately elsewhere (G. Blomqvist, in preparation). Currently, expressing the data in terms of standardized uptake value (SUV) appears preferable because it does not introduce assumptions about the kinetics which have not yet been adequately explored. SUV was obtained by normalizing tissue concentration (nCi/ml) by injected dose (nCi) and body mass (in units of ml, making the approximation that 1gm equals 1ml). Note that, although not yet optimized, preliminary modeling approaches produced results that were entirely consistent with the SUV results.

^{18}F-fluorodeoxyglucose Analysis

Parametric maps of glucose metabolic rate ($rCMR_{glc}$) were generated by the Patlak technique using the time course of the tracer in arterialized-venous plasma as the input function.[22,23] Taking advantage of the 20-minute half-life of carbon 11, ^{18}FDG scans could be performed 120 minutes after the injection of PIB.

Statstical Analyses

Statistical comparisons utilized a two-sample, unequal variance, two-tailed Student's t test. Linear regression analyses were conducted to yield the Pearson product moment correlation coefficient, r. Because of the multiple comparisons in eight brain areas, a Bonferroni correction was applied to set statistical significance to p value of 0.05/8 (ie, $p = 0.006$) to declare a significant difference to be present between two groups.

Results

Characterization of PIB Binding to Postmortem Tissue

In sections of fresh-frozen postmortem tissue, PIB showed little binding to the amyloid-free frontal cortex of a cognitively normal elderly control brain (Fig 2A, B). In contrast, PIB bound specifically to the amyloid-laden frontal cortex of an age-matched AD brain in a manner that could be blocked by an excess of the structural analog, BTA-1 (see Fig 2C, D). The nonspecific retention of PIB in white matter was overshadowed by the cortical binding in AD brain but predominated in control brain (see Fig 2). Note that Figure 2 represents fresh-frozen tissue sections that have not been treated to mask white matter binding (ie, the tissue was not defatted and washings were performed using phosphate-buffered saline without ethanol).

Plasma Metabolism of PIB

The plasma concentration of PIB was studied in the nine HC subjects and 16 AD patients. All PIB metabolites were very polar. No substantial differences in the metabolism of PIB were seen between the AD patients and the HC subjects. The amount of unchanged PIB decreased rapidly and was 65.5 ± 8.7% in HC subjects and 68.1 ± 12.9% in AD patients after 5 minutes, 30.7 ± 7.3% (HC) and 33.5 ± 8.9% (AD) after 12 minutes, and 7.2 ± 3.6% (HC) and 9.8 ± 3.0% (AD) after 60 minutes. Furthermore, no differences between the time course of labeled metabolites in arterial and/or venous plasma could be seen. Of note, in vivo mouse studies using PIB showed similarly rapid peripheral metabolism, whereas greater than 95% of the radioactivity in brain could be recovered as unchanged parent compound.[10] Studies in other species are ongoing.

Time-Activity Data

The six OC subjects showed a brain entry and clearance pattern very similar to that found in the YC subjects, and there was no statistically significant difference between the two healthy control (HC) groups. Therefore, young and older control groups were combined to form the HC group for comparison with the AD patients. All statistically significant findings reported below remained significant ($p < 0.006$) in a separate analysis comparing AD patients to only the six OC subjects. The data from 1 of the 16 AD patients (AD1) were excluded from the SUV analyses because of low radioactivity values in all brain areas (including cerebellum and white matter), possibly caused by extravasation of an unknown portion of the injected dose.

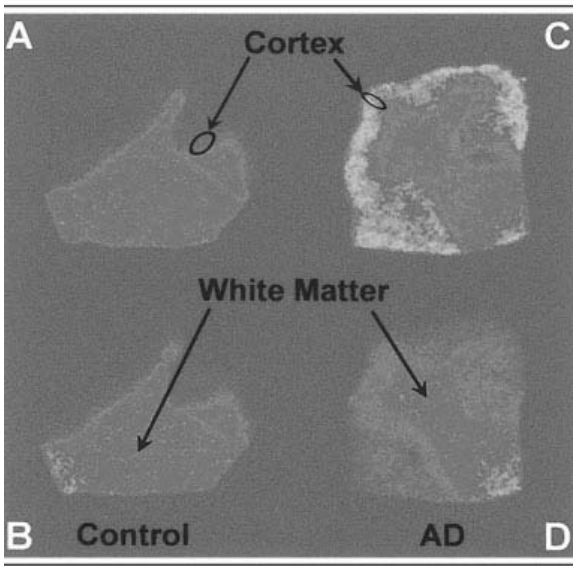

Fig 2. Specific and displaceable PIB binding occurs in the cortex of postmortem Alzheimer's disease (AD) brain, but not in white matter or control brain cortex. Autoradiograms showing the binding of PIB to fresh-frozen, post-mortem control (A, B) and AD brain sections (C, D). All sections were incubated with 10nM PIB. Excess nonradioactive BTA-1(10μM) was added in B and D to demonstrate displaceable binding. Arrows indicate the location of white matter and cortex (gray matter area is circled in A, C). Cortex is barely visible on control sections because of lack of binding.

As a group, the HC subjects showed rapid entry and clearance of PIB in all cortical and subcortical gray matter areas, including cerebellar cortex (Fig 3A, C, D). Cerebellum, an area lacking fibrillar amyloid plaques, showed nearly identical uptake and clearance of PIB in the HC and AD groups (see Fig 3A). Subcortical white matter showed relatively lower entry and slower clearance in both HC subjects and AD patients, but PIB retention did not differ significantly between the two groups (see Fig 3B). In contrast, the AD patients showed a marked retention of PIB compared with HC subjects in areas of the brain known to contain large amounts of amyloid deposits in AD, such as parietal and frontal cortices[25,26] (see Fig 3C, D, E). The SUV values over the late time points (40–60 minutes) were averaged to calculate the SUV values shown in the group comparisons and to generate the images shown below.

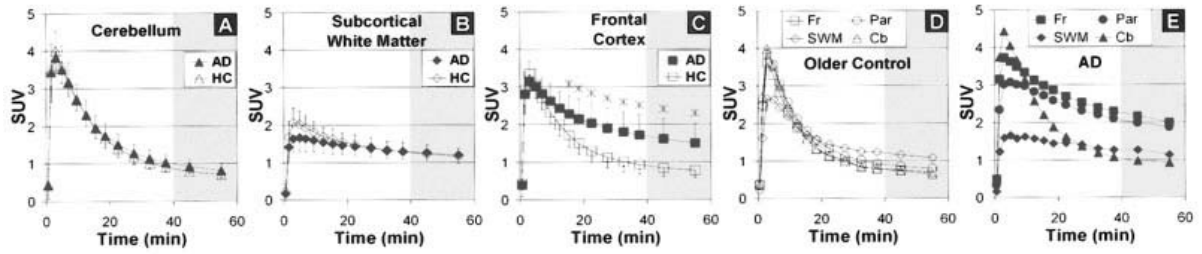

*Fig 3. PIB is differentially retained only in amyloid-laden cortical areas of AD brain. Standardized uptake values (SUVs) demonstrating brain entry and clearance of PIB. A to C represent averaged SUV values for all HC subjects (*open, black symbols*; n = 9) and all AD patients (*filled, red symbols*; n = 15) in cerebellum, subcortical white matter, and frontal cortex. D and E show brain entry and clearance in cerebellum* (triangles)*, subcortical white matter* (diamonds)*, frontal cortex* (squares)*, and parietal cortex* (circles) *for an older control subject (D) and an AD patient (E). Error bars represent one standard deviation (SD) and are too small to be seen in some of the HC subject data in A to C. Asterisks (e.g., in C) indicate a significant difference between AD and HC values (*$p < 0.006$*). Shaded areas highlight the 40 to 60-minute time period used for the summed SUV data displayed in Figures 4 to 7.*

Standardized Uptake Value Images

As the time-activity data would predict, the topographical pattern of PIB retention was clearly different in AD patients compared with the HC subjects (Fig 4). PIB accumulation in AD patients as a group was most prominent in cortical association areas and lower in white matter areas. This pattern is very consistent with that described in postmortem studies of amyloid deposition in AD brain.[25,26] PIB images from HC subjects showed little or no PIB retention in cortical areas, leaving the subcortical white matter regions highest in relative terms. Note that, in absolute terms, the accumulation of PIB in white matter was essentially the same in AD patients and HC subjects (see Figs 3B, 6B).

A series of axial and sagittal images give a better three-dimensional sense of the topography of PIB retention (Fig 5). The marked difference between PIB retention in the AD patient and the HC subject is apparent throughout most of the forebrain. Frontal cortex was widely affected in the AD patient, but intense PIB retention also was observed in temporal and parietal cortices, portions of occipital cortex, and in the striatum. Lateral temporal cortex appeared to have greater PIB accumulation than medial temporal areas. Cerebellar cortex (see Fig 5) showed little PIB retention and was similar in AD patients and HC subjects.

Quantitative Comparisons of Alzheimer's Disease and Healthy Control Group Data

In cortical areas, the mean PIB SUV value of AD patients was significantly greater than the mean PIB SUV value of control subjects (Fig 6A; Table 3). This indicates increased retention of PIB in areas known to have extensive amyloid deposition in AD.

Three patients diagnosed with AD (AD4, AD12, and AD14) had high MMSE scores (28–29) and

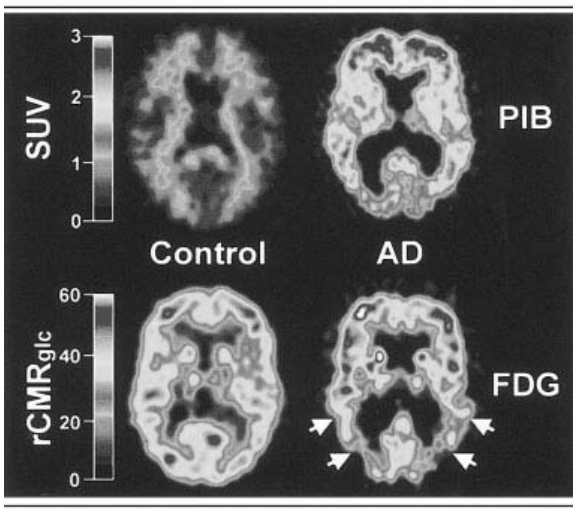

Fig 4. PIB standardized uptake value (SUV) images demonstrate a marked difference between PIB retention in Alzheimer's disease (AD) patients and healthy control (HC) subjects. PET images of a 67-year-old HC subject (left) and a 79-year-old AD patient (AD6; MMSE = 21; right). (top) *SUV PIB images summed over 40 to 60 minutes;* (bottom) ^{18}*FDG* $rCMR_{glc}$ *images (μmol/min/100ml). The left column shows lack of PIB retention in the entire gray matter of the HC subject (top left) and normal* ^{18}*FDG uptake (bottom left). Nonspecific PIB retention is seen in the white matter (top left). The right column shows high PIB retention in the frontal and temporoparietal cortices of the AD patient (top right) and a typical pattern of* ^{18}*FDG hypometabolism present in the temporoparietal cortex (*arrows*; bottom right) along with preserved metabolic rate in the frontal cortex. PIB and* ^{18}*FDG scans were obtained within 3 days of each other.*

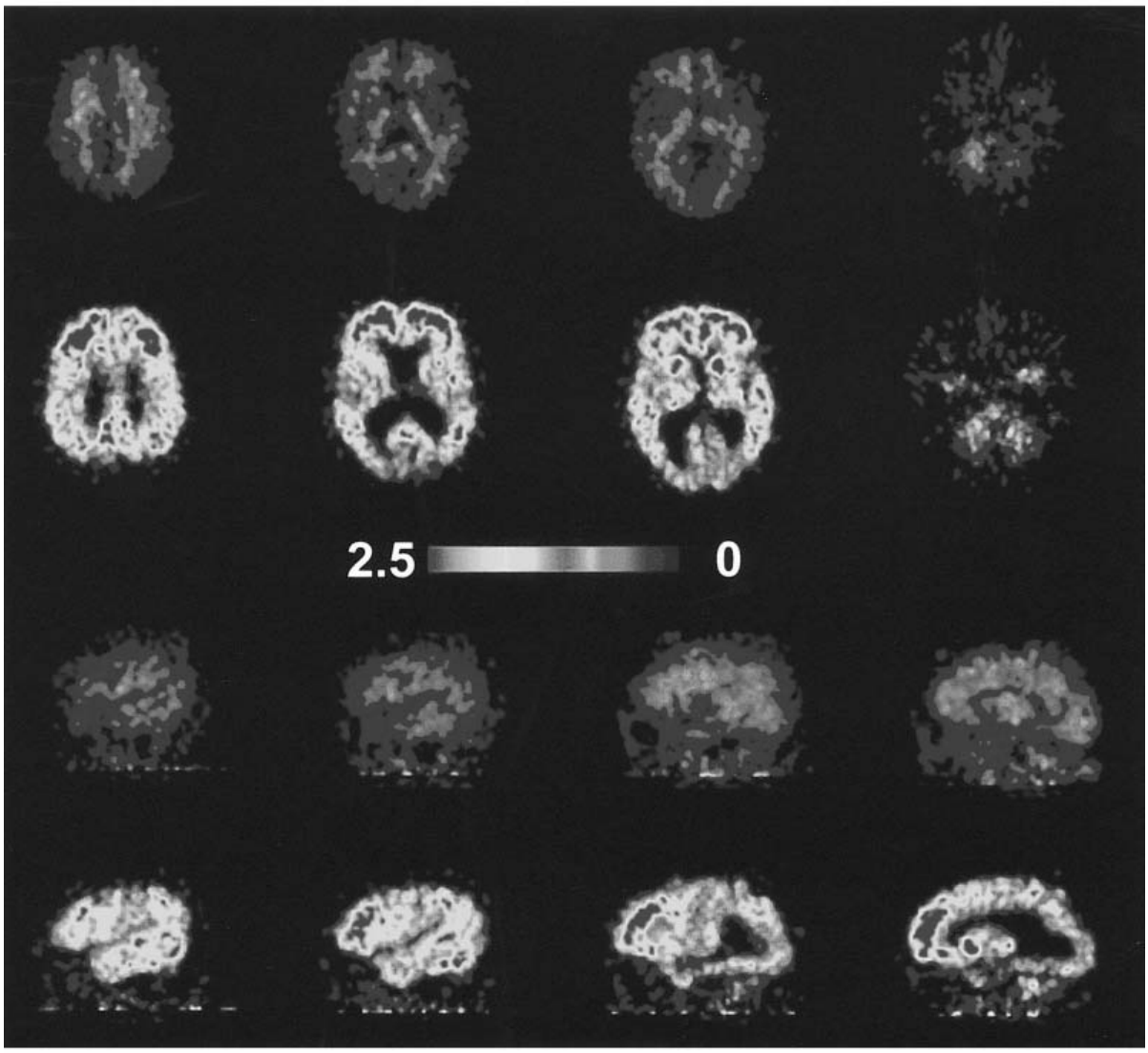

Fig 5. Serial planes demonstrate the topography of PIB retention. Axial (top two rows) and sagittal (bottom two rows) standardized uptake value (SUV) PIB images of the subjects shown in Figure 4. The healthy control subject data are shown in rows 1 and 3. The Alzheimer's disease patient data are shown in rows 2 and 4. The reference region, the cerebellum, can best be appreciated in the images at the far right. The cerebellar peduncles (white matter) show some nonspecific retention, but the cerebellar cortex shows negligible retention. Scale bar indicates relative levels of PIB SUV values.

showed no significant deterioration over the 2 to 4-year follow-up period (see Table 1). These subjects had levels of PIB retention in cortical regions typical of controls (see open triangles in Fig 6). They also had $rCMR_{glc}$ values similar to controls in the brain areas presented in Figure 6. These three subjects were retained in the AD group for all analyses. In the OC group, the oldest subject consistently showed the highest cortical PIB retention and the lowest cortical $rCMR_{glc}$ (see boxed circles in Fig 6). This subject had not expressed any subjective memory complaints and performed within the reference range on the neuropsychological test battery except for difficulty copying a complex cube.

The average PIB SUV values in the HC subjects were low and similar to each other in all cortical and

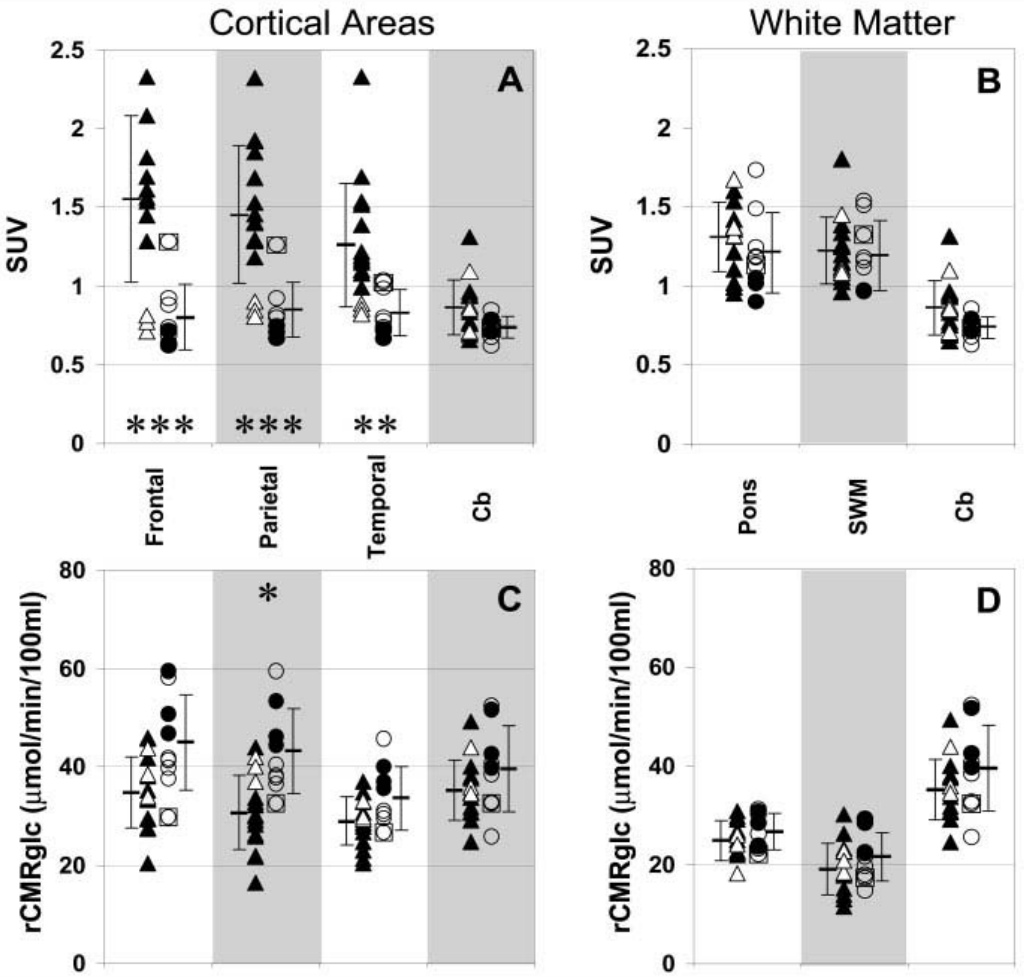

Fig 6. The differences in PIB retention between Alzheimer's disease (AD) patients and healthy control (HC) subjects can be quantified and are statistically significant. Shown is the accumulation of PIB and rCMRglc in selected regions. Average PIB standardized uptake value (SUV) values were summed over 40 to 60 minutes in cortical areas (A) or white matter areas (B) and compared with cerebellum. Values for ^{18}FDG uptake were calculated with the Gjedde-Patlak method in cortical areas (C) or white matter areas (D) and compared with cerebellum. The mean and one SD are indicated with the error bars beside the individual points. HC subjects: circles*; n = 9;* filled circles *represent the three young HC subjects;* boxed circle *represents the outlier in the HC group (oldest subject). AD patients:* triangles*; n = 15 (SUV) or n = 16 (FDG);* open triangles *represent the three outliers in the AD group. AD mean and SD values include all 15 (SUV) or 16 (^{18}FDG) AD subjects;* $p < 0.01$ *(*);* $p < 0.002$ *(**);* $p < 0.0002$ *(***).*

subcortical gray matter areas. In HC subjects and AD patients, the retention also was similar in the cerebellar gray matter (see Table 3), a cortical area that lacks fibrillar amyloid plaques.[18] This indicates the lack of PIB retention in control cortex and in the cerebellum of both AD and controls, brain areas which would not be expected to have significant amyloid deposition.

In HC subjects, the PIB SUV values in pons and subcortical white matter (see Fig 6B) were higher than in cortical areas and very similar to the SUV values found in pons and subcortical white matter of AD patients (see Table 3). This suggests higher, nonspecific retention of PIB in white matter than in gray matter areas.

We found the striatum, consistent with previous reports of extensive amyloid deposition in the striatum of virtually all AD patients,[27–30] to have significantly higher PIB retention in AD patients than in HC subjects (see Table 3).

Table 3. PIB Retention in Various Brain Areas (SUV)

	Fr	Par	Temp	Occ	Striatum	Pons	SWM	Cb
AD mean (n = 15)	1.56	1.45	1.26	1.24	1.47	1.31	1.22	0.86
AD SD	0.53	0.43	0.39	0.43	0.41	0.22	0.21	0.17
HC mean (n = 9)	0.80	0.85	0.83	0.80	0.84	1.21	1.19	0.74
HC SD	0.21	0.18	0.15	0.13	0.19	0.26	0.22	0.07
AD vs HC (p)	**0.0001**	**0.0001**	**0.0011**	**0.0017**	**0.00004**	0.3563	0.7238	0.0205
AD:HC ratio	1.94	1.71	1.52	1.54	1.76	1.08	1.03	1.17

Statistically significant results ($p < 0.006$) are boldface and underlined.

SUV = standardized uptake value; AD = Alzheimer's disease; HC = healthy control; SD = standard deviation.

Comparison of PIB Retention to Cerebral Metabolic Rate

The $rCMR_{glc}$ in cortical areas was lower in the AD patients compared with HC subjects in most regions (Table 4) as has been established in many previous studies.[31–34] The largest and only significant difference ($p < 0.006$) in $rCMR_{glc}$ was observed in parietal cortex (see Fig 6C; Table 4). The relative differences in $rCMR_{glc}$ between AD patients and HC subjects were in general smaller (eg, 41% in parietal cortex; see Table 4) than the relative differences in PIB retention (eg, 94% in frontal cortex; see Table 3). The correlation between PIB retention and $rCMR_{glc}$ in all subjects and in AD patients alone is shown in Table 4. When all HC subjects and AD patients were combined, a significant negative correlation ($p < 0.006$) was observed only in the parietal cortex (Fig 7). Clear negative trends were observed in all cortical areas, but not in white matter areas. These correlations did not remain significant at the p value 0.006 level (see Subjects and Methods) when only AD patients were included, although the negative trend remained obvious in the parietal cortex (see Table 4, Fig 7).

The relative changes in PIB and $rCMR_{glc}$ for each individual patient also can be appreciated from the data in Figure 7. For this purpose, low $rCMR_{glc}$ values were defined as those more than one SD below the mean $rCMR_{glc}$ of the HC subjects (ie, $rCMR_{glc}$ $<34.6\mu mol/min/100ml$) and high PIB SUV values were defined as those more than one SD above the mean PIB SUV of the HC subjects (ie, PIB SUV >1.03). These areas are indicated in Figure 7, and it can be seen that all AD patients with abnormally low parietal rCMRglc values also had abnormally high parietal PIB SUV values. Interestingly, all three AD patients (MMSE 28–29) with parietal PIB SUV values less than 1.03 also had normal parietal rCMRglc values (see open triangles in Fig 7). However, one AD patient with a normal rCMRglc had a high PIB SUV value (see double asterisks in Fig 7). None of the HC subjects with PIB SUV values less than 1.03 showed low rCMRglc values. The one HC subject (the

Table 4. rCMRglc and Correlation to PIB Retention

	Fr	Par	Temp	Occ	Striatum	Pons	SWM	Cb
rCMRglc (μmol/min/100 ml)								
AD mean (n = 16)	34.8	30.6	28.9	38.5	47.8	25.2	19.0	34.9
AD SD	7.2	7.6	4.9	6.6	6.8	3.9	5.1	6.0
HC mean (n = 9)	45.0	43.2	33.6	49.3	55.5	26.7	21.6	39.6
HC SD	9.7	8.6	6.4	10.3	11.4	3.6	4.9	8.7
(AD vs HC) (p)	0.0163	**0.0024**	0.0801	0.0149	0.0914	0.3304	0.2255	0.1716
AD:HC ratio	0.77	0.71	0.86	0.78	0.86	0.94	0.88	0.88
Correlation of rCMRglc to PIB SUV								
All Subjects (n = 24)								
r	−0.43	−0.72	−0.31	−0.48	−0.26	0.28	−0.08	−0.19
p	0.037	**0.0001**	0.187	0.017	0.323	0.266	0.99	0.776
AD only (n = 15)								
r	−0.03	−0.61	−0.15	−0.34	−0.03	0.34	0.27	−0.32
p	0.99	0.015	0.99	0.258	0.99	0.257	0.438	0.305

Statistically significant results ($p < 0.006$) are boldface and underlined.

rCMRglc = regional cerebral glucose metabolic rate; AD = Alzheimer's disease; SD = standard deviation; HC = healthy control; SUV = standardized uptake value.

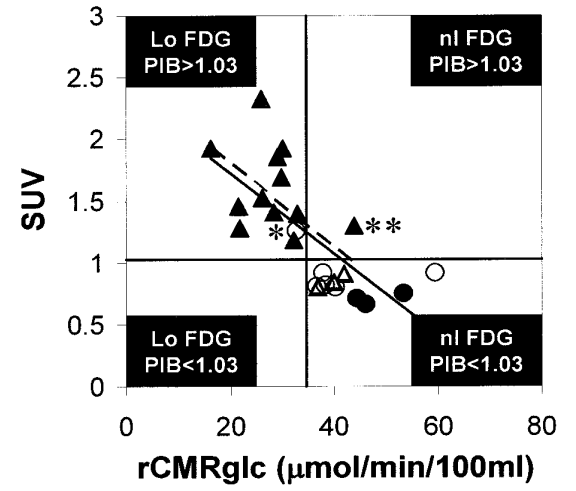

Fig 7. PIB retention is inversely correlated with $rCMR_{glc}$. Correlation of $rCMR_{glc}$ in parietal cortex versus parietal PIB standardized uptake value (SUV) values. Correlations were performed separately on all subjects (n = 24, R^2 *= 0.511;* p *= 0.0001;* solid line*) and only Alzheimer's disease (AD) patients (n = 15,* R^2 *= 0.377;* p *= 0.015;* dotted line*). AD patients are represented by* triangles *(outliers are* open triangles*) and HC subjects are represented by* circles *(young controls are* filled circles*). Also indicated is a horizontal line that represents one SD above the HC mean PIB SUV value (at 1.03 SUV) and a vertical line that represents one SD below the HC mean rCMRglc (at 34.6μmol/min/100ml). See text for further details.*

oldest) with a slightly low rCMRglc value also had an increased PIB SUV value (see single asterisk in Fig 7).

Correlations between PIB Retention and Clinical/ Biochemical Variables

There was a trend in all brain areas for higher PIB SUV values to be observed in AD patients having lower MMSE scores, but none of these correlations reached statistical significance. There was no significant correlation of PIB retention with age in either the AD or HC groups. However, the oldest HC subject showed consistently higher PIB retention than the other controls (see Fig 6).

In the AD patient group, there was no significant correlation in any brain area studied between PIB SUV values and duration of illness (from either onset or time of diagnosis) or number of years on cholinesterase inhibitors. Comparing AD patient subtypes, treatment with cholinesterase inhibitors and sex showed no significant effect on PIB values in any brain area. ApoE genotype had no effect on PIB SUV values in any brain area of AD patients. Furthermore, there was no trend toward increased PIB SUV values in the 4/4 AD patients (n = 6) compared with the 3/3 AD patients (n = 8).

Discussion

In autoradiographic studies of postmortem brain tissue, PIB showed specific and displaceable binding to AD cortical areas containing amyloid deposits, but not to control cortex. These studies are consistent with several previous studies which support the specificity of benzothiazole, thioflavin-T derivatives for amyloid deposits.[8,10–12] Plasma metabolism of PIB was rapid and all metabolites were polar, suggesting that blood metabolites are not likely to enter the brain. This is consistent with metabolic data in mice.[10] Further studies are under way in other species and with human tissue in vitro to determine whether radioactive metabolites could be present in human brain. Determination of the optimal pharmacokinetic modeling method will be ongoing as more arterial data are collected and scan time is increased to 90 minutes. Until this issue can be clarified, we prefer to express the data in terms of SUV.

In this study, both imaging and time-activity curves showed that the retention of PIB provided a quantifiable discrimination between most mild AD patients and HC subjects. In HC subjects, there was very little retention of PIB in cortical regions. In contrast, frontal and temporoparietal cortical areas, known to contain amyloid deposits in AD, showed preferential retention of PIB. The absolute level of PIB retention was approximately the same in the cerebellum and white matter of AD patients and HC subjects, brain areas known to lack substantial deposits of fibrillar amyloid. Time-activity curves demonstrated that the absolute amount of PIB retained in the frontal cortex of AD patients was greater than 90% higher than that retained in control frontal cortex or cerebellum of either controls or AD patients.

In general, this pattern of PIB retention is consistent with the pattern of amyloid plaque deposition described in postmortem studies of AD brain.[25,26] These postmortem studies showed that, from the earliest stages, amyloid plaque deposition was distributed fairly evenly across neocortical association cortices in AD. In contrast, mesial temporal lobe areas (including hippocampus) showed relatively low plaque burdens.[26] Unlike plaque deposition, the topographical development of neurofibrillary tangles begins focally in the transentorhinal cortex and progresses predictably through limbic areas to the neocortex.[35] PIB retention typically predominated in frontal cortex, but note that frontal cortex did not always show the highest PIB retention in a given subject and mean levels of frontal PIB retention exceed parietal levels by less than 10%. Postmortem studies using silver stains, antibodies to Aβ, or thioflavin-S do identify frontal cor-

tex as a brain area very high in amyloid deposition but have not identified it as the site of greatest deposition.[25,26] This raises the question of whether the observation of highest PIB retention in the frontal cortex is real or an artefact. There is evidence that the nature of amyloid deposits varies across the neocortex.[36] It also is possible that there are additional regional variations in amyloid processing and fibrillogenesis that can be detected in vivo but cannot be detected in postmortem tissue, particularly after fixation. Another possible reason for the greater PIB SUV values in frontal cortex compared with temporal and parietal cortex could be the fact that, in AD, regional cerebral blood flow (rCBF) to the frontal cortex is relatively preserved compared with the well-described decreases in temporal and parietal cortex.[37] Currently, the presence or absence of a rCBF effect on PIB measures has not yet been determined, and careful studies exploring the relationship between changes in rCBF and PIB retention will be needed to fully address this issue. Whether or not SUV measures of PIB retention are found to be affected by rCBF differences, compartment models will be applied to PIB data in the future and the optimal PIB retention measures derived from these models would be expected to be much less influenced by rCBF differences than those derived from SUV-type analyses.

Extensive amyloid deposition has been reported to occur in the striatum of virtually all AD patients,[28–30] and we observed substantial PIB retention in the striatum of AD patients in this study. Striatal plaque deposition appears to occur early in the progression of AD pathology and coincides with neocortical pathology and cognitive changes.[27] Although neuritic elements have been described in ventral striatum,[29] most striatal Aβ deposits are not associated with dystrophic neurites.[28,29] Despite this poorly understood absence of neuritic changes in the striatum, striatal plaques appear to be fibrillar as evidenced by the fact that they are stained well by the fibril-specific Congo red derivative, X-34.[38] PIB and related benzothiazoles also stain striatal amyloid deposits in postmortem AD brain (W.E. Klunk, unpublished data) in a manner similar to the staining of cortical deposits by other benzothiazole derivatives.[11] Therefore, the observation of significant PIB retention in the striatum is not surprising.

Three patients with very mild AD (AD4, AD12, and AD14) had cortical PIB retention similar to the HC subjects. Note that these three patients had MMSE scores between 28 and 29 after 2 to 4 years of follow-up. At the time of the PIB study, AD4, AD12, and AD14 all had temporal and parietal rCMRglc values that were not typical of AD patients and more closely resembled the HC subjects. Other mild AD patients with similar clinical profiles showed typical AD-like changes in PIB retention and $rCMR_{glc}$. For example AD11, AD13, and AD15 all had an MMSE score of 27 at the time of study but had increased PIB retention and decreased $rCMR_{glc}$. Treatment with cholinesterase inhibitors was not related to the differences observed. Therefore, it is unclear whether this amyloid imaging technique was simply insensitive to the amount of amyloid deposits in the brains of AD4, AD12, and AD14 or whether PIB imaging has correctly identified subjects without amyloid deposits in whom the clinical diagnosis would not be confirmed by postmortem evaluation.

Conversely, the oldest control in this study showed PIB retention typical of AD patients and could be described as an asymptomatic amyloid-positive case. This type of case brings up issues of specificity versus early detection. One possibility could be that a high PIB signal was obtained in the absence of amyloid deposits (ie, a false-positive). However, if this finding does represent the true presence of amyloid in an asymptomatic individual, the question becomes whether substantial amyloid deposition can be found as part of the normal aging process in subjects who will never develop AD[39] or is increased amyloid deposition always a sign of preclinical AD[40–42]? The ability to longitudinally follow PIB retention as an in vivo measure of amyloid deposition now gives us a tool through which we may be able to answer this question in a manner that postmortem studies can not.

Note that this initial proof-of-concept study was not designed to determine the sensitivity and specificity of amyloid imaging with PIB for the diagnosis of AD. Many very mild cases (MMSE $\geq$25 in 12 of 16 cases) were included, and the accuracy of the clinical diagnosis of AD is not clearly defined at this stage. Therefore, we cannot assess the utility of PIB for the diagnosis of AD from this study. Further studies that include only more typical, moderately impaired AD patients will be needed to address sensitivity issues and more controls and patients with non-AD dementias must be studied to define specificity issues.

The coupling between increased PIB retention and decreased ^{18}FDG metabolism was not an unexpected finding, given the well-known decrease in temporoparietal metabolism in AD patients[31] and the presence of extensive amyloid deposition in these same areas.[25,26] PET with ^{18}FDG and PIB might be considered as complementary methods, one looking directly at amyloid pathology and the other looking at metabolic dysfunction at the synapse that may or may not be related to the local pathology. Thus far, we have studied only mild AD patients with PIB, but ^{18}FDG imaging has been shown to be sensitive enough to demonstrate metabolic changes before the onset of clinical symptoms in subjects at risk for AD due to the presence of the ApoE4 allele[43,44] or the presence of chromosome

21 or 14 mutations.[45,46] Inevitably, a comparison of the relative "sensitivities" of imaging with PIB and ^{18}FDG for detecting changes in the brains of AD patients will be necessitated. Our data showed that the largest mean difference between AD patients and HC subjects in $rCMR_{glc}$ was approximately 40% in the parietal cortex (or approximately 1.5 SD from the control mean), whereas the largest mean difference in PIB retention was greater than 90% in frontal cortex (or approximately 3.6 SD from the control mean). All AD patients with low parietal $rCMR_{glc}$ also had high PIB retention, but one AD subject (AD16) with normal parietal $rCMR_{glc}$ had elevated PIB retention.

No significant correlation was observed between PIB accumulation and MMSE scores in this sample of AD patients, but this may be because 12 of the 16 AD patients fell into the narrow range of 25 to 29 on MMSE score. In this initial study, the reported association between ApoE4 genotype and increased postmortem cortical amyloid load was not reflected by increased PIB retention in AD patients having an ApoE4 allele.[47,48] However, the relationship between ApoE4 and postmortem amyloid load is complex and not always observed.[49]

Although this "proof-of-concept" study represents the first evaluation of a benzothiazole compound as an in vivo radiotracer for imaging amyloid deposition in human brain, two previous attempts have been made to image amyloid deposition in living AD patients using other tracers. The first attempt used single-photon emission computed tomography and a ^{99m}Tc-labeled antibody to Aβ, but there was no evidence of cerebral uptake of the antibody.[50] The second in vivo human amyloid-imaging study used the tracer ^{18}F-FDDNP to quantify amyloid in nine AD patients and seven controls.[51] The time-activity data from an AD patient included in that study indicated that, at late time points (90–120 minutes), the absolute retention of ^{18}F-FDDNP in neocortical areas exceeded that in the reference region, the pons, by 10 to 15%. The area of highest retention at late time points was the hippocampus/amygdala/entorhinal cortex region, an area that exceeded the reference region by approximately 30%.

As the technology of amyloid imaging moves forward, it will be important to avoid the circular reasoning inherent in the association of amyloid deposition with both the diagnosis and the cause of AD. Therefore, at the outset, it may be best to not equate amyloid deposition to clinical diagnosis. Rather than as a method of diagnosis, it might be best to first think of PIB retention more fundamentally as a method to detect and quantify brain β-amyloidosis, a term first used in reference to AD by Glenner.[52] Several basic, unbiased questions then can be asked regarding (1) the correlation of β-amyloidosis with clinical diagnosis; (2) the natural history of β-amyloidosis and its onset relative to clinical symptoms of dementia; and (3) the ability of β-amyloidosis to serve as a surrogate marker of efficacy for antiamyloid therapeutics.

The relationship of brain β-amyloidosis to clinical AD and the natural history of that relationship can be determined only by large and careful longitudinal human studies. We have so far investigated only mild AD patients. To sort out the relationship between brain β-amyloidosis and AD, it will be important to perform further studies in subjects with mild cognitive impairment, carriers of familial AD mutations and other types of increased genetic risk, and in larger groups of AD patients and HC subjects. Another potential use of in vivo amyloid imaging could be as an aid to the development of a variety of antiamyloid therapeutic candidates. Such antiamyloid drug studies may provide new knowledge concerning the relevance of β-amyloidosis to the clinical symptoms of AD. Although these and other issues are yet to be fully resolved, this study strongly suggests that PIB retention may be a good indicator of amyloid deposition in vivo.

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Disclosure

During the process of this study, Amersham Health provided research grant support to the University of Pittsburgh and entered into a License Agreement with the University of Pittsburgh based on the technology described in this article. Drs Klunk, Mathis, and Wang are coinventors of PIB and, as such, have a financial interest in this License Agreement. Also during the process of this study, the Uppsala University PET Centre became partially owned by a subsidiary of Amersham Health called Imanet and was named Uppsala Imanet AB. Uppsala Imanet AB is a joint venture created by Amersham Health and Uppsala University Holdings. All authors listed as having a Uppsala Imanet AB affiliation are Imanet employees. Dr Langstrom holds the titles of Head of R&D of Uppsala Imanet AB and Chief Scientific Officer of Imanet.

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Cellular/Molecular

Binding of the Positron Emission Tomography Tracer Pittsburgh Compound-B Reflects the Amount of Amyloid-β in Alzheimer's Disease Brain But Not in Transgenic Mouse Brain

William E. Klunk,[1] Brian J. Lopresti,[2] Milos D. Ikonomovic,[3] Iliya M. Lefterov,[4] Radosveta P. Koldamova,[5] Eric E. Abrahamson,[3] Manik L. Debnath,[1] Daniel P. Holt,[2] Guo-feng Huang,[2] Li Shao,[1] Steven T. DeKosky,[3] Julie C. Price,[2] and Chester A. Mathis[2]

Departments of [1]Psychiatry, [2]Radiology, [3]Neurology, [4]Environmental and Occupational Health, and [5]Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

During the development of *in vivo* amyloid imaging agents, an effort was made to use micro-positron emission tomography (PET) imaging in the presenilin-1 (PS1)/amyloid precursor protein (APP) transgenic mouse model of CNS amyloid deposition to screen new compounds and further study Pittsburgh Compound-B (PIB), a PET tracer that has been shown to be retained well in amyloid-containing areas of Alzheimer's disease (AD) brain. Unexpectedly, we saw no significant retention of PIB in this model even at 12 months of age when amyloid deposition in the PS1/APP mouse typically exceeds that seen in AD. This study describes a series of *ex vivo* and postmortem *in vitro* studies designed to explain this low retention. *Ex vivo* brain pharmacokinetic studies confirmed the low *in vivo* PIB retention observed in micro-PET experiments. *In vitro* binding studies showed that PS1/APP brain tissue contained less than one high-affinity (K_d = 1–2 nM) PIB binding site per 1000 molecules of amyloid-β (Aβ), whereas AD brain contained >500 PIB binding sites per 1000 molecules of Aβ. Synthetic Aβ closely resembled PS1/APP brain in having less than one high-affinity PIB binding site per 1000 molecules of Aβ, although the characteristics of the few high-affinity PIB binding sites found on synthetic Aβ were very similar to those found in AD brain. We hypothesize that differences in the time course of deposition or tissue factors present during deposition lead to differences in secondary structure between Aβ deposited in AD brain and either synthetic Aβ or Aβ deposited in PS1/APP brain.

Key words: transgenic mouse; amyloid-β; plaques; neuroimaging; positron emission tomography; benzothiazole

Introduction

Modification of the amyloid-binding dye thioflavin-T showed that neutral benzothiazole-anilines could bind to amyloid with low nanomolar affinity, enter the brain in amounts sufficient for imaging with positron emission tomography (PET), and clear rapidly from normal brain tissue (Klunk et al., 2001; Mathis et al., 2002). A structure–activity study of benzothiazole compounds suggested that a hydroxylated derivative, termed Pittsburgh Compound-B (PIB; [^{11}C]6-OH-BTA-1), had brain clearance properties typical of many useful PET radiotracers (Mathis et al., 2003). Using *in vivo* multiphoton microscopy, PIB has been shown to label individual amyloid plaques in transgenic (Tg) mouse models of Alzheimer's disease (AD) within 3 min after intravenous injection and clear rapidly from normal brain parenchyma (Bacskai et al., 2003).

In the first human study using PIB in 16 mild AD patients and 9 healthy controls, there was a robust group difference in the PIB retention pattern (Klunk et al., 2004b), and this has been replicated in subsequent studies (Price et al., 2005). Compared with controls, AD patients typically showed twofold to threefold greater retention of PIB in areas of association cortex known to contain large amounts of amyloid deposits in AD. In areas known to be relatively unaffected by amyloid deposition, such as the cerebellum, PIB retention was equivalent in AD patients and controls.

During the development of PIB for *in vivo* imaging of AD plaque pathology, we sought to make use of micro-PET imaging technology (Cherry, 2001) and Tg mouse models of amyloid deposition. Micro-PET imaging in Tg mice could be an ideal complement to the other screening tests used to identify optimal lead imaging agents (Mathis et al., 2003). For this purpose, we chose the presenilin-1 (PS1)/amyloid precursor protein (APP) Tg mouse model because of the rapid and extensive nature of fibrillar amyloid deposition in these mice (McGowan et al., 1999). The

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Correspondence should be addressed to Dr. William E. Klunk, Western Psychiatric Institute and Clinic, Room 1422 Thomas Detre Hall, 3811 O'Hara Street, Pittsburgh, PA 15213-2593. E-mail: klunkwe@upmc.edu.

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PS1/APP mouse develops amyloid-β (Aβ) deposits beginning at 3 months of age, and these are quite extensive by 8–9 months of age (McGowan et al., 1999).

Surprisingly, initial PIB micro-PET studies in PS1/APP mice up to 12 months of age showed no significant retention compared with PS1 controls (Klunk et al., 2004a). Toyama et al. (2005) have reported similar micro-PET findings in Tg mice using PIB (also known as [^{11}C]6-OH-BTA-1). To understand why the binding of PIB appears so different in human and Tg mouse brain, we undertook a series of *in vivo*, *ex vivo*, and *in vitro* studies examining the interaction of PIB with brain tissue in PS1/APP mice that were characterized immunohistochemically and biochemically for the extent of Aβ deposition. Here, we report that despite the presence of large amounts of insoluble Aβ deposits, PIB binds very poorly to PS1/APP mouse brain tissue. The binding of PIB to PS1/APP mouse brain closely resembles the binding of PIB to synthetic Aβ fibrils and differs considerably from the binding of PIB to homogenates of postmortem AD brain because of the low number of high-affinity PIB binding sites per mole of Aβ.

Materials and Methods

Chemicals

All reagents were purchased from Sigma (St. Louis, MO), unless noted otherwise.

Mice

Double Tg PS1/APP mice were generated by mating male APP Tg2576 (K670N/M671L) mice (Taconic Farms, Germantown, NY) (Hsiao et al., 1996) with female M146L PS1 mice (mutant PS1, line 6.2; University of South Florida, Tampa, FL) (Duff et al., 1996)]. The Tg 2576 mice were derived from a C57B6/SJL × C57B6 background, whereas the M146L PS1 animals were derived from a Swiss-Webster/B6D2F$_1$× B6D2F$_1$ background (Holcomb et al., 1998). Food and water were available *ad libitum*, and a 12 h light/dark cycle was maintained. Mice were studied at 6, 9, and 12 months of age with micro-PET and at 15 months of age for postmortem biochemical and histological studies. Swiss-Webster mice (25–35 g; Harlan Sprague Dawley, Indianapolis, IN) were studied at 3 months of age. All studies were approved by the University of Pittsburgh Institutional Animal Care and Use Committee. Brain tissue from two 28-month-old PS1/APP mice and age-matched PS1 controls was provided by Dr. Karen Duff (Nathan Kline Research Institute, New York University, New York, NY).

Postmortem human brain tissue

Autopsy tissue was obtained from the University of Pittsburgh Alzheimer's Disease Research Center Brain Bank. Clinical and postmortem diagnoses were made by standardized procedures as described in detail previously (Lopez et al., 2000). All five AD brains represented fairly advanced stages of pathology, as is typical of postmortem tissue. Three control brains were selected for having no significant evidence of neuritic plaques or cerebrovascular amyloid. In addition, there were no neurofibrillary tangles in the frontal cortex of the control brains. Samples of mediofrontal cortex gray matter were dissected at autopsy from 1-cm-thick coronal slices and frozen at −80°C.

In vivo *micro-PET imaging*

PET imaging of PS1/APP and PS1 littermate control mice was performed using a micro-PET P4 scanner (Concorde Microsystems, Knoxville, TN) at 6, 9, and 12 months of age. At each age, one pair of mice consisting of a PS1/APP and a PS1 littermate was imaged in the scanner simultaneously. Before PET imaging, mice were anesthetized with pentobarbital (50 mg/kg, i.p.) and immobilized with Velcro and elastic restraints. Animals were positioned in the scanner field of view (FOV) such that the cranium occupied the central 2 cm of the axial FOV, at which volume resolution and sensitivity of the micro-PET system are maximal. Animals were given injections in the lateral tail vein with 100–150 μCi of high-specific activity [^{11}C]PIB (>1000 Ci/mmol) dissolved in <200 μl of sterile isotonic saline. PET emission data were collected in list mode for 60 min, commencing with the injection of [^{11}C]PIB. A region of interest was drawn on three to five contiguous image planes encompassing the entire cerebrum and used to sample each frame of the dynamic micro-PET image to determine the function representing the time-varying radioactivity concentration averaged over the entire cerebrum. Arbitrary micro-PET counts were converted to an absolute measure of radioactivity concentration (microcurie/cubic centimeter or microcurie/gram assuming 1 g/cc) using a phantom-derived calibration factor before being normalized to the injected dose (ID) of [^{11}C]PIB and the body mass of the animal (%ID-kilogram/gram). This normalization enables the comparison of brain radioactivity concentrations assessed by other methods as well as across animals of different weights and even across species.

Ex vivo *brain tissue radioassay*

Ex vivo regional brain radioactivity concentrations were assessed in PS1/APP mice (n = 4; age, 15 months) and control littermates (n = 4) after the injection of 100–150 μCi of [^{11}C]PIB. In addition, nine Swiss-Webster mice were given injections to compare the radioactivity concentration measured dynamically using the micro-PET system with the concentration determined using a well-type gamma counter. Mice were killed by intraperitoneal injection of 100 mg/kg pentobarbital, followed by thoracotomy, cardiac puncture to obtain a terminal blood sample (for carbon-11 counting and weighing), and cardiac excision. PS1/APP and PS1 mice were killed 15 min after injection of [^{11}C]PIB. The Swiss-Webster mice were killed at 2, 30, and 60 min after injection (n = 3 at each time point).

The brains were be removed and dissected into forebrain and cerebellum, which were weighed and counted using a gamma counter (model 5003; Packard Bioscience, Meridian, CT) with an overall sensitivity for detecting 511 keV annihilation photons of ~35%, which is far in excess of the 1–2% overall system sensitivity of the micro-PET P4 scanner. Raw counts were decay-corrected and converted to an absolute measure of radioactivity concentration (microcurie/gram of brain) using a constant efficiency factor and normalized to both ID and body mass (%ID-kilogram/gram). After the carbon-11 radioactivity was quantified, the PS1/APP and PS1 brains were hemisectioned. One half was frozen at −80°C (for ELISA and postmortem [^{3}H]PIB binding), and the other half was placed in 4% paraformaldehyde (for histological studies). The carbon-11 radioactivity was allowed to decay to background for at least 10 half-lives (>200 min) before the brain samples were further processed for histology, ELISA, or postmortem [^{3}H]PIB binding.

Histological and immunohistochemical techniques

Brain hemispheres for histological/immunohistochemical (IHC) evaluation were immersion-fixed in cold 4% paraformaldehyde for 24 h and cryoprotected by sequential immersion into 15 and 30% sucrose in 0.1 M phosphate buffer, pH 7.4. Forty-micrometer-thick coronal brain sections were collected serially and stored at −20°C in cryoprotectant (0.3 g/ml sucrose, 0.01 g/ml polyvinylpyrrolidone-40, and 30% v/v ethylene glycol in 0.05 M sodium phosphate buffer, pH 7.4), as described previously (Watson et al., 1986), until processed further. Throughout the anteroposterior length of the hippocampus, three sets of five adjacent tissue sections were processed for IHC evaluation using antibodies against total Aβ (6E10), Aβ1–40 and Aβ1–42, or histological staining with 1,4-bis(3-carboxy-4-hydroxyphenylethenyl)-benzene (X-34) (Styren et al., 2000) and 2-(4′-methylaminophenyl)-6-cyanobenzothiazole (6-CN-BTA-1), a highly fluorescent analog of PIB (Mathis et al., 2003). Before histological/IHC evaluation, sections were washed in PBS. For IHC evaluation, endogenous peroxidase activity was inhibited by incubating the tissue in 1.5% H_2O_2 in 0.1 M PBS for 30 min. Sections were rinsed in 0.1 M PBS, followed by permeabilization and blockade with 0.2% Triton-X and 5% normal goat serum in 0.1 M PBS, and incubated overnight in primary antisera at 4°C. After washing in 0.1 M PBS, sections were incubated in the appropriate biotinylated IgG (Vector Laboratories, Burlingame, CA) in 5% normal serum and 0.1 M PBS for 1 h, washed in 0.1 M PBS, and incubated with ABC (Vector Laboratories) in 0.1 M PBS for 1 h at room temperature. The sections were washed repeatedly, and the color reaction was developed using a 0.05% solution of 3′,3-diaminobenzidine tetra-hydrochloride and 0.03% H_2O_2. Sections were

washed in 0.1 M PBS, mounted on gelatinized slides, dehydrated in alcohols, cleared in xylene, and coverslipped with Permount (Fisher Scientific, Pittsburgh, PA).

X-34 and 6-CN-BTA-1 histological staining procedures were performed on tissue sections mounted on gelatin-coated slides. X-34 staining was performed as described previously (Styren et al., 2000). Briefly, tissue sections were washed in PBS and incubated in 100 μM X-34 solution in 40% ethanol and 60% distilled H_2O (dH_2O), pH 10, for 10 min. After washing in water, there was a 2 min differentiation in 0.2% NaOH in 80% ethanol, followed by a 10 min wash in water. For 6-CN-BTA-1 staining, slides were placed in PBS for 2 min, followed by application of 100 nM 6-CN-BTA-1 in PBS for 10 min in the dark. Slides were subsequently dipped three times in dH_2O, differentiated for 2 min in a solution of 0.2% NaOH in 80% ethanol, and dipped again in dH_2O. Both X-34- and 6-CN-BTA-1-stained slides were coverslipped using Fluoromount (Southern Biotechnology, Birmingham, AL) and examined on an Olympus (Melville, NY) microscope equipped with a fluorescent attachment.

ELISA analysis of Aβ levels

Extraction of Aβ from brain tissue. Frozen mouse hemibrains or fresh-frozen human brain samples were homogenized (150 mg/ml) in a tissue homogenization buffer (250 mM sucrose, 20 mM Tris base, 1 mM EDTA, 1 mM EGTA, plus protease inhibitors: 10 μg/ml each of leupeptin hemisulfate salt, antipain HCl, pepstatin-A, and 4-(2-aminoethyl)benzenesulfonylfluoride) using a glass vessel and piston-type Teflon pestle, and Aβ was extracted essentially as described previously (Refolo et al., 2000, 2001). Briefly, soluble Aβ was extracted using cold 0.4% diethylamine in 100 mM NaCl, spun at 135,000 × *g* for 1 h at 4°C, and neutralized by adding 0.5 M Tris-HCl, pH 6.8. The pellet was further extracted using 70% cold formic acid, sonicated for 1 min, spun as above, and neutralized (1 M Tris base, 0.5 M Na_2HPO_4, and 0.05% NaN_3).

ELISA for soluble and insoluble Aβ. The soluble and insoluble Aβ extracts were additionally diluted in ELISA buffer [20 mM sodium phosphate, 2 mM EDTA, 400 mM NaCl, 0.2% BSA, 0.05% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate choline acetyltransferase, 0.4% Block Ace (Serotec, Raleigh, NC), and 0.05% NaN_3, pH 7.0], and Aβ1–40 and Aβ1–42 concentration was measured by sandwich ELISA as described previously (Koldamova et al., 2005). Briefly, 6E10 monoclonal antibody (Signet, Dedham, MA) was used as a capture antibody. Horseradish peroxidase-conjugated anti-Aβ40 and anti-Aβ42 (Genetics Company, Schlieren, Switzerland), which are specific for Aβ ending at residues 40 and 42, respectively, were used as detection antibodies. Aβ values, based on standard curves using synthetic Aβ1–40 and Aβ1–42 peptide standards (Bachem Biosciences, King of Prussia, PA), were expressed as picomoles per gram of wet brain.

Quantitative postmortem binding of [^{3}H]PIB

Binding to brain homogenates was performed with slight modifications of a procedure described in detail previously (Klunk et al., 2003). Briefly, 150 mg/ml tissue homogenates prepared in tissue homogenization buffer for ELISA analysis were diluted 150-fold in PBS to 1 mg/ml. The K_d and B_{max} values for [^{3}H]PIB binding to brain homogenates were determined using increasing concentrations of [^{3}H]PIB between 0.2 and 1 nM and, for total PIB concentrations from 1 to 1000 nM, a constant 1 nM concentration of [^{3}H]PIB (specific activity, 61.4 Ci/mmol; American Radiolabeled Chemicals, St. Louis, MO) plus additional unlabeled PIB. The labeled and unlabeled PIB were prepared in 900 μl of PBS, binding was initiated by the addition of 100 μl of the 1 mg/ml brain homogenate (in triplicate), and the samples were incubated at 22°C for 60 min. For comparison of [^{3}H]PIB binding to brain homogenates in human control and AD brain and PS1 and PS1/APP mouse brain, 1 nM [^{3}H]PIB was incubated with 100 μg of tissue in 1 ml of PBS. Nonspecific binding was defined as the number of counts remaining in the presence of 1 μM unlabeled PIB. The binding mixtures were filtered through a Whatman (Maidstone, UK) GF/B glass filter via a Brandel (Gaithersburg, MD) M-24R cell harvester and washed rapidly five times with 3 ml of PBS. The filters are counted in Cytoscint-ES after thorough vortexing. Results were corrected for nonspecific, nondisplaceable binding in the presence of 1 μM PIB and expressed as picomoles of [^{3}H]PIB bound per gram of wet tissue weight in the homogenate. Linearity of [^{3}H]PIB binding was confirmed using 1 nM [^{3}H]PIB and 20–500 μg/ml of the AD brain homogenate with the highest level of [^{3}H]PIB binding. Likewise, linearity with respect to [^{3}H]PIB was confirmed using 100 μg of tissue per milliliter and 1–6 nM [^{3}H]PIB. Binding results between groups were compared using an unpaired sample, unequal variance *t* test.

To facilitate straightforward comparison of the *in vitro* [^{3}H]PIB binding data from human AD brain to *in vivo* data obtainable from PET tracer studies, the data also were expressed in terms of binding potential (BP), where $BP_{total} = B_{max}/K_d$ (Mintun et al., 1984). To calculate this unitless measure, B_{max} was first converted from units of picomoles of [^{3}H]PIB bound per gram of brain to nanomolar units by assuming that 1 g of brain = 1 ml (picomoles/gram = picomoles/milliliter = nanomoles/liter). Division by K_d in nanomolar units directly results in BP.

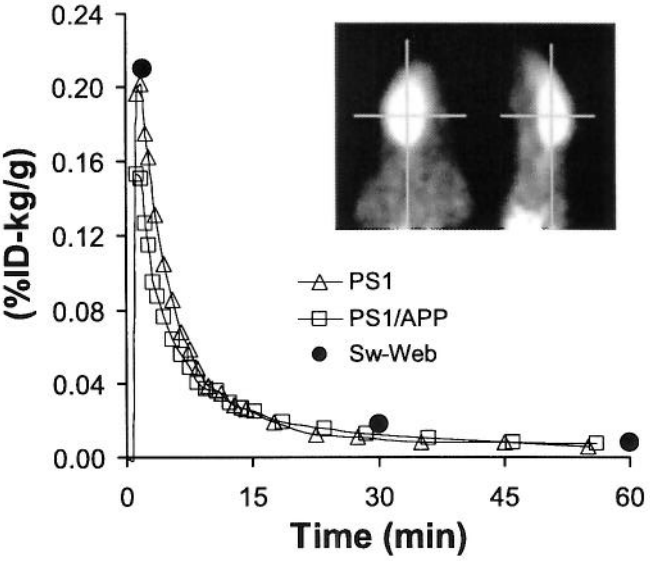

Figure 1. Micro-PET time–activity curves show no difference in the retention of [^{11}C]PIB in PS1/APP and PS1 mice. Brain radioactivity was determined with micro-PET in a 12-month-old PS1/APP mouse (□) and a PS1 littermate (△) imaged simultaneously. [^{11}C]PIB retention is expressed as %ID per gram of brain normalized to the body weight (in kilograms). The [^{11}C]PIB retention from an *ex vivo* study with Swiss-Webster (Sw-Web) mice ($n = 3$ at each time point; ●) is also shown. Inset, Axial (left) and sagittal (right) image of the PS1/APP mouse.

Results

Micro-PET studies

Preliminary micro-PET studies were performed in pentobarbital-anesthetized PS1/APP mice and PS1 littermate controls at 6, 9, and 12 months of age (one PS1/APP–PS1 pair imaged simultaneously at each age). After intravenous injection of 100–150 μCi of [^{11}C]PIB, dynamic imaging data were collected for 60 min and the time–radioactivity course was established (Fig. 1). As expected, the time–activity curve from the PS1 control mice (Fig. 1, open triangles) showed rapid brain entry and clearance. These pharmacokinetics were quantitatively very similar to those observed in previously reported *ex vivo* studies in Swiss-Webster mice (Mathis et al., 2003) (Fig. 1, filled circles). Although PS1 mice have elevated levels of soluble Aβ1–42 (Duff et al., 1996), neither PS1 nor Swiss-Webster mice have brain amyloid deposits. Surprisingly, the time–activity curves of the PS1/APP mice were nearly identical to that of the PS1 littermate controls, even at 12 months of age (Fig. 1, open squares). The normalized [^{11}C]PIB concentration (%ID-kilogram/gram) in the brain of PS1/APP mice equilibrated at 100–120% of that observed in the PS1 mice between 15 and 60 min (i.e., nonsignificantly higher in PS1/APP brain). This was unexpected given the previously reported extensive amyloid plaque deposition in the

PS1/APP mouse, which begins by 3 months of age and is well established by 8 months of age (McGowan et al., 1999; Takeuchi et al., 2000; Wengenack et al., 2000). Subsequently, a very similar finding of low [^{11}C]PIB retention was reported in Tg2576 mice (Toyama et al., 2005). Because of this unanticipated low retention of [^{11}C]PIB, we suspended the micro-PET studies until we could explore the nature of PIB binding to PS1/APP brain in the more detailed *ex vivo* and *in vitro* studies described below. When possible, we compared PIB binding to PS1/APP brain with PIB binding to postmortem AD brain tissue.

Ex vivo [^{11}C]PIB binding in PS1/APP mice

Compared with *in vivo* micro-PET (~2% detection efficiency), the higher counting efficiency of the gamma-well counter (~35%) increases the sensitivity to detect differences in the *in vivo* retention of [^{11}C]PIB between PS1/APP and PS1 mice. In addition, we performed the *ex vivo* studies on older (15 months of age) mice that would be expected to have even higher levels of amyloid deposition. [^{11}C]PIB injections similar to those administered in the micro-PET study were given to four 15-month-old PS1/APP mice and four littermate controls 15 min before injection of pentobarbital and cardiac exanguination, followed by removal of the brain and *ex vivo* gamma counting to detect retained [^{11}C]PIB. The 15 min time point was based on a trade-off between maximizing the time for clearance of free and nonspecifically bound [^{11}C]PIB and minimizing the time for radioactive decay to retain good counting statistics (because of the ~20 min $t_{1/2}$ of carbon-11). At 15 min after injection, the amount of [^{11}C]PIB retained in PS1 forebrain was 0.041 ± 0.010%ID-kg/g, and that in PS1/APP forebrain was 0.064 ± 0.024%ID-kg/g. This 56% increase was not significant ($p = 0.13$) and was mainly attributable to a single high outlier in the PS1/APP group (Fig. 2). This outlier did not prove to have significantly higher Aβ levels in the ELISA studies described below (data not shown). The importance of correcting brain uptake for body weight can be seen in Figure 2. At 15 months of age, the PS1 mice had 22% higher body weight than the PS1/APP mice, and therefore %ID/gram values are artifactually increased in the PS1/APP mice relative to the heavier PS1 mice, although the difference was still not significant ($p = 0.08$).

Histochemical and biochemical analysis of the PS1/APP mice

To verify that the particular mice used for the *ex vivo* studies had the expected degree of brain amyloid deposition, the brains of these PS1/APP and PS1 mice were submitted to histochemical and biochemical analysis. After gamma counting as described above, the forebrains (cerebellum and brainstem removed) were bisected along the midline; half was immersion-fixed in 4% paraformaldehyde for histology, and the other half was frozen for biochemical analysis. IHC analysis showed the expected degree and type of amyloid deposition in all four PS1/APP mice and the lack of amyloid deposition in all four PS1 mice (Fig. 3). It has been previously reported that PS1/APP mice have a heavy plaque burden with levels approaching that seen in the human AD brain by ~6 months of age (Takeuchi et al., 2000; Wengenack et al., 2000). The 15-month-old PS1/APP mouse brains stained heavily with 6E10 antibody (total Aβ) (Fig. 3*A*) and C-terminal-specific antibodies to Aβ1–40 and Aβ1–42 (Fig. 3*C*,*E*). As is typical of PS1/APP mice, staining to Aβ1–40 predominated. Plaques in the PS1/APP mice stained heavily with the highly fluorescent, fibril-specific Congo red derivative X-34 (Fig. 3*G*) (Styren et al., 2000). PIB itself is only weakly fluorescent and difficult to detect in tissue sections, but a derivative of PIB in which the 6-hydroxy group is

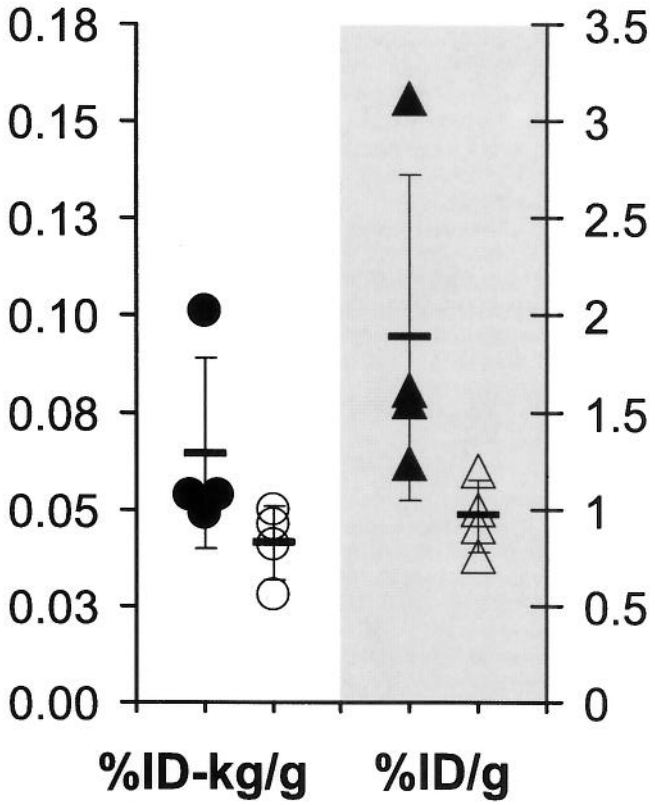

Figure 2. *Ex vivo* assessment of radioactivity shows no significant difference in the retention of [^{11}C]PIB in PS1/APP and PS1 mice. Fifteen-month-old PS1/APP mice (filled symbols) and PS1 littermate controls (open symbols) were given intravenous injections of [^{11}C]PIB in the tail vein and killed 15 min later. The brains were removed rapidly, and retained radioactivity was assessed in a gamma counter. The same data are expressed as %ID per gram on the right and as the weight-normalized %ID-kilogram/gram on the left. Neither show a significant difference.

replaced by a 6-cyano group (6-CN-BTA-1) is more fluorescent (Mathis et al., 2003). When stained with 100 nM 6-CN-BTA-1, numerous plaques are detected in PS1/APP brain (Fig. 3*I*). PS1 brain tissue did not stain with any of the amyloid stains (Fig. 3*B*,*D*,*F*,*H*,*J*).

The Aβ content also was determined in the frozen half of the forebrains used in the *ex vivo* studies. The PS1 mice had undetectable amounts of human Aβ, as expected. The PS1/APP mice had very large amounts of insoluble Aβ1–40 and Aβ1–42 that exceeded that observed in typical human AD brain by 7- to 40-fold (Table 1). Soluble Aβ in PS1/APP brain exceeded that in human AD brain by 180- to 200-fold but accounted for only 4–5% of total Aβ. These histological and biochemical analyses confirmed the presence of large amounts of typical Aβ deposits in the mice studied and rule out the lack of Aβ as a cause for poor [^{3}H]PIB binding.

In vitro [^{3}H]PIB binding analysis of human AD brain and PS1/APP brain

Human brain

Binding to postmortem human brain homogenates was used extensively in the development of amyloid imaging agents, including PIB (Klunk et al., 1995, 2003; Mathis et al., 2003). This *in vitro* method of binding analysis appears to be the most sensitive technique available to detect the binding of compounds to Aβ and to demonstrate differences between amyloid-containing brain and amyloid-free control brain under conditions that mimic the low

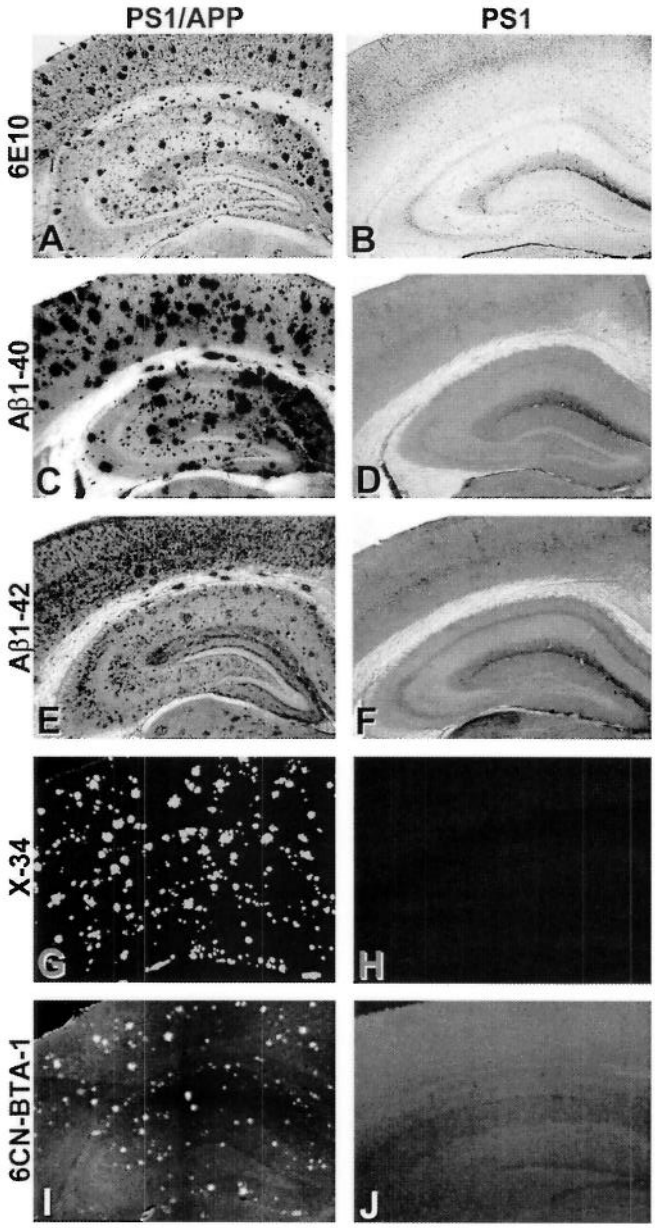

Figure 3. Histological analysis shows extensive amyloid deposition in the PS1/APP mice but not the PS1 mice. Tissue sections from PS1/APP (***A, C, E, G, I***) and PS1 (***B, D, F, H, J***) mice were immunostained with antibodies to total Aβ (***A, B***; 6E10), Aβ1–40 (***C, D***), and Aβ1–42 (***E, F***). Sections also were stained with the fluorescent Congo red derivative X-34 (***G, H***), which stains fibrillar amyloid, and the fluorescent PIB analog 6-CN-BTA-1 (***I, J***).

nanomolar concentrations attainable in PET studies (Klunk et al., 2003). In addition, *in vitro* binding to brain homogenates negates the effects of variable brain entry and clearance that could affect binding *in vivo*.

Scatchard analysis demonstrates a high-affinity [^{3}H]PIB binding site in AD brains ($n = 5$) having a K_d of 2.5 ± 0.2 nM and a B_{max} for [^{3}H]PIB binding sites of 1407 ± 328 pmol/g wet weight (BP = 563 ± 131). In two of the five AD brain homogenates, a lower-affinity [^{3}H]PIB binding site with K_d values of ~250 nM and B_{max} values of ~13,000 pmol/g (BP ~50) was observed (Fig. 4). Human control brain ($n = 3$) showed only this low-affinity component (Fig. 4). In the presence of the high-affinity binding component of AD brain, these low-affinity sites would not contribute significantly to *in vivo* binding at [^{11}C]PIB concentrations around 1 nM (see Discussion). In AD brain, the ratio of the [^{3}H]PIB B_{max} to total Aβ was 0.57 ± 0.072 mol of [^{3}H]PIB bound per mole of total insoluble Aβ. In human brain, there was a very good correlation between the B_{max} for [^{3}H]PIB binding and total Aβ levels ($r = 0.91$; $p = 0.03$) and Aβ1–42 levels ($r = 0.92$, $p = 0.03$) (Fig. 5*A*). There was a trend toward a correlation between the B_{max} for [^{3}H]PIB binding and Aβ1–40 levels ($r = 0.75$), but this did not reach statistical significance with this small number of samples ($p = 0.13$).

In addition to determining B_{max} (which can be heavily influenced by binding at saturating concentrations of [^{3}H]PIB in the high nanomolar and low micromolar range), it is important to determine the amount of [^{3}H]PIB bound at concentrations in the low nanomolar range that are attainable in PET studies. The amount of [^{3}H]PIB bound to human AD brain homogenates in the presence of 1 nM [^{3}H]PIB is tightly correlated with the B_{max} and BP for [^{3}H]PIB binding to the same brain samples ($r = 0.99$; $p < 0.0001$) and thus to the amount of Aβ in those brain samples (Fig. 5*B*). The amount of 1 nM [^{3}H]PIB bound to human AD brain homogenates is significantly correlated to total Aβ ($r = 0.92$; $p = 0.03$) and Aβ1–42 ($r = 0.92$; $p = 0.03$). As was the case with B_{max}, there was a trend toward a correlation between the amount of 1 nM [^{3}H]PIB bound to human AD brain homogenates and Aβ1–40 ($r = 0.79$), but again this did not reach statistical significance ($p = 0.11$). This indicates that the amount of 1 nM [^{3}H]PIB bound to human AD brain homogenates is a good indication of both the B_{max} and BP for [^{3}H]PIB binding and for the amount of total insoluble Aβ in that AD brain homogenate. [^{3}H]PIB binding did not correlate significantly with soluble Aβ, and it should be noted that, on a molar basis, the amount of [^{3}H]PIB bound was 40-fold higher than the amount of soluble Aβ in the AD brain homogenates.

Tg mouse brain

Scatchard analysis showed a very small high-affinity [^{3}H]PIB binding component in PS1/APP mouse brain (Fig. 4, filled arrow) having a calculated K_d value of 0.1 nM and B_{max} value of 7.8 pmol/g wet weight. Because of the very small nature of this high-affinity component relative to the low-affinity background, these K_d and B_{max} values are of doubtful accuracy, as is the resultant value of BP (BP = 78). The low-affinity site had a K_d value of 32 nM and a B_{max} value of 4300 pmol/g (BP = 134), suggesting that most of [^{3}H]PIB binding to PS1/APP brain occurs at this low-affinity component (see Discussion). A very similar low-affinity component was present in PS1 brain (Fig. 4). [^{3}H]PIB binding to homogenates of 15-month-old PS1/APP mouse brain ($n = 4$) did not correlate with Aβ content in the manner observed in AD brain (Fig. 5). Essentially, no relationship was observed between the amount of 1 nM [^{3}H]PIB bound to PS1/APP brain homogenates and the amount of Aβ1–40 ($r = 0.29$; $p > 0.9$), Aβ1–42 ($r = 0.19$; $p > 0.9$), or total insoluble Aβ ($r = 0.21$; $p > 0.9$) present in the homogenates (Fig. 5*C*).

The amount of 1 nM [^{3}H]PIB bound to various brain homogenates is shown in Table 2. Despite the very large difference in amounts of Aβ, the amount of 1 nM [^{3}H]PIB bound to PS1/APP brain exceeded that bound to PS1 brain by only 3.5-fold. Brain homogenates from two 28-month-old PS1/APP mice also were studied and showed [^{3}H]PIB binding of 3.2- and 2.8-fold higher than age-matched PS1 controls (i.e., no greater than 15-month-old mice). In contrast, the amount of 1 nM [^{3}H]PIB bound to AD brain exceeded human control brain by >15-fold. When compared in terms of [^{3}H]PIB binding per mole of total insoluble Aβ, the binding of [^{3}H]PIB in PS1/APP brain homogenates was 40-

fold less than that in AD brain (0.004 vs 0.167 mol [^{3}H]PIB/mol Aβ; $p = 0.0001$).

In vitro [^{3}H]PIB binding to aggregated, synthetic Aβ1–40 and Aβ1–42

The high-affinity K_d for [^{3}H]PIB binding to synthetic Aβ is very similar to that determined in binding studies with AD brain homogenates (Table 3). There was no significant difference in the affinity of [^{3}H]PIB for Aβ1–40 and Aβ1–42 (Fig. 6). However, when normalized to the amount of Aβ present, the high-affinity B_{max} determined for [^{3}H]PIB binding to aggregated, synthetic Aβ was ~1000-fold lower for both Aβ1–40 and Aβ1–42 than that observed in AD brain but was very similar to the B_{max} observed for the high-affinity binding site in PS1/APP brain (Table 3).

To determine whether there was a soluble factor in AD brain necessary for optimal [^{3}H]PIB binding that was missing in and could be transferred to PS1/APP brain or synthetic preparations of Aβ fibrils, a mixing experiment was performed. The addition of AD brain homogenates to PS1/APP and PS1 homogenates or preparations of synthetic Aβ1–40 or Aβ1–42 fibrils showed no synergistic increase in binding (Fig. 7). Binding to the mixture was very close to the sums of the two preparations. Another similar experiment was performed in which serum amyloid protein was added to the mouse brain homogenate, and again no augmentation of [^{3}H]PIB binding was observed (data not shown).

Discussion

Aβ plaque-depositing Tg mice are an obvious model system for the development of PET tracers aimed at imaging amyloid. In the PS1/APP mouse, the time course of amyloid deposition is among the fastest, and the density of fibrillar Aβ deposits is among the highest, of any Tg mouse model (McGowan et al., 1999), making it a likely candidate to show *in vivo* retention of a fibril-selective radiotracer. Therefore, the failure to detect a significant difference in [^{11}C]PIB retention in the brains of PS1/APP mice compared with PS1 littermate controls as reported above was unexpected.

By histological and biochemical analysis, the 15-month-old PS1/APP mice studied here showed the typical, extensive amyloid deposition described previously in this mouse model. Total, insoluble Aβ levels were 30-fold higher than those observed in AD brain, yet [^{3}H]PIB binding was much lower. Based on the amount of Aβ present in the PS1/APP brain homogenate, the B_{max} for the binding of [^{3}H]PIB to PS1/APP brain more closely resembled the B_{max} for the binding of [^{3}H]PIB to synthetic Aβ in that both were ~1000-fold lower than the B_{max} for the binding of

Table 1. Biochemical analysis of PS1/APP and human AD brain tissue

	Aβ1–40 (pmol/g wet weight)	Aβ1–42 (pmol/g wet weight)	Total Aβ (pmol/g wet weight)
Insoluble			
PS1/APP ($n = 4$)	35,002 ± 21,266	12,838 ± 4453	47,840 ± 25,288
Human AD ($n = 5$)	764 ± 155	1715 ± 265	2479 ± 404
Soluble			
PS1/APP ($n = 4$)	1056 ± 302	573 ± 96	1629 ± 380
Human AD ($n = 5$)	5.4 ± 1.9	3.2 ± 0.73	8.6 ± 2.1
% Soluble			
PS1/APP ($n = 4$)	3.9 ± 2.7%	4.9 ± 2.5%	4.2 ± 2.6%
Human AD ($n = 5$)	0.73 ± 0.36%	0.19 ± 0.06%	0.36 ± 0.14%

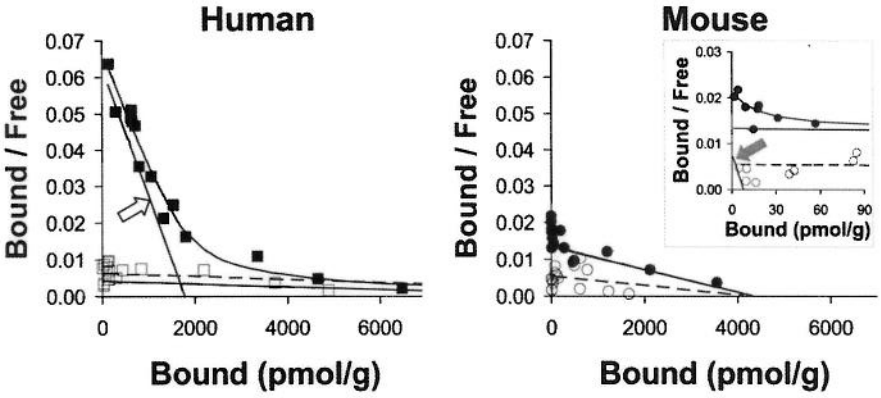

Figure 4. Scatchard analyses of [^{3}H]PIB binding shows a significant high-affinity binding component in human AD brain but not in PS1/APP brain. Left, This human AD brain (■) showed a large high-affinity component (open arrow) with a K_d value of 2.8 nM and a B_{max} value of 1780 pmol/g (BP = 636) and a low-affinity component with a K_d value of 264 nM and a B_{max} value of 11,000 pmol/g (BP = 42). The human control brain (□) showed only the low-affinity component with a K_d value of 242 nM and a B_{max} value of 15,000 pmol/g (BP = 62). Right, This PS1/APP brain (●) showed a very small high-affinity component (filled arrow) with a K_d value of 0.10 nM and a B_{max} value of 7.78 pmol/g (BP = 78), along with a much larger low-affinity component with a K_d value of 32 nM and a B_{max} value of 4300 pmol/g (BP = 134). The PS1 brain (○) showed the low-affinity component with a K_d value of 79 nM and a B_{max} value of 4200 pmol/g (BP = 53).

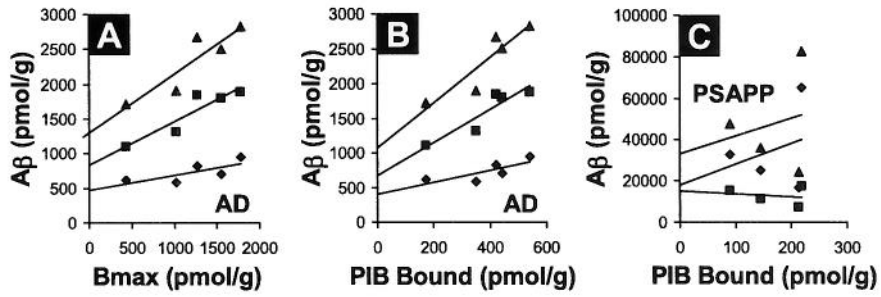

Figure 5. The binding of [^{3}H]PIB reflects the total amount of Aβ in AD brain but not in PS1/APP brain. Correlation of the B_{max} for [^{3}H]PIB binding (***A***) or correlation of the amount of [^{3}H]PIB bound (***B***) (using a concentration of 1 nM [^{3}H]PIB) to levels of Aβ1–40 (◆), Aβ1–42 (■), and total insoluble Aβ (▲) in AD brain ($n = 5$) is shown. ***C***, Correlation analogous to that in ***B*** performed in PS1/APP (PSAPP) brain ($n = 4$).

Table 2. PIB binding to homogenates from 15-month-old PS1/APP and PS1 mice and human AD and control brain in the presence of 1 nM [^{3}H]PIB

	PIB bound (pmol/g wet weight)	Fold difference
PS1/APP ($n = 4$)	166 ± 61	3.5
PS1 ($n = 4$)	47.5 ± 11	
Human AD ($n = 4$)	415 ± 81	16.3
Human control ($n = 3$)	25.4 ± 16	

Table 3. Scatchard analysis of [^{3}H]PIB binding to aggregated, synthetic Aβ1–40 and1–42 fibrils and PS1/APP and AD brain homogenates

	K_d (nM) (High Aff)	B_{max}[a] (High Aff)	BP[b] (High Aff)	K_d (nM) (Low Aff)	B_{max}[a] (Low Aff)	BP[b] (Low Aff)	BP[b] (total)	% High Aff 1 nM PIB[d]
Aβ1–40	1.02	0.61	[c]	50.1	8.1	[c]	[c]	79
Aβ1–42	0.91	0.45	[c]	51.5	9.6	[c]	[c]	73
PS1/APP	0.10	0.21	78	32.5	119	134	212	37
AD	2.5	565	563	264[e]	3888[e]	50	613	92

High Aff, High affinity; Low Aff, low affinity.

[a]Picomoles of [^{3}H]PIB bound per nanomole of Aβ.

[b]BP = B_{max}/K_d after conversion of B_{max} values to nanomolar units.

[c]BP data are not meaningful for synthetic Aβ because the concentration of the Aβ is arbitrarily set and not based on *in vivo* concentrations.

[d]Expected percentage of PIB bound to the high-affinity binding site in the presence of 1 nM PIB. This was determined from the BP values because binding at tracer concentrations is proportional to BP.

[e]The low-affinity component is detectable in less than half of AD brain samples.

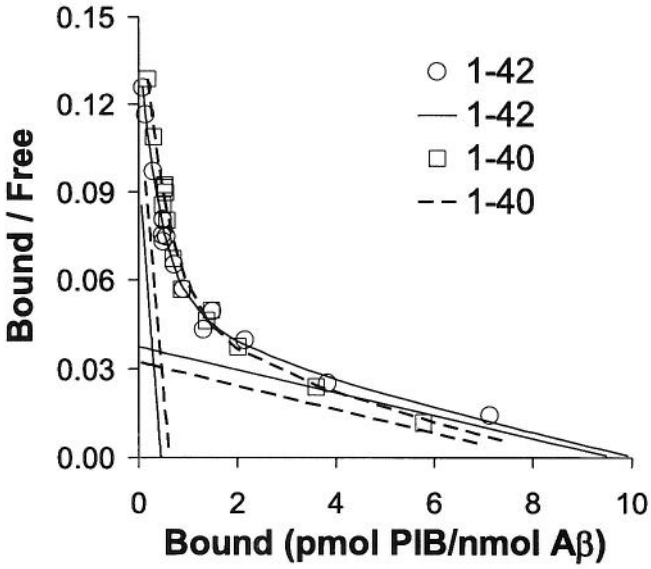

Figure 6. The binding of [^{3}H]PIB to synthetic Aβ1–40 and Aβ1–42 is nearly identical, and the B_{max} is very small as in PS1/APP brain (see Table 3).

[^{3}H]PIB to AD brain. This suggests that there is a very low efficiency for forming high-affinity PIB binding sites during *in vitro* aggregation of synthetic Aβ and a similarly low efficiency during plaque deposition *in vivo* in the PS1/APP mouse. In AD brain homogenates, PIB bound with high-affinity and total binding to AD brain was >15-fold higher than in control human brain. There was a tight correlation between PIB binding to AD brain and levels of insoluble Aβ. There was very little high-affinity binding of PIB to PS1/APP brain homogenates and total binding was increased only threefold compared with PS1 brain. No correlation was observed between PIB binding and levels of Aβ in PS1/APP brain. This suggests that, at the low nanomolar concentrations typically used in PET studies, the majority of PIB binding to PS1/APP brain is not mediated by Aβ. Because binding at tracer concentrations is proportional to the BP of each binding site, the BP data presented in Table 3 can be used to estimate that only ~37% of the binding to PS1/APP brain would be to the high-affinity component (compared with ~92% high-affinity binding in AD brain).

In contrast to AD brain, the PS1/APP mouse shows higher levels of Aβ1–40 than Aβ1–42. However, this is unlikely to be the explanation for poor PIB binding because we have seen similarly low PIB binding in other APP Tg mouse models in which Aβ1–42 predominates (data not shown), and the current study shows that PIB binds similarly to synthetic Aβ1–40 and Aβ1–42 (Fig. 6). Another possible explanation for the low PIB binding in PS1/APP brain could be that PIB does not bind directly to Aβ but binds to a component of human Aβ plaques that is missing in mouse brain. If this component is loosely associated with human plaques, then the addition of human amyloid deposits to PS1/APP brain or synthetic, aggregated Aβ would be expected to synergistically increase the binding of PIB, but this was not observed. Thus, if there is a plaque-associated factor other than Aβ important for the binding of PIB to human plaques, it must be very tightly associated with the plaque during the aggregation process. It is not likely that any missing component is tau related, because at the nanomolar concentrations used in PET studies and this study, PIB binding to tau deposits (i.e., neurofibrillary tangles) cannot be detected in AD brain (Klunk et al., 2003).

Evidence that the high-affinity PIB binding site measured in AD brain could be on the Aβ molecule itself or on a molecule that associates with Aβ with a 1:1 stoichiometry comes from the tight correlation between PIB binding and levels of insoluble Aβ in AD brain. In addition, the fact that the high-affinity K_d component in AD brain is very similar to that found on synthetic Aβ suggests that the high-affinity PIB binding site in AD brain may be present on Aβ itself. Additional evidence that the PIB-binding component of AD brain is on Aβ comes from binding studies with PIB analogs. Despite the low B_{max} for high-affinity PIB binding, PIB binding to pure Aβ is not obscured by other sources of nonspecific binding as it is in the PS1/APP mice. This has allowed a comparison of rank-order potencies for the binding of PIB analogs to synthetic Aβ fibrils and AD brain across a range of K_i values from 2 to 3000 nM (Klunk et al., 2003). Correlation of potencies between two pharmacological systems is classic evidence for a structurally common binding site in those two systems (Guidotti et al., 1979). The strong correlation between the potencies of PIB analogs in the Aβ and AD brain binding assays ($r = 0.9$, with a slope near unity) suggests that a very similar binding site is being measured in both assays (Klunk et al., 2003). This has two implications. First, the high-affinity PIB binding site in AD brain is likely to be on the Aβ molecule itself. Second, this implies that when a high-affinity PIB binding site is formed on synthetic Aβ *in vitro*, this site is very similar to those found in AD brain, although the frequency of formation is only 1/1000th that in AD brain. Thus, it appears that Aβ itself may contain the entire PIB binding site and other molecules are not absolutely required.

The pathology of AD develops over one or more decades, whereas mouse pathology develops over months. The long time frame of deposition in human brain allows for many post-translational and post-deposition modifications including oxidation, cross-linking, racemization, N- and C-terminal truncation, and others. In addition, even if Aβ alone (in the proper conformation) is sufficient for high-affinity PIB binding, this does not

exclude the likely possibility that other molecules could be involved in a scaffolding function during the Aβ aggregation process in AD brain. This scaffolding could increase the frequency with which Aβ assembles to form high-affinity PIB binding sites. A alternative possibility is that high- and low-affinity PIB binding sites are formed at similar frequencies *in vivo* and *in vitro* but that Aβ deposits formed *in vivo* with low-affinity PIB binding sites happen to be cleared more efficiently over the decades-long process that occurs in the human disease, leaving a large percentage of Aβ deposits with high-affinity PIB binding sites.

The phenomenon of low PIB binding would not be expected to be unique to the PS1/APP strain, and indeed preliminary experiments in our laboratory with Tg2576 and several proprietary strains show the same phenomenon. This is consistent with a recent report by Toyama et al. (2005) showing little retention of [^{11}C]PIB (called [^{11}C]6-OH-BTA-1 in that report) in 22-month-old Tg2576 mice. To our knowledge, none of the laboratories working to develop amyloid imaging agents has reported the successful application of micro-PET imaging with their agents in Tg mouse models of AD.

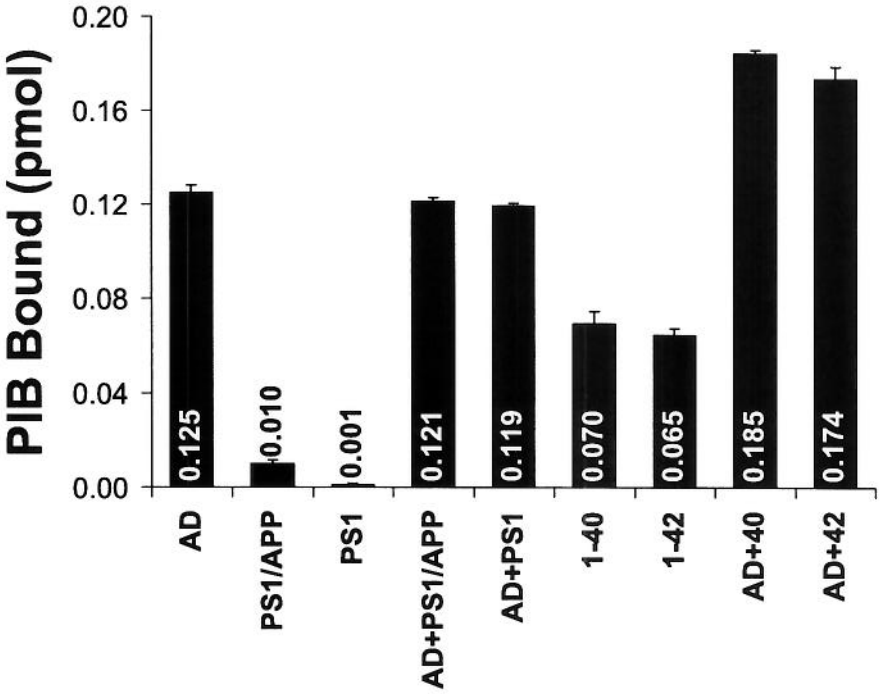

Figure 7. Mixing experiments do not indicate the presence of an easily transferable factor responsible for high-affinity [^{3}H]PIB binding in AD brain. Homogenates of AD, PS1/APP, and PS1 brain (containing 100 μg of tissue) and suspensions of Aβ1–40 and Aβ1–42 fibrils (containing 200 pmol of Aβ) or the mixtures indicated were incubated with 1 nM [^{3}H]PIB in a total volume of 1 ml. The picomoles of [^{3}H]PIB bound are indicated inside or above the bars. The amount of [^{3}H]PIB bound to the mixtures is approximately equal to the sum of the binding to the two individual components, indicating no synergy.

Using micromolar concentrations of PIB that are 1000-fold greater than levels achievable in PET studies that use high, specific-activity ligands, plaques in PS1/APP mice can be detected *in vitro* and *ex vivo* by histological staining and *in vivo* using multiphoton microscopy (Bacskai et al., 2003). Use of low, specific-activity PIB for PET studies to attain these micromolar concentrations would be expected to decrease the ratio of specific to nonspecific binding, so other factors must explain the success of *ex vivo* and *in vivo* microscopy. These microscopic techniques take advantage of a relatively small FOV that can exclude some of the potential sources of nonspecific background binding that would be detected using micro-PET or *ex vivo* radioassays. In addition, similar to the β-sheet detecting characteristics of thioflavin-T (the structural prototype for PIB) (LeVine, 1993), the actual binding of PIB to Aβ can lead to increased fluorescence compared with PIB bound to background structures making plaque-bound PIB preferentially detectable.

It is not clear whether the findings presented here have significance limited only to *in vivo* model systems used for the development of PIB and structurally related amyloid-binding compounds, or whether the implications extend beyond that. It may be that PIB can act as a probe for the structure of amyloid proteins at the molecular level. The differences in structure between synthetic Aβ, Aβ in Tg mouse models, and Aβ in AD brain suggested by the differences in PIB binding may have no significance beyond this, or they could be a cause of the differences seen in the tissue reaction to these deposits in AD and Tg mouse brain. If other macromolecules are important as scaffolding for the AD-like aggregation of Aβ or if macromolecules become important components of the Aβ fibril structure, then the differences in PIB binding may draw our attention to molecular targets that are important for the development of improved Tg mouse models or, more significantly, are important for the development of new therapeutic agents.

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AMERICAN ACADEMY OF NEUROLOGY

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PRACTICE PARAMETER: DIAGNOSIS OF DEMENTIA (AN EVIDENCE-BASED REVIEW)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

D.S. Knopman, MD; S.T. DeKosky, MD; J.L. Cummings, MD; H. Chui, MD; J. Corey–Bloom, MD, PhD; N. Relkin, MD, PhD; G.W. Small, MD; B. Miller, MD; and J.C. Stevens, MD

Article abstract—*Objective*: To update the 1994 practice parameter for the diagnosis of dementia in the elderly. *Background:* The AAN previously published a practice parameter on dementia in 1994. New research and clinical developments warrant an update of some aspects of diagnosis. *Methods:* Studies published in English from 1985 through 1999 were identified that addressed four questions: 1) Are the current criteria for the diagnosis of dementia reliable? 2) Are the current diagnostic criteria able to establish a diagnosis for the prevalent dementias in the elderly? 3) Do laboratory tests improve the accuracy of the clinical diagnosis of dementing illness? 4) What comorbidities should be evaluated in elderly patients undergoing an initial assessment for dementia? *Recommendations:* Based on evidence in the literature, the following recommendations are made. 1) The DSM-III-R definition of dementia is reliable and should be used (Guideline). 2) The National Institute of Neurologic, Communicative Disorders and Stroke–AD and Related Disorders Association (NINCDS-ADRDA) or the *Diagnostic and Statistical Manual*, 3rd edition, revised (DSM-IIIR) diagnostic criteria for AD and clinical criteria for Creutzfeldt–Jakob disease (CJD) have sufficient reliability and validity and should be used (Guideline). Diagnostic criteria for vascular dementia, dementia with Lewy bodies, and frontotemporal dementia may be of use in clinical practice (Option) but have imperfect reliability and validity. 3) Structural neuroimaging with either a noncontrast CT or MR scan in the initial evaluation of patients with dementia is appropriate. Because of insufficient data on validity, no other imaging procedure is recommended (Guideline). There are currently no genetic markers recommended for routine diagnostic purposes (Guideline). The CSF 14-3-3 protein is useful for confirming or rejecting the diagnosis of CJD (Guideline). 4) Screening for depression, B_{12} deficiency, and hypothyroidism should be performed (Guideline). Screening for syphilis in patients with dementia is not justified unless clinical suspicion for neurosyphilis is present (Guideline). *Conclusions:* Diagnostic criteria for dementia have improved since the 1994 practice parameter. Further research is needed to improve clinical definitions of dementia and its subtypes, as well as to determine the utility of various instruments of neuroimaging, biomarkers, and genetic testing in increasing diagnostic accuracy.

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Introduction. *Mission statement.* The Quality Standards Subcommittee of the American Academy of Neurology (AAN) is charged with developing practice parameters for physicians. This evidence-based review addresses major issues in the diagnosis of dementia.

Background and justification. Dementia is a common disorder in the elderly, involving as many as 10% of those over 65 years of age. The AAN previously published a practice parameter on dementia in 1994,[1] and since that time many new clinical and research developments have occurred. The purpose of the current practice parameter is to highlight and to update major areas of current interest and investigation in the diagnosis of dementia in the elderly. It is not intended to serve as a comprehensive review of the differential diagnosis of dementia.

The appointment of authors for this guideline was done in cooperation with the Alzheimer's Association and overlaps significantly with the membership of the Medical and Scientific Advisory Council and the Board of Directors of the association. The Alzheimer's Association agrees with the content of this paper in all important regards.

This guideline has been endorsed by the American Association of Neuroscience Nurses and the American Geriatrics Society.

From the Department of Neurology (Dr. Knopman), Mayo Clinic, Rochester, MN; Departments of Neurology and Psychiatry (Dr. DeKosky), University of Pittsburgh, PA; Departments of Neurology and Psychiatry & Biobehavioral Science (Dr. Cummings), University of California at Los Angeles; Department of Neurology (Dr. Chui), University of Southern California, Los Angeles; Department of Neurosciences (Dr. Corey–Bloom), University of California at San Diego; Department of Neurology and Neuroscience (Dr. Relkin), New York Presbyterian–Weill Cornell Medical College; Neuropsychiatric Institute and Hospital (Dr. Small), University of California at Los Angeles; Department of Neurology (Dr. Miller), University of California at San Francisco; Lutheran Medical Office (Dr. Stevens), Fort Wayne, IN.

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Clinical question statement. The Diagnosis of Dementia Committee reviewed the issues, problems, and challenges related to the diagnosis of dementia. Based on work that has been published since 1994, the Committee formulated four questions to be addressed in the practice parameter:

1. Are the current criteria for the diagnosis of dementia reliable?
2. Are current diagnostic criteria sufficiently accurate to establish a diagnosis for the prevalent dementias in the elderly?
3. Do laboratory tests improve the accuracy of the clinical diagnosis of dementing illness?
4. What comorbidities should be evaluated in elderly patients undergoing an initial assessment for dementia?

Process. *Panel selection.* A group of clinicians from various disciplines with extensive experience in diagnosing and caring for patients with dementia was assembled. The group was charged with focusing on the diagnosis of dementia. Committee members disclosed any real or potential conflicts of interest. Other work groups formulated practice parameters on the detection of dementia[1] and the management of dementia.[2]

Literature review process. A literature search was conducted using MEDLINE, Excerpta Medica, and BIOSIS. The search included articles published from January 1985 through November 1999. The search strategy sought only studies published in English and studies on human disease. The principal search term was dementia. Other terms entered into the search included neuroimaging, diagnostic techniques, diagnostic imaging, biologic markers, CSF, diagnostic errors, differential diagnosis, and neuropsychologic tests. The original search yielded 1,175 articles of which approximately 300 articles were identified as relevant to our search questions. For articles on AD, we included only those based on more than 25 patients. For the less common dementias there was no minimal sample size. An additional 300 articles not identified by the literature search strategy, including ones published after the initial search was conducted, were submitted by committee members or obtained from bibliographies of articles identified in the search.

Each article was classified based on the quality of evidence (Class I through IV, table 1). After review of the evidence, recommendations were drafted, reviewed by all committee members, and identified as a Practice Standard, Guideline, or Option (table 2). When appropriate, data on specificity, sensitivity, and other numerical measures of diagnostic precision were extracted from the articles and placed in tables. Final inclusion of articles in this Practice Parameter was based on consensus of the Committee that they were relevant and informative in consideration of the four questions.

In addition to the review and final approval by the Quality Standards Subcommittee and the Practice Committee of the AAN, this Practice Parameter was reviewed by AAN members who had identified themselves as interested reviewers, by the Geriatric and Behavioral Neurology Sections of the AAN, by representatives of the American Geriatrics Society, and by representatives of the Alzheimer's Association.

Analysis of the evidence. *Are the current criteria for the diagnosis of dementia reliable?* The diagnostic formulations of dementia that are the most widely used in North America are based on definitions contained in the National Institute of Neurologic, Communicative Disorders and Stroke–AD and Related Disorders Association (NINCDS-ADRDA) Work Group,[2] the *Diagnostic and Statistical Manual*, 3rd edition, revised (DSM-IIIR),[3] and the *Diagnostic and Statistical Manual*, 4th edition (DSM-IV).[4] The DSM-IIIR states:

> The essential feature of Dementia is impairment in short- and long-term memory, associated with impairment in abstract thinking, impaired judgment, other disturbances of higher cortical function, or personality change. The disturbance is severe enough to interfere significantly with work or usual social activities or relationships with others. The diagnosis of Dementia is not made if these symptoms occur. . .in Delirium. . .[3]

The DSM-IIIR definition of dementia has good to very good reliability (kappa's ranging from 0.5 to 0.9).[5-7] The closely related NINCDS-ADRDA and DSM-IV definitions of dementia have not been subjected to assessment of reliability.

Practice recommendations.

The DSM-IIIR definition of dementia, which is identical to the DSM-IV definition, is reliable and should be used routinely (Guideline).

Are current diagnostic criteria able to establish a diagnosis for the prevalent dementias?

Alzheimer's disease. The reliability of the diagnosis of AD is moderate (generalized kappa's in the 0.51 to 0.73 range) in Class II studies.[8-10] When standardized clinical diagnostic criteria are used, interrater reliability[6] and consistency of diagnosis between the initial visit and 1-year follow-up is high (95% in Forette[11]).

There are 13 studies, 3 Class I[12-14] and 10 Class II,[9,15-22] that have addressed the diagnostic accuracy of the clinical diagnosis of AD using neuropathologic confirmation as the "gold standard." Both the DSM-IIIR "Dementia of the Alzheimer type" (DAT) and the NINCDS-ADRDA "probable" AD definitions achieved either good sensitivity (average across cited studies = 81%, range 49 to 100%) for AD at the expense of specificity (average across cited studies = 70%, range 47 to 100%) or vice versa in the majority of the cited studies. A diagnosis of "possible" AD achieved very high

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Table 1 *Classification of evidence*

Class	Description
I	Evidence provided by a well designed prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, in which test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.
II	Evidence provided by a well designed prospective study of a narrow spectrum of persons with the suspected condition, or a well designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared with a broad spectrum of controls, in which test is applied in blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.
III	Evidence provided by a retrospective study in which either persons with the established condition or controls are of a narrow spectrum, and in which test is applied in a blinded evaluation.
IV	Any design in which test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls).

Table 2 *Definitions for practice recommendations based on classification of evidence*

Recommendation	Description
Standard	Principle for patient management that reflects a high degree of clinical certainty (usually this requires Class I evidence that directly addresses the clinical question, or overwhelming Class II evidence when circumstances preclude randomized clinical trials).
Guideline	Recommendation for patient management that reflects moderate clinical certainty (usually this requires Class II evidence or a strong consensus of Class III evidence).
Practice Option	Strategy for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion).
Practice Advisory	Practice recommendation for emerging and/or newly approved therapies or technologies based on evidence from at least one Class I study. The evidence may demonstrate only a modest statistical effect or limited (partial) clinical response, or significant cost-benefit questions may exist. Substantial (or potential) disagreement among practitioners or between payers and practitioners may exist.

sensitivity (average across 4 studies = 93%, range 85 to 96%) but at the price of specificity (average across 4 studies = 48%, range 32 to 61%),[13,14,17,22] reflecting the many features that non-AD dementias share with AD.

Vascular dementia (VAD). Four criteria for vascular dementia that are currently used include the State of California AD Diagnostic and Treatment Centers criteria (the "California" criteria),[23] the National Institute of Neurologic Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria,[24] the Hachinski Ischemic Score (HIS) as modified by Rosen,[25,26] and those found in DSM-IV.[4] In studies that compared clinical diagnoses and neuropathologic findings, the NINDS-AIREN and the California criteria (as well as DSM-IIIR) had very low sensitivity but higher specificity. Only one Class I study[12] reported the sensitivity (43%) and specificity (95%) of a published criteria, NINDS-AIREN, for VAD. Four Class II studies with patient samples drawn from referral cohorts[15-17,27,28] reported sensitivity and specificity of the diagnosis of vascular dementia with any criteria. With one exception, their results had the same diagnostic accuracy as the population-based studies, with low sensitivity (average across 5 studies = 50%, range 20 to 89%) but higher specificity (average across 5 studies = 87%, range 64 to 98%) for the HIS, DSM-IIIR, NINDS-AIREN, or California clinical criteria. A retrospective (Class II) study[27] in which the HIS showed better sensitivity and specificity (both 89%) was the one analysis of six in which the diagnosis of vascular dementia appeared both sensitive and specific.

Recent neuropathologic analyses[12,14] offer a perspective on the difficulty in correctly diagnosing cerebrovascular pathology in dementia. Rather than considering vascular dementia as simply present or absent, these studies distinguished between "some or any" vascular lesions versus "pure" vascular pathology, i.e., the circumstance in which vascular pathology was both sufficient to account for cognitive symptoms and unaccompanied by other pathology. Some vascular pathology exists in 29 to 41% of dementia cases coming to autopsy in population-based cohorts, even though pure vascular pathology accounted for dementia in only 9 to 10%.[12,14] The Hachinski Ischemic Score, while lacking neuroimaging criteria, may be more suitable for identifying the majority of dementia patients with vascular dementia, i.e., those with at least some cerebrovascular pathology,[27] because of the low sensitivity of the NINDS-AIREN and California criteria.[12,15-17,28]

Dementia with Lewy bodies (DLB). DLB has been defined clinically by the presence of dementia, gait/balance disorder, prominent hallucinations and delusions, sensitivity to traditional antipsychotics, and fluctuations in alertness.[29] Two Class II studies evaluated the interrater reliability of the diagnosis of DLB based on the Consortium for DLB diagnostic criteria[29] and found it to be relatively low.[10,30]

One Class I study[12] investigated the diagnostic accuracy of DLB criteria against neuropathologic findings and found that sensitivity was low (22%) but specificity (100%) was high. Five Class II studies also showed low sensitivities (average across 5 studies = 58%, range 34 to 75%) but higher specificities (average across 5 studies = 87%, range 71 to 94%) for the diagnostic criteria of Consortium for DLB.[10,30-33] In a prospective clinical study based on a DLB case registry with neuropathologically confirmed cases, hallucinations, depression, delusions, and delusional misidentification were all significantly higher in patients with DLB than AD.[34] However, all of these features occurred in patients with AD

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as well. The presence of visual hallucinations and delusional misidentification as early symptoms showed sensitivities and specificities of >50% but <75%. In another study, the clinical diagnosis of DLB was confirmed in only 5 of 10 cases at postmortem examination.[35] The lack of specificity of the DLB clinical diagnosis appeared attributable to an equivalent amount of spontaneous extrapyramidal disturbance between the five cases with DLB at autopsy and the five without DLB at autopsy (four with AD, one with progressive supranuclear palsy).[35]

Prominent deficits in attention, profound deficits in visuo-constructional skills, and relative sparing of memory are the neuropsychologic features of DLB.[36,37] However, neuropsychologic tests do not reliably differentiate DLB from either AD or VAD.[37] Similarly, even though patients with DLB show less temporal lobe atrophy on MRI than do patients with AD[38] and more hypoperfusion in the occipital lobes,[39] neuroimaging has not proven successful in differentiating DLB from AD.

Frontotemporal dementia (FTD). FTD is less common than AD, VAD, or DLB,[14,17,40] particularly in very elderly dementia cohorts. An autopsy-based Class II study (using retrospective clinical diagnoses determined from review of medical records) showed that most patients with FTD fulfill diagnostic criteria for AD.[41] In contrast, a Class II study without autopsy confirmation[42] found that the Lund-Manchester criteria[43] (an earlier version of the Consensus diagnostic criteria for FTD[44]) differentiated 100% of FTD and AD patients. Early loss of personal awareness, early loss of social awareness, hyperorality, and stereotyped, perseverative behavior were somewhat sensitive (63 to 73%) and highly specific (97 to 100%) for differentiating the two conditions.[42]

Neuropsychologic test profiles of patients with FTD typically reveal deficits on frontal systems tasks, including verbal fluency, abstraction, and executive function.[45] Using discriminant analysis, one study found that the FAS word fluency test was the instrument that best differentiated FTD from AD.[46] Although it has been suggested that tests of constructional ability differ significantly between FTD and AD,[43] this is not always the case.[46] Some patients with AD demonstrate substantial executive deficits;[47] hence neither the clinical nor neuropsychologic profile of the frontotemporal syndrome is specific for FTD. There are no clinical features that are useful for establishing either the histologic subtype of FTD or linkage to tau mutations.

Prion diseases. Until recently, diagnosis of Creutzfeldt–Jakob disease (CJD) disease rested on clinical symptoms, the characteristic electroencephalographic pattern of periodic sharp wave complexes and the pathologic examination of brain tissue. The diagnostic criteria for CJD were tested in a prospective, Class I study[48] in which 188 autopsy-confirmed cases (97%) were identified of 193 cases diagnosed with "probable" CJD based on criteria of Masters et al.[49] In this same cohort, among 54 cases diagnosed with "possible" CJD, the diagnosis was confirmed in 44 (81%). Only 2 pathologically diagnosed CJD cases were found among 111 patients who had been given other clinical diagnoses. Brown et al.[50] proposed a simplified diagnostic scheme that has not been subjected to prospective study but is very similar to that used by Poser et al.[48]

Conclusions. The criteria of probable AD has good sensitivity for neuropathologic AD but less optimal specificity. The clinical phenotypes embodied in the diagnostic criteria for VAD, DLB, and FTD do not map precisely onto neuropathologic phenotypes. Although there are strong clinical-pathologic relationships for these disorders in the majority of patients, there are many patients with atypical or nonspecific clinical presentations. The clinical phenotype of CJD is more tightly linked to its expected CJD pathology.

Practice recommendations.

- The NINCDS-ADRDA for the diagnosis of probable AD or DSM-IIIR criteria for DAT should be routinely used (Guideline).
- The Hachinski Ischemic Index criteria may be of use in the diagnosis of cerebrovascular disease in dementia (Option).
- The Consortium for DLB diagnostic criteria may be of use in clinical practice (Option).
- The Consensus diagnostic criteria for FTD may be of use in clinical practice (Option).
- Clinical criteria for CJD should be used in rapidly progressive dementia syndromes (Guideline).

Do laboratory tests improve the accuracy of clinical diagnosis of dementing illness?

Structural neuroimaging for differential diagnosis. Since the previous practice parameter on dementia,[1] one additional Class II study[51] has addressed structural imaging in the diagnostic evaluation of patients with dementia. The study[51] found that 5% of patients had a clinically significant structural lesion but no features in the history or examination that would have predicted the lesions. Other Class II studies that have examined the decision to order a brain imaging study on clinical history and examination alone have shown imperfect precision, although specificity and sensitivity may be approximately 90%.[52,53] Given the goal of minimal undetected structural lesions, the data supports the use of a neuroimaging examination—either a noncontrast CT or MR scan—under most circumstances at the time of the initial dementia assessment to identify pathology such as brain neoplasms or subdural hematomas. A third condition, normal pressure hydrocephalus, which might be detected by CT or MR and might be responsive to treatment is very rare.[54]

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Quantitative imaging to diagnose AD. Only one prospective (Class I) study of quantitative computed tomographic imaging was found that used autopsy-confirmed diagnosis as the diagnostic standard.[55] Among 86 autopsied cases, a minimum width of the medial temporal lobe falling below the 5th percentile was 95% sensitive but only 40% specific for AD.

Several Class II studies without neuropathologic confirmation of the diagnosis have reported the utility of medial temporal lobe atrophy, particularly hippocampal or entorhinal atrophy, for the clinical diagnosis of AD.[56,57] In differentiating clinically diagnosed AD (NINCDS-ADRDA criteria) from elderly normal controls, the sensitivity of various medial temporal atrophy measures on CT[58] or MRI[59-62] ranged from 77 to 92%, with specificities ranging from 49 to 95%. Automated volumetric techniques with MRI were most reliable but are currently labor-intensive and not widely available. There are no studies that have determined the added value of measurements of hippocampal or entorhinal volume once a clinical diagnosis of AD has been made. The range of estimates suggests that measurement of hippocampal atrophy by MRI may not be useful in clinical practice because of its low precision.

Combining medial temporal measures with other potentially informative markers, such as functional neuroimaging[58] or apolipoprotein E genotyping, may improve diagnostic accuracy.[63] Determination of the rate of change of hippocampal atrophy[64] may also be of value diagnostically but is unlikely to be of use in clinical practice. Prediction of subsequent AD in individuals without dementia has also been attempted with MRI of the hippocampus and entorhinal cortex,[65,66] but that is beyond the scope of this parameter.

Functional neuroimaging. SPECT and AD. Based on Class II studies, the sensitivity of SPECT was lower than that of the clinical diagnosis.[58,67] In a single prospective study, when specificity was set at 89% overall sensitivity was 43%.[67] Sensitivity increased as the severity of dementia worsened, but the pretest probability of AD also became higher.[68,69] The added value of SPECT was greatest for a positive test among patients with mild dementia in whom there was substantial doubt about the diagnosis of AD (e.g., prior probability between 30 and 50%).[68] In this situation, a positive SPECT would have increased the posttest probability of AD by 30%, whereas a negative test result would have increased the likelihood of no AD by only 10%. Higher sensitivity (77 to 86%) and specificity (90 to 94%) have been reported using automated and quantitative methods for SPECT analysis.[70,71]

To assess the value of SPECT in the differential diagnosis of dementia, we identified two SPECT studies (Class I) with autopsy-confirmed diagnoses in a large number of subjects.[55,72] For the differentiation of AD versus non-AD dementia, hypoperfusion in the temporal–parietal lobe(s) was reported to be 86 to 95% sensitive and 42 to 73% specific. Although encouraging, these figures are not consistently better than those obtained by diagnosis with established clinical criteria.

PET and AD. The largest series of dementia cases who underwent PET scans and also had autopsy confirmation was reported in a Class II study[73] that included 22 patients with various types of dementia (64% AD). In this study, visual interpretations of PET scans, which have high interrater reliability,[74] yielded a sensitivity of 93% and a specificity of 63%.

A direct comparison (Class II) of FDG-PET and HMPAO-SPECT in their ability to differentiate AD from vascular dementia indicated higher diagnostic accuracy for PET regardless of dementia severity.[75] Using receiver–operator characteristic curves, SPECT diagnostic accuracy was 62.9% for Mini-Mental State Examination (MMSE) score >20 and 81.2% for MMSE score <20. For PET, diagnostic accuracy was 87.2% for MMSE score >20 and 100% for MMSE score <20. Other Class II studies confirmed a lower sensitivity for high-resolution SPECT compared with PET.[76] FDG-PET appears superior to MRI measures of hippocampal atrophy because changes in cerebral glucose metabolism antedate the onset of memory decline whereas the MRI hippocampal changes do not.[77]

PET scanning appears to have promise for use as an adjunct to clinical diagnosis, but further prospective studies with PET are needed to establish the value that it brings to diagnosis over and above a competent clinical diagnosis.

SPECT, PET, and FTD. SPECT and PET may be helpful in distinguishing FTD from AD. Many patients with FTD show hypoperfusion of anterior cerebral cortex with relative sparing of posterior cortex with SPECT[78-80] and PET.[81] In these four Class II studies, the highly selected study participant pool makes it difficult to generalize on the reported specificities and sensitivities. In patients with cognitive or behavioral deficits suggestive of FTD, no studies addressed what additional value a SPECT or PET scan provides.

Genetic biomarkers. No studies have addressed the value of genetic counseling for patients with dementia or their families when autosomal dominant disease is suspected. Because the genetics of dementing illnesses is a very young field, expertise in genetic counseling for the dementias of the elderly is likely to be found only in specialized dementia research centers. Advances in the identification of genetic markers for AD and other dementias have raised awareness of the familial nature of the dementias, even when autosomal dominant transmission is not evident.

AD and genetic risks. In a large neuropathologically confirmed cohort of patients with dementia, the use of apolipoprotein E4 slightly increased the positive predictive value of the AD diagnosis (Class II).[18] These authors showed that relative to the neuropathologic diagnosis of AD, the sensitivity of the clinical diagnosis of AD was 92%, whereas sensitivity of having at least one APOE E4 allele was only 65%. However, in patients with clinical diagnoses of AD, the addition of APOE testing increased the positive predictive value (using the prevalence of AD in this dementia autopsy series) of a diagnosis of AD by approximately 4% (from 90 to 94%) if an APOE E4 allele was present. In patients with a

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clinical diagnosis of non-AD, the absence of an APOE E4 allele increased the negative predictive value by 8% (from 64 to 72%).

FTD and genetic risks. A relatively high prevalence of tau mutations was found in a Dutch population (17.8% of all FTD cases and 40.3% of all familial FTD cases).[82] In contrast, no tau mutations were found in a large U.S. clinical non-AD dementia sample.[83] The yield of diagnostic and prognostic information from screening of sporadic cases of suspected FTD for the known mutations of the tau gene is likely to be very low.

DLB and genetic risks. There are no clinically relevant associations between any genetic markers and DLB.

CJD and genetic risks. Although familial CJD has been linked to a number of different mutations in the prion gene,[84] and a polymorphism at one codon has been shown to be more common in sporadic CJD,[85,86] there is no evidence currently that genetic analysis of the prion gene is of value in the diagnosis of suspected CJD.

CSF markers. Since the publication of the previous practice parameter, we encountered no new published studies that addressed the issue of routine versus selective CSF analysis in the evaluation of a patient with dementia. However, since 1994, there has been intense interest in developing markers related to the neuropathology of AD in CSF.

CSF ß-amyloid$_{1-42}$. Reduced levels of ß-amyloid$_{1-42}$ in CSF of patients with AD compared with normal elderly controls have been observed repeatedly in Class II and III studies.[87-90] Using post-hoc cut-points, moderate sensitivities (78 to 92%) and specificities (81 to 83%) have been achieved in distinguishing patients with AD from normal elderly controls.[87-89] It is unclear whether CSF levels of ß-amyloid$_{1-42}$ retain diagnostic usefulness in patients with very mild AD.[91]

CSF tau. CSF tau level was shown to be significantly elevated in patients with AD compared with normal controls in Class II and III studies.[92-95] CSF tau distinguished AD from normal controls with 80 to 97% sensitivity and 86 to 95% specificity. However, elevated CSF tau level has also been detected in patients with other neurodegenerative diseases.[92] CSF tau levels may be useful in supporting a diagnosis of AD early in the course of dementia.[93,95] Although sensitivity and specificity of CSF tau measurements appear very good, there are no studies that determine the benefits of CSF tau over a good clinical diagnosis.

CSF ß-amyloid$_{1-42}$ and tau. The diagnostic yield may be improved by the simultaneous measurement of CSF ß-amyloid$_{1-42}$ and tau. In Class II and III studies, sensitivities of 85% and specificities of 87% have been reported.[88-90] Additional studies are needed to establish the value that the combined use of these markers brings to diagnosis over and above a competent clinical diagnosis.

CSF AD7C-NTP. Although specificities of 89 and 94% have been cited for CSF AD7C protein in early AD and possible or probable AD versus demented controls, patient selection and characterization in the studies[96-98] lacked scientific rigor. A recent Class II study with better methodology[99] showed that CSF AD7C-NTP had a specificity of 87% and a sensitivity of 70%.

CSF 14-3-3 protein and neuron-specific enolase. An immunoassay for the detection of the 14-3-3 protein in CSF has been described[100] that had a specificity of 99% and a sensitivity of 96% for the diagnosis of CJD among patients with dementia who had not had a stroke within one month of testing. A large German national surveillance study (Class I) of CJD also reported a sensitivity of 94%, specificity of 93%, and positive predictive value of 95% for 14-3-3 CSF assay.[101] In this same population, the CSF 14-3-3 protein assay was superior to EEG or MR in identifying cases of CJD.[48] However, other acute neurologic conditions such as stroke, viral encephalitis, and paraneoplastic neurologic disorders can provide false positive results.[100-103] A negative 14-3-3 immunoassay does not rule out CJD.[104] The additional use of neuron-specific enolase does not appear to substantially improve diagnostic accuracy.[105]

Other biomarkers. No other biomarkers that had been extensively studied and had promising detection abilities for AD or other dementias were uncovered in the literature search.

Conclusions. The CSF 14-3-3 protein assay is useful for confirming the diagnosis of CJD. In contrast, no laboratory tests have yet emerged that are appropriate for routine use in the clinical evaluation of patients with suspected AD. Several promising avenues—genotyping, imaging and biomarkers—are being pursued, but proof that a laboratory test has value is arduous. Ultimately, the putative diagnostic test must be administered to a representative sample of patients with dementia who eventually have pathologic confirmation of their diagnoses. A valuable test will be one that increases diagnostic accuracy over and above a competent clinical diagnosis.

Practice recommendations.

- Structural neuroimaging with either a noncontrast CT or MR scan in the routine initial evaluation of patients with dementia is appropriate (Guideline).
- Linear or volumetric MR or CT measurement strategies for the diagnosis of AD and are not recommended for routine use at this time (Guideline).
- For patients with suspected dementia, SPECT cannot be recommended for routine use in either initial or differential diagnosis as it has not demonstrated superiority to clinical criteria (Guideline).
- PET imaging is not recommended for routine use in the diagnostic evaluation of dementia at this time (Guideline).

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- Genetic testing of patients with suspected DLB and CJD is not recommended (Guideline).
- Routine use of APOE genotyping in patients with suspected AD is not recommended at this time (Guideline).
- There are no other genetic markers recommended for routine use in the diagnosis of AD (Guideline).
- Testing for tau mutations or AD gene mutations is not recommended for routine evaluation in patients with FTD at this time (Guideline).
- There are no CSF or other biomarkers recommended for routine use in determining the diagnosis of AD at this time (Guideline).
- The CSF 14-3-3 protein is recommended for confirming or rejecting the diagnosis of CJD in clinically appropriate circumstances (Guideline).

What comorbidities should be screened for in elderly patients undergoing an initial assessment for dementia? The prior Practice parameter[1] recommended a number of laboratory tests (including complete blood count, serum electrolytes, glucose, blood urea nitrogen/creatinine, folate, B_{12}, thyroid function, and syphilis serology) as routine assessment in patients undergoing assessment for dementia. Since that time, no studies were identified that evaluated these recommendations. However, since 1994, several studies have been published that specifically addressed the diagnostic value of vitamin B_{12} levels, thyroid function analysis, and syphilis screening. No studies were identified that addressed the utility of such tests as 24-hour urine collection for heavy metals or serum toxicology screens.

Depression. Prospective studies show that individuals with depression and coexistent cognitive impairment are highly likely to have an underlying dementia on longitudinal follow-up.[106-111] In one of the studies,[110] nearly 12% of patients with dementia were also depressed. Validated instruments for screening for depression exist, such as the Geriatric Depression Scale, short form,[112] the Centers for Epidemiologic Studies Depression scale,[113] and the Hamilton Depression Scale.[114]

Vitamin B_{12}. Vitamin B_{12} deficiency is common in the elderly.[115] Reports of improvement in cognitively impaired individuals with B_{12} deficiency are equivocal.[116-119] Patients with B_{12} deficiency have had slightly lower cognitive performance than nondeficient subjects,[120] but low vitamin B_{12} levels in nondemented subjects carried no risk for the subsequent development of dementia.[121] The number of patients with dementia caused by B_{12} deficiency states has been very small in prevalence studies[122] or meta-analyses of clinic samples.[123,124] Diagnostic algorithms for refined diagnoses of vitamin B_{12} deficiencies have been published.[125]

Thyroid functions. Hypothyroidism is common in the elderly.[126-128] Nondemented patients with hypothyroidism had lower mental status test scores, word fluency, visuospatial abilities, and learning than euthyroid controls,[129] but two other studies[128,130] found no relationship between TSH and cognitive function. The vast majority of patients with clinically significant hypothyroidism in these studies[128-130] lacked dementia. On the other hand, elevated TSH levels carried an increased risk for dementia in a population-based study.[131] In dementia prevalence studies[122] and clinic sample meta-analyses,[123,132] there were only a very small number of patients with dementia attributable to hypothyroidism, which was either partially or completely reversed with treatment of hypothyroidism.

Other common metabolic abnormalities possibly associated with dementia. Other metabolic disturbances are also sometimes included in the differential diagnosis of dementia. In the series of Clarfield[123] and Weytingh,[124] hypoparathyroidism and hepatic encephalopathy were mentioned as illnesses that with treatment resulted in complete resolution of dementia.

Tests for syphilis. There are only a few areas in the United States, mainly in the southern tier of the country and in some regions of the Midwest, with high numbers of syphilis cases.[133] Thirty-one U.S. counties account for 50% of all reported cases of primary and secondary syphilis.[133] Within the last 20 years, there have been no reported cases of tertiary syphilis in any of the incidence[134-138] or prevalence[122,135,139-145] studies conducted in North America. Except in these high-incidence regions, screening for the disorder in patients with dementia without an increased pretest probability would appear to be ill-supported because positive serum Venereal Disease Research Laboratory, rapid plasma reagin, and fluorescent treponemal antibody tests are nonspecific.[146,147]

Conclusions. Depression, B_{12} deficiency, and hypothyroidism are comorbidities that are likely to appear in the elderly and in patients with suspected dementia in particular. Although treatment of these disorders may not completely reverse cognitive dysfunction, they should be recognized and treated. No new evidence has appeared since 1994 to support or refute the recommendation to perform "routine" blood tests in patients being evaluated for dementia.

Practice recommendations.

- Depression is a common, treatable comorbidity in patients with dementia and should be screened for (Guideline).
- B_{12} deficiency is common in the elderly, and B_{12} levels should be included in routine assessments of the elderly (Guideline).
- Because of its frequency, hypothyroidism should be screened for in elderly patients (Guideline).

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- Unless the patient has some specific risk factor or evidence of prior syphilitic infection, or resides in one of the few areas in the United States with high numbers of syphilis cases, screening for the disorder in patients with dementia is not justified (Guideline).

Recommendations for future research. Although the DSM-IIIR definitions of dementia are reliable, clarification of the cognitive domains of dementia in the definitions would allow diseases such as some forms of VAD, as well as DLB and FTD, to be better integrated. Memory disorders are not necessarily part of the initial presentation of these disorders. Therefore, memory disorder should not be a required part of the definition of dementia. In addition, the definitions of the specific, common diseases that cause dementia—AD, VAD, DLB, and FTD—should be refined to minimize incompatibilities and confusing overlap between categories. Explicit recognition of the pathologic overlap of AD, VAD, and DLB in the diagnostic criteria might lead to a more realistic approach to clinical diagnosis. Further work must be done to improve the precision of the diagnoses of VAD and DLB in particular. The diagnosis of mild cognitive impairment (see Practice Parameter on Early Detection of Dementia) also should be integrated with the definition of dementia as well as the definitions of specific diseases. As we move into an era of earlier recognition of cognitive impairment, clarification of the distinctions between no cognitive impairment, mild cognitive impairment, and early dementia is needed.

Biomarkers for AD and other dementias are critically needed, and the validation of these markers will require cross-sectional studies and longitudinal, population-based studies with diagnosis confirmation at autopsy. If a goal of therapy for patients with dementia is to intervene before the disease has diminished cognitive function, imaging techniques or biomarkers must be capable of detecting AD pathology in asymptomatic individuals. The same consideration applies to DLB and FTD pathology. Even if a biomarker does not substantially enhance diagnostic precision in symptomatic patients, a biomarker with high sensitivity and specificity for a particular dementing disorder in symptomatic patients is one that could be of use in presymptomatic detection. The genomic identification of specific dementias and risk of their development offer prospects for future research.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use specific procedures. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all the circumstances involved.

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Appendix
Quality Standards Subcommittee Members: Gary Franklin, MD, MPH, Co-Chair; Catherine Zahn, MD, Co-Chair; Milton Alter, MD, PhD; Stephen Ashwal, MD; John Calverley, MD; Richard M. Dubinsky, MD; Jacqueline French, MD; Michael Glantz, MD; Gary Gronseth, MD; Deborah Hirtz, MD; Robert G. Miller, MD; James C. Stevens, MD, Facilitator; and William J. Weiner, MD.

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Annals of Internal Medicine | ARTICLE

Survival after Initial Diagnosis of Alzheimer Disease

Eric B. Larson, MD, MPH; Marie-Florence Shadlen, MD; Li Wang, MS; Wayne C. McCormick, MD, MPH; James D. Bowen, MD; Linda Teri, PhD; and Walter A. Kukull, PhD

Background: Alzheimer disease is an increasingly common condition in older people. Knowledge of life expectancy after the diagnosis of Alzheimer disease and of associations of patient characteristics with survival may help planning for future care.

Objective: To investigate the course of Alzheimer disease after initial diagnosis and examine associations hypothesized to correlate with survival among community-dwelling patients with Alzheimer disease.

Design: Prospective observational study.

Setting: An Alzheimer disease patient registry from a base population of 23 000 persons age 60 years and older in the Group Health Cooperative, Seattle, Washington.

Patients: 521 newly recognized persons with Alzheimer disease enrolled from 1987 to 1996 in an Alzheimer disease patient registry.

Measurements: Baseline measurements included patient demographic features, Mini-Mental State Examination score, Blessed Dementia Rating Scale score, duration since reported onset of symptoms, associated symptoms, comorbid conditions, and selected signs. Survival was the outcome of interest.

Results: The median survival from initial diagnosis was 4.2 years for men and 5.7 years for women with Alzheimer disease. Men had poorer survival across all age groups compared with females. Survival was decreased in all age groups compared with the life expectancy of the U.S. population. Predictors of mortality based on proportional hazards models included a baseline Mini-Mental State Examination score of 17 or less, baseline Blessed Dementia Rating Scale score of 5.0 or greater, presence of frontal lobe release signs, presence of extrapyramidal signs, gait disturbance, history of falls, congestive heart failure, ischemic heart disease, and diabetes at baseline.

Limitations: The base population, although typical of the surrounding Seattle community, may not be representative of other, more diverse populations.

Conclusions: In this sample of community-dwelling elderly persons who received a diagnosis of Alzheimer disease, survival duration was shorter than predicted on the basis of U.S. population data, especially for persons with onset at relatively younger ages. Features significantly associated with reduced survival at diagnosis were increased severity of cognitive impairment, decreased functional level, history of falls, physical examination findings of frontal release signs, and abnormal gait. The variables most strongly associated with survival were measures of disease severity at the time of diagnosis. These results should be useful to patients and families experiencing Alzheimer disease, other caregivers, clinicians, and policymakers when planning for future care needs.

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See editorial comment on pp 573-574.

Alzheimer disease is one of the leading causes of death in older people (1). One recent study suggests that 7.1% of all deaths in 1995 were attributable to Alzheimer disease, placing it on a par with cerebrovascular disease as the third leading cause of death (2). Estimates of predicted survival of persons who have received a diagnosis of Alzheimer disease should be useful for patients, caregivers, clinicians, and policy planners. Previous studies that relied on epidemiologic surveys had little opportunity to analyze clinical factors and also may not be generalizable to everyday clinical settings. Results from other studies that were based on convenience samples of persons from specialized Alzheimer disease centers are probably subject to referral bias. Our study design allowed us to estimate the magnitude of the reduction in age-adjusted life expectancy attributable to Alzheimer disease in a cohort of patients similar to those encountered in the clinical setting where Alzheimer disease is initially recognized.

It is not surprising that patients with Alzheimer disease probably have reduced survival compared with older persons without dementia (3–6). Certain characteristics, particularly male sex (7–11), initial dementia severity (5, 9, 12–17), presence of behavioral disturbances, wandering and falling (18), comorbid conditions (19), and presence of extrapyramidal signs (5, 20), are reported to be associated with decreased survival among patients with Alzheimer disease.

In 1987, we began a prospective observational study to investigate the natural history of persons with newly diagnosed Alzheimer disease in a community-dwelling population (21). This report describes overall survival and examines the association between factors hypothesized to affect survival in 521 patients with Alzheimer disease newly recognized between 1987 and 1996 and followed until time of death or 2001.

METHODS

Cases

From 1987 to 1996, an Alzheimer's disease patient registry enrolled persons receiving care in the Seattle and western King County clinics of the Group Health Cooperative (a well-established staff-model health maintenance organization with an enrollment population base age 60 years and older of 23 000) in Washington. The research protocol for this study was reviewed and approved by the health maintenance organization and the University of Washington's institutional review boards.

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Context

The prognosis in patients with Alzheimer disease may be associated with specific patient characteristics observed shortly after diagnosis.

Contribution

Severity of initial cognitive impairment and deterioration in the Mini-Mental State Examination score during the first year after diagnosis were strongly associated with decreased survival. Men had shorter survival than women across all age groups. Frontal lobe release signs, gait disturbances, falling, congestive heart failure, and diabetes were all associated with decreased survival.

Implications

Early appraisal of patients with Alzheimer disease may help set expectations and priorities for planning patient care.

–The Editors

The registry's objective was to identify all persons enrolled in the base population with newly recognized symptoms of possible dementia (for example, memory loss, confusion, or wandering). The goal of enrollment was to assemble a series of incident cases from a defined population, that is, possible patients with dementia who had presented for medical care within the health maintenance organization 1 year or less before enrollment in the registry. Study methods have been reported previously (4, 21). The following strategy was used to detect possible incident cases. Research associates systematically searched for patients with symptoms of memory loss, confusion, or wandering; for tests or treatments potentially indicative of dementia (by review of computed tomography and magnetic resonance imaging logbooks); for discharge diagnoses from the hospital information system; for logbook records of visits to neurology, geriatrics, and mental health clinics; for emergency department logs; and for computerized clinic treatment record files. In addition, primary care physicians were invited to refer suspected new cases for evaluation through brochures and mailings describing the registry. These primary care physicians also received a monthly newsletter describing clinical research advances in aging and dementia and reminding them of our study.

The process of patient identification through consensus diagnosis took an average of 12 weeks. A research assistant screened the medical charts of persons identified as potential cases. If the person's record contained any information indicating memory loss or other cognitive changes indicating that the person might have Alzheimer disease, the primary care physician was contacted to obtain permission to contact that person.

Persons who were judged to possibly have newly recognized dementia were contacted to request that they participate in the program. After we obtained informed consent, the research nurse interviewed the person and began collecting data, usually in the home. A psychometrist research assistant administered standard neuropsychological testing. Persons who agreed to participate in the registry underwent a complete, standardized physical and neurologic examination, administered by one of the study physicians, and the usual laboratory work-up (including neuroimaging) to rule out other causes of dementia and complicating illnesses. Chronology of symptoms was determined by study clinicians from interviews of the patient and informants and by review of medical records. The examining physician from the registry estimated the duration of symptoms before evaluation to the nearest year after resolving any discrepant information through further questioning and by relating time frames to the patient's life events. All eligible persons met criteria of the revised third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) for dementia and criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (22) for probable or possible Alzheimer disease at a consensus diagnosis conference that included at least 2 physicians (including the examining physician), a neuropsychologist, an epidemiologist, and study staff. On the basis of chart review, persons whose symptoms led to a diagnosis of dementia or Alzheimer disease more than 1 year before the time the registry detected them were excluded as not being incident cases. Of 1028 patients who consented to participate and who potentially could have been incident cases after chart review, 58 were excluded from the study before the standardized evaluation because of intervening death or acute illness.

A total of 970 participants identified with suspected dementia (from 1987 to 1996) were evaluated and followed annually. When discrepant findings or clinical course indicated a possible change from the initial diagnosis, we reevaluated the person according to the standardized protocol, which included an evaluation by a study physician to verify or modify the initial diagnoses. Persons initially classified with possible or probable Alzheimer disease but who were subsequently given a different diagnosis were excluded from these analyses. Persons with more than one cause of dementia (so-called *mixed dementia*) were excluded from these analyses. Of the individuals with suspected dementia (n = 970), 521 received a diagnosis of probable or possible Alzheimer disease (431 probable, 90 possible), 174 received diagnoses of other causes of dementia, and 237 did not meet DSM-III-R criteria for dementia within 18 months from their initial intake. The remaining 38 met diagnostic criteria of Alzheimer disease after at least 18 months of follow-up. Of the 174 persons with other causes of dementia, 74 were classified as having vascular dementia, 12 were classified as having alcohol-related causes, 54 were classified as having mixed and other causes (such as Parkinson disease or progressive supranuclear palsy), and 34 were classified as having unknown causes by

DSM-III-R criteria. Duration of survival was assessed annually. The dates of death were available for all study participants who died during the study period. Mean (±SD) follow-up time was 5.2 ± 3.1 years (range, 0.2 to 14 years).

The ethnic composition of the persons in the registry was 88% white, 8.7% black, and 3.3% Asian or Hispanic. The ethnic composition from the King County 1990 census was 84.8% white, 5.1% black, and 10.1% Asian or Hispanic. The overall ethnic composition of adults in the Group Health Cooperative was 90.2% white, 3.3% black, and 6.5% other.

Study Variables

The research nurse interviewed the patient and caregiver before scheduling an examination. The baseline information determined by questionnaire and physician interview included age (categorized as ≤75, 76 to 80, 81 to 85, and >85 years for analyses), sex (male vs. female), ethnicity (white, black, other), baseline systolic blood pressure (<110 mm Hg, 110 to 160 mm Hg, and ≥160 mm Hg), and education (<12 years, 12 years, >12 years, or unknown). As reported previously (4, 21), the severity of symptoms of Alzheimer disease was determined on the basis of the baseline Mini-Mental State Examination (MMSE) as continuous and categorical (≤17, 18 to 21, 22 to 24, or ≥25 points) variables (23) and baseline Dementia Rating Scale (DRS) as continuous and categorical (≤2, 2.5 to 3, 3.5 to 5, >5 points) variables (24).

Symptoms of dementia (for example, agitation, paranoia, and wandering) were assessed with the Revised Memory and Behavior Problems Checklist (25, 26). Physical signs of frontal release reflexes and other neurologic changes associated with dementia (for example, glabellar sign and grasp reflex) were categorized as present or not present by the examining physician. Study physicians assessed the presence or absence of rigidity on the basis of passive range of motion of the right and left elbow and wrist joints. The presence of a gait disorder was also determined through observation by the study physicians. All persons completed a general medical history and a review of systems questionnaire administered by a trained interviewer (4, 21). Comorbid conditions included hypertension, diabetes, ischemic heart disease, congestive heart failure, and history of strokes. Onset of symptoms, as estimated at the time of diagnosis, and the age at enrollment into the study were used to calculate the reported duration of disease symptoms (defined as <1, 1 to 3, or >3 years).

Statistical Analysis

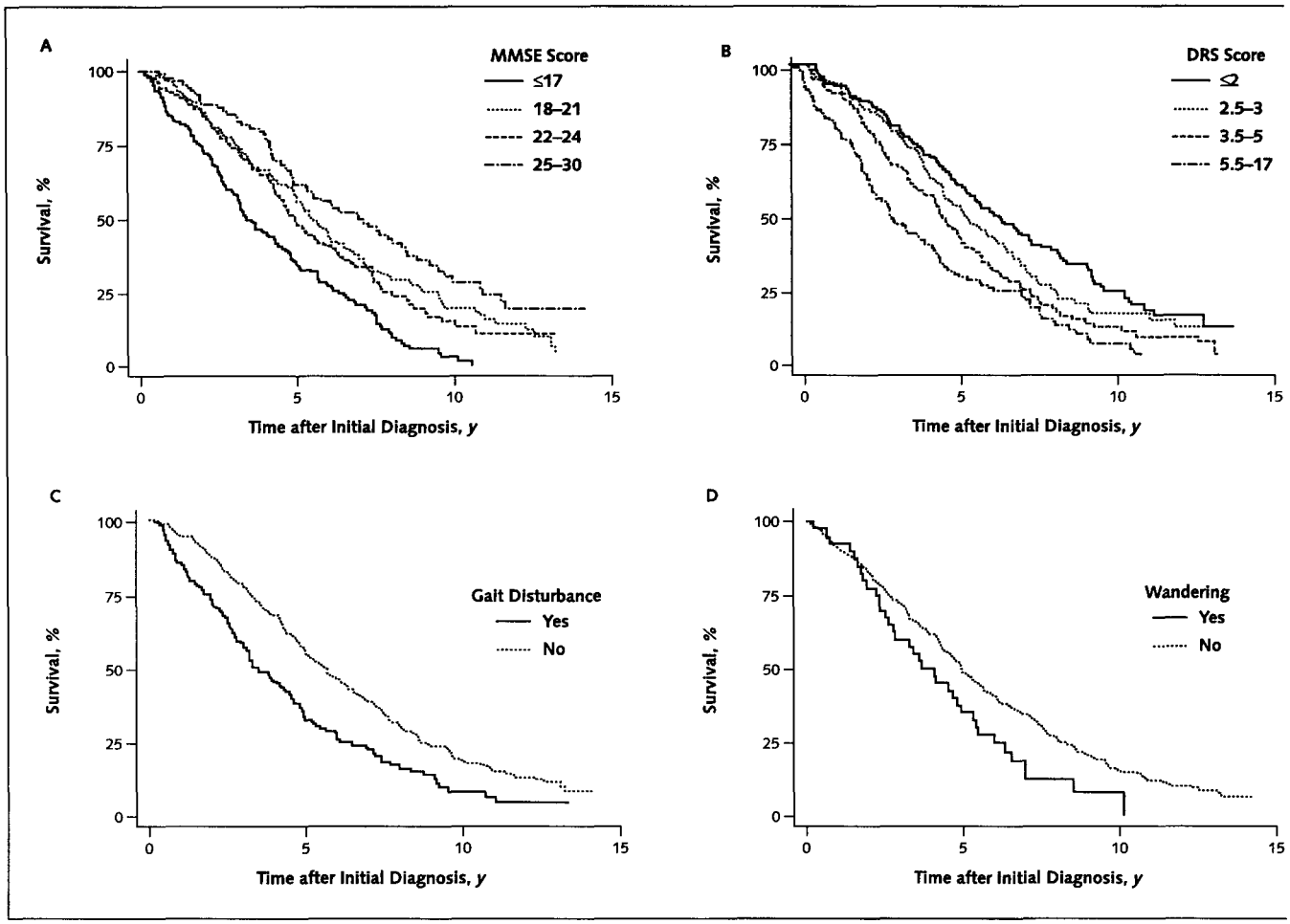
Our general hypothesis was that the severity of Alzheimer disease at the time of diagnosis, as measured by cognitive and functional measures as well as symptoms of dementia, would be associated with survival. The event time was the time of death. Persons who were still alive at the end of the study on 12 September 2001 were censored at that time. Survival time was defined as the time from the initial date of diagnosis of Alzheimer disease until the date of death or study conclusion. Patients who did not receive in-person follow-up were tracked for vital status through Group Health Cooperative records, informant reports, or local newspaper obituaries.

Variables investigated were 1) baseline MMSE score; 2) baseline DRS score; 3) psychiatric symptoms of paranoia or hallucinations at the time of evaluation; 4) behavioral disturbances, including agitation, irritability, or emotional lability; 5) frontal release signs, including glabellar, snout, or grasp; 6) extrapyramidal signs, including rigidity or tremor; 7) wandering; 8) falls; 9) gait disorder; 10) urinary incontinence; and 11) depression. Variables adjusted as potential confounders included 1) age, 2) sex, 3) ethnicity, 4) education, 5) ischemic heart disease, 6) congestive heart failure, 7) diabetes, 8) hypertension, and 9) stroke.

To describe associations of baseline factors with mortality, we calculated both proportions of patients who died and the time until death by baseline variables. Survival time quartiles were used to describe the time until death when 25%, 50%, and 75% of patients died. Log-rank tests were used for testing the equality of survival among groups. We compared the estimated life expectancy, expressed in quartiles, of patients with Alzheimer disease in the study sample with the reported life expectancy of the U.S. population by sex and age strata (27). Cox proportional hazards regression models were used to examine how baseline characteristics affected risk for death during the study period (28). The associations of predictors and mortality are estimated, with adjustments by age, sex, and ethnicity. We also adjusted for medical conditions that were found to be associated with survival and repeated analyses on the predictors of interest. Schoenfeld residual tests (29) were used to evaluate the proportional hazard assumption. If the assumption failed, time-varying covariates were introduced. To help illustrate the findings, Kaplan–Meier curves were estimated. All data were analyzed by using Stata software, version 7 (Stata Corp., College Station, Texas).

A secondary investigation of potential interest to clinicians was determining whether patients who had greater cognitive decline during the first year after diagnosis had a higher risk for dying after the first year. Greater decline during the first year was defined as a decrease of 5 or more points in MMSE score (that is, MMSE score at diagnosis [baseline MMSE score] minus MMSE score at the first year). This value was chosen a priori to reflect clinically meaningful cognitive decline (30). The Cox proportional hazards model was used to estimate the risk for dying by adjusting for baseline MMSE scores, age at diagnosis, sex, ethnicity, and comorbid conditions. The Schoenfeld residual test was used to evaluate the proportional hazards assumptions. Sensitivity analyses (Appendix, available at www.annals.org) were performed to evaluate potential biases that could be introduced because of missing data on follow-up MMSE scores and floor effect of low baseline MMSE scores. Logistic regression analyses were performed on the patients who had follow-up MMSE scores to ex-

Figure. **Kaplan–Meier survival estimates.**



A. By Mini-Mental State Examination (*MMSE*) score categories. B. By Dementia Rating Scale (*DRS*) categories. C. By presence or absence of gait disturbance. D. By presence or absence of wandering.

plore which baseline factors predict greater decline during the first year (**Appendix Table**, available at www.annals.org). On the basis of the risk factors for decline identified by logistic regression, we divided those with missing data on follow-up MMSEs into declined and nondeclined groups. Then, we repeated the Cox model to see whether any change in estimates resulted from adding those without follow-up MMSEs into the analytic sample. The **Appendix Figure** (available at www.annals.org) is a Kaplan–Meier survival graph of these results.

Role of the Funding Sources

The funding sources had no role in the design, conduct, or reporting of this study or in the decision to submit the manuscript for publication.

RESULTS

Table 1 shows quartile estimates of survival for patients with Alzheimer disease according to baseline characteristics. Median survival was longer for younger persons and women but did not vary by education level. Patients age 85 years and older, with gait disturbance, wandering, and comorbid diabetes and congestive heart failure had the poorest survival (median survival times were 3.2 years, 3.5 years, 4.1 years, 3.8 years, and 3.0 years, respectively; $P < 0.01$ for all comparisons [log-rank test]). Other predictors of decreased survival were male sex, lower MMSE score, higher (worse) DRS score, presence of frontal release signs, presence of extrapyramidal signs, history of falls, presence of urinary incontinence, history of ischemic heart disease, and history of stroke. Duration of survival among patients with Alzheimer disease did not differ by ethnicity, presence of hypertension, presence of psychiatric symptoms, presence of behavioral disturbances, presence of depression symptoms, or duration of dementia symptoms at the time of diagnosis.

Table 2 compares the life expectancy of patients with Alzheimer disease in this study with that of the U.S. population (27). Patients with Alzheimer disease at 70 years of age had a significantly decreased survival compared with the life expectancy of the U.S. population. Median survival

Table 1. **Baseline Characteristics and Survival of Alzheimer Disease Participants***

Variable	Patients	Patients Who Died	Survival Time Quartiles†			P Value‡
			25%	50%	75%	
	n	n (%)	←	y	→	
Age						
≤75 y	103	75 (73)	4.2	7.5	10.9	<0.001
76–80 y	137	105 (77)	3.1	5.6	8.5	
81–85 y	159	133 (84)	2.6	4.9	7.7	
>85 y	122	106 (87)	1.9	3.2	5.7	
Sex						
Male	180	160 (89)	2.3	4.2	6.3	<0.001
Female	341	259 (76)	3.1	5.7	9.0	
Ethnicity						
White	462	379 (82)	2.6	4.9	7.9	0.128
Black	38	25 (66)	3.7	6.0	9.0	
Other	21	15 (71)	2.3	4.9	13.1	
Education						
<12 y	156	125 (80)	2.6	4.4	7.7	>0.2
12 y	174	136 (78)	3.2	5.2	8.7	
>12 y	189	156 (83)	2.6	5.0	8.0	
MMSE score						
25–30	89	62 (70)	4.1	6.9	10.9	<0.001
22–24	125	96 (77)	3.2	5.5	8.0	
18–21	154	122 (79)	2.9	5.0	9.5	
≤17	152	138 (91)	2.0	3.6	6.5	
DRS score						
≤2	148	109 (74)	3.8	6.5	10.0	<0.001
2.5–3	119	91 (76)	3.5	5.6	8.3	
3.5–5	133	111 (83)	2.5	4.5	7.2	
5.5–17	121	108 (89)	1.7	3.2	6.3	
Psychiatric symptoms						
No	326	258 (79)	3.0	5.0	8.3	>0.2
Yes	195	161 (83)	2.3	4.8	8.0	
Behavioral change						
No	253	202 (80)	2.9	5.0	8.3	>0.2
Yes	268	217 (81)	2.6	4.9	8.0	
Frontal release signs						
No	253	190 (75)	3.2	5.6	8.8	0.002
Yes	229	194 (85)	2.3	4.6	7.3	
Extrapyramidal signs						
No	444	352 (79)	2.8	5.1	8.5	0.016
Yes	76	67 (88)	2.2	3.6	7.2	
Gait disturbance						
No	376	293 (78)	3.2	5.6	8.6	<0.001
Yes	144	125 (87)	1.9	3.5	6.1	
Wandering						
No	480	382 (80)	2.7	5.0	8.3	0.007
Yes	40	36 (90)	2.3	4.1	6.0	
Falls						
No	355	273 (77)	3.1	5.4	8.9	<0.001
Yes	162	142 (88)	2.1	4.3	6.8	
Urinary incontinence						
No	426	336 (79)	2.8	5.2	8.5	0.007
Yes	95	83 (87)	2.5	4.2	7.1	
Depression						
No	352	281 (80)	2.6	4.8	8.1	>0.2
Yes	166	135 (81)	3.1	5.3	8.0	
Duration of symptoms						
<1 y	99	73 (73)	3.2	5.3	9.2	0.188
1–3 y	299	241 (81)	2.6	4.8	8.0	
>3 y	119	101 (85)	2.7	5.0	7.4	
Ischemic heart disease						
No	380	293 (77)	3.2	5.4	8.6	<0.001
Yes	141	126 (89)	2.2	4.1	6.8	
Congestive heart failure						
No	461	365 (79)	3.0	5.2	8.5	<0.001
Yes	60	54 (90)	1.5	3.0	5.6	
History of strokes						
No	459	367 (80)	3.0	5.2	8.3	0.026
Yes	51	42 (82)	1.6	3.1	7.4	
Hypertension						
No	369	303 (82)	2.7	4.9	8.0	>0.2
Yes	152	116 (76)	2.6	5.0	8.3	
Diabetes						
No	477	379 (79)	2.8	5.1	8.3	0.004
Yes	43	39 (91)	2.3	3.8	6.3	

* DRS = Dementia Rating Scale; MMSE = Mini-Mental State Examination.
† Survival time quartiles describe the time until death when 25%, 50%, and 75% of patients died.
‡ The log-rank test was used to determine *P* values. The test was used to evaluate the equality of survival among groups.

Table 2. **Comparison of Life Expectancy by Quartiles of Study Participants and U.S. Population***

	Life Expectancy Quartiles†														
	Age 70 y			Age 75 y			Age 80 y			Age 85 y			Age 90 y		
	75%	50%	25%	75%	50%	25%	75%	50%	25%	75%	50%	25%	75%	50%	25%
	← y →														
Women															
U.S. population	21.3	15.7	9.5	17	11.9	6.8	13	8.6	4.6	9.6	5.9	2.9	6.8	3.9	1.8
Patients with Alzheimer disease (n = 341)	12.3	8.0	5.9	10.0	5.8	4.0	8.7	5.3	3.2	6.7	3.9	2.4	5.2	2.1	1.6
Men															
U.S. population	18	12.4	6.7	14.2	9.3	4.9	10.8	6.7	3.3	7.9	4.7	2.2	5.8	3.2	1.5
Patients with Alzheimer disease (n = 180)	5.1	4.4	3.1	7.2	4.5	2.3	6.8	3.6	2.2	5.0	3.3	2.3	4.9	2.7	0.9

* The source of the data on life expectancy in the U.S. population is cited in Walter LC and Covinsky KE (27).
† Life expectancy quartiles presented in the table correspond to upper, middle, and lower quartiles of estimated survival at each age–sex strata, that is, 75%, 50%, and 25% of the population will live less than the corresponding years listed, respectively.

time for women with Alzheimer disease at 70 years of age was 8.0 years compared with 15.7 years for the U.S. population. Survival time for the 50% quartile (median) for men at 70 years of age was 4.4 years compared with 9.3 years for the U.S. population. Across all age groups, men had poorer survival than women. At progressively older ages, the absolute survival difference between patients with Alzheimer disease and the U.S. population diminished. For example, survival time for the 50% quartile (median) for women at 85 years of age was 3.9 years compared with 5.9 years for the U.S. population. Survival time for the 50% quartile (median) for men at 85 years of age was 3.3 years compared with 4.7 years for the U.S. population. As expected, survival declined with age, but the decline for men with Alzheimer disease with increasing age was less than for women. Median life expectancy for men with Alzheimer disease was 4.4 years at 70 years of age versus 3.3 years at 85 years of age, and median life expectancy for women was 8.0 years at 70 years of age versus 3.9 years at 85 years of age.

Table 3 shows the hazard ratios of death according to the severity of symptoms and typical symptoms of dementia. Compared with the presence or absence of dementia signs and symptoms at baseline, measures of the severity of symptoms at the time of diagnosis were the strongest predictors of survival. The independent risk factors in proportional hazards models adjusted by age, sex, and ethnicity were low MMSE score, poor DRS score, presence of baseline frontal lobe release signs, presence of baseline gait disturbance, history of falls, congestive heart failure, history of diabetes, and history of ischemic heart disease. After adjustment for age, sex, ethnicity, ischemic heart disease, congestive heart failure, and diabetes, the presence of extrapyramidal signs and symptoms of wandering became more significant as independent risk factors for death. The hazard ratio of death for older age increased over time by an exponential factor. Comorbid conditions further reduced survival, with hazard ratios for death of 1.2 for ischemic heart disease, 1.3 for congestive heart failure, and 1.7 for diabetes.

A 5-point or greater decline in the MMSE score after the first year of follow-up was also associated with a significantly increased risk for death. The estimated hazard ratio for death in patients with a 5-point or greater decline in MMSE score was between 1.60 and 1.66 in 4 models controlling for age, baseline MMSE score, sex, ethnicity, ischemic heart disease, congestive heart failure, and diabetes. In sensitivity analyses, we found that the floor effect of low baseline MMSE scores led to slight underestimates of the hazard ratio of death for the declined group, but missing data on follow-up MMSE scores did not.

The **Figure** contains graphic illustrations of Kaplan–Meier survival curves by MMSE score category, DRS category, presence or absence of gait disorder, and presence or absence of wandering at baseline.

DISCUSSION

In all age groups, patients with Alzheimer disease in our study had decreased survival compared with survival in the general U.S. population (27). Men had a median survival of 4.2 years from their initial diagnosis, and women had a median survival of 5.7 years. Our findings differ from estimates of median survival from the onset of symptoms of dementia in the Canadian Study of Aging (3.17 years for men and 3.36 years for women) (3). The shorter survival estimates in the Canadian study could relate to 2 issues. First, the patients in that study were older (average age, 83.8 years); second, because the study dealt with a population-based prevalence sample, it included a relatively greater proportion of persons with severe dementia and nursing home residents who were at later stages in the course of the natural history of this progressive disease (3). Also, sex was not associated with Alzheimer disease survival in the Canadian study (3). By contrast, we found the median life expectancy for a 70-year-old man with Alzheimer disease to be 4.4 years compared with 8.0 years for a woman of the same age with Alzheimer disease. This sex gap narrowed at more advanced ages. Our findings are

Table 3. **Hazard Ratios for Death by Mini-Mental State Examination Scores, Dementia Rating Scale Scores, and Associated Symptoms***

Variable	Multivariate Analysis Adjusted by Age,† Sex, and Ethnicity		Multivariate Analysis Adjusted by Age,† Sex, Ethnicity, Ischemic Heart Disease, Congestive Heart Failure, and Diabetes	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
MMSE score				
25–30	1		1	
22–24	1.41 (1.02–1.95)	0.039	1.40 (1.01–1.94)	0.042
18–21	1.67 (1.23–2.28)	0.001	1.69 (1.24–2.31)	0.001
≤17	2.58 (1.88–3.53)	<0.001	2.67 (1.94–3.66)	<0.001
DRS score				
≤2	1		1	
2.5–3	1.18 (0.89–1.56)	>0.2	1.12 (0.84–1.48)	>0.2
3.5–5	1.52 (1.16–1.99)	0.002	1.51 (1.15–1.98)	0.003
5.5–17	2.15 (1.62–2.84)	<0.001	2.04 (1.54–2.71)	<0.001
Psychiatric symptoms				
No	1		1	
Yes	1.08 (0.88–1.32)	>0.2	1.06 (0.86–1.29)	>0.2
Behavioral change				
No	1		1	
Yes	1.02 (0.84–1.24)	>0.2	0.98 (0.81–1.20)	>0.2
Frontal release signs				
No	1		1	
Yes	1.26 (1.03–1.54)	0.026	1.27 (1.03–1.55)	0.022
Extrapyramidal signs				
No	1		1	
Yes	1.28 (0.98–1.67)	0.067	1.35 (1.03–1.76)	0.028
Gait disturbance				
No	1		1	
Yes	1.50 (1.20–1.87)	<0.001	1.40 (1.12–1.76)	0.004
Wandering				
No	1		1	
Yes	1.41 (0.99–2.01)	0.060	1.45 (1.02–2.08)	0.040
Falls				
No	1		1	
Yes	1.30 (1.05–1.60)	0.015	1.22 (0.98–1.51)	0.069
Urinary incontinence				
No	1		1	
Yes	1.29 (1.00–1.65)	0.047	1.22 (0.95–1.57)	0.120
Depression				
No	1		1	
Yes	0.96 (0.78–1.18)	>0.2	0.94 (0.76–1.16)	>0.2
Duration of symptoms				
<1 y	1		1	
1–3 y	1.35 (1.04–1.76)	0.026	1.30 (0.998–1.70)	0.051
>3 y	1.28 (0.94–1.73)	0.115	1.23 (0.90–1.66)	0.193
Ischemic heart disease				
No	1			
Yes	1.30 (1.05–1.61)	0.017		
Congestive heart failure				
No	1			
Yes	1.48 (1.10–1.99)	0.010		
History of stroke				
No	1			
Yes	1.21 (0.87–1.67)	>0.2		
Hypertension				
No	1			
Yes	0.96 (0.77–1.19)	>0.2		
Diabetes				
No	1			
Yes	1.87 (1.34–2.61)	<0.001		

* DRS = Dementia Rating Scale; MMSE = Mini-Mental State Examination.
† Age, defined as the age at diagnosis of Alzheimer disease, was used as the time-varying covariate in the model (Age(t) = age exp(0.03 t)).

consistent with previous reports that men with Alzheimer disease have approximately half the life expectancy estimated for women with Alzheimer disease (5, 7, 9–11, 31). Our sample and study design are arguably more typical of the persons clinicians see in everyday medical practice and who may be recognized as having typical symptoms and

signs of dementia. Our results are also consistent with our previously reported average survival from study entry (5.3 years) in a consecutive outpatient (convenience) sample of patients with existing Alzheimer disease in King County, Washington (18).

As reported previously, the association between measures of the severity of Alzheimer disease symptoms and survival was strong (5, 9, 12–17). We found that the effect of cognitive performance scores and dementia severity scores on survival remained significant even after adjustment for age, sex, ethnicity, and presence of vascular comorbid conditions. Comorbid conditions, such as a history of diabetes, congestive heart failure, and ischemic heart disease, reduced survival of patients with Alzheimer disease in this cohort, with hazard ratios of 1.7, 1.3, and 1.2, respectively. In addition, survival was reduced by the symptoms and signs of the disease. Few studies of similar design have taken into account the influence of possible confounders, such as vascular disease comorbid conditions, on estimates of survival in Alzheimer disease.

The data in **Table 2** can be used as a reference to estimate age- and sex-adjusted life expectancy for patients with Alzheimer disease. The information in **Table 3** can be used to estimate additional reductions in survival on the basis of the presence or absence of other signs and symptoms of dementia. A recent report also showed that the presence of a gait disorder was associated with increased risk for death in older persons (32). The presence of extrapyramidal signs can be a manifestation of Lewy body disease. Without neuropathologic data, we cannot rule out the possibility that some of our patients might have had concomitant Lewy body disease. Although symptoms of agitation, irritability, emotional lability, paranoia, or hallucinations affect the quality of life of patients with Alzheimer disease, survival did not differ among patients with or without these symptoms in our study. The relationship of psychiatric or behavioral symptoms and Alzheimer disease mortality has been difficult to study because of the variability of presentation of these symptoms during the natural history of the disease. Patients with early dementia can present with behavioral symptoms, such as wandering, that subside at later stages of the disease when mobility is diminished. Conversely, patients without behavioral symptoms at initial presentation can develop paranoid ideations and delusions at a later course of their illness. By only examining the influence of baseline psychiatric symptoms on the outcome of interest, we may not have captured the dynamic interactions of change in the frequency and intensity of behavioral symptoms on survival.

We believe that our observations, if confirmed, would be of great interest to patients with Alzheimer disease and family members making plans for future care needs.

The strengths of this study are the ability to examine demographic factors, signs and symptoms of dementia, measures of the severity of symptoms, and the presence of comorbid conditions in a community-based cohort. The study had a large sample size and relatively long duration of follow-up. We must caution, however, that this health maintenance organization–based sample may not be representative of patients with Alzheimer disease in the U.S. population as a whole, although the demographic features of the sample do resemble those of the surrounding Seattle community. We think that the lack of association between duration of dementia symptoms and survival reflects the variability of self-reports and informant reports of duration for an illness that is typically insidious in onset and often difficult to distinguish from age-related decline. These measurement errors would bias the results toward the null. It would be useful to analyze the interrelationships of comorbid conditions and the actual cause of death for our participants. However, we do not have reliable data on causes of death. Because of the study design, we could not evaluate the potential confounding effect of use of drugs with potential psychiatric effects in this cohort.

The most powerful predictors of reduced survival were a poor score on the MMSE and increased Alzheimer disease–related functional impairment, as measured by the DRS. Baseline psychiatric symptoms or behavioral disturbances were not strongly associated with survival. The conventional wisdom that persons with Alzheimer disease who experience a rapid decline in cognitive performance in the first year will have a more malignant course is confirmed by our findings that an MMSE score decline of 5 points or more at 1 year of follow-up was associated with a 60% increased risk for death. Our findings suggest that a straightforward clinical evaluation consisting of the patient's history, a cognitive screening test, functional assessment from an informant, and a careful neurologic examination can detect features associated with prognosis for survival of patients with Alzheimer disease typically seen in clinical practice.

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Requests for Single Reprints: Eric B. Larson, MD, MPH, Center for Health Studies, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101-1448; e-mail, larson.e@ghc.org.

Current author addresses and author contributions are available at www.annals.org.

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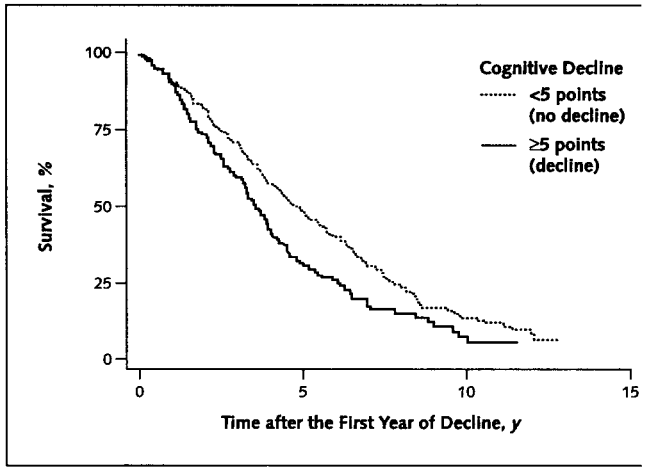
Appendix: Sensitivity Analysis

Sensitivity analyses were performed to examine potential biases that may have been introduced because of the inability to observe a decline in patients with no follow-up MMSE scores and in patients who had very low baseline MMSE scores. Sixty-two patients survived for more than 1 year but did not have follow-up MMSEs. Logistic regression analyses were performed on the patients who had follow-up MMSE scores to explore which baseline factors predict significant cognitive decline during the first year. We found that only the baseline MMSE score was a significant predictor for the first year decline. Patients with baseline MMSE scores between 10 and 20 were 2 times more likely (odds ratio, 2.16 [95% CI, 1.43 to 3.27]; $P < 0.001$) to decline during the first year than were the patients with baseline MMSE scores between 21 and 30. Therefore, on the basis of their baseline MMSE scores, we classified patients who had survived for more than 1 year but without follow-up MMSE scores (62 patients) into declined (22 patients) or nondeclined (40 patients) groups. Cox regression models, in which analysis time was truncated at the first year of follow-up, were performed on 4 different analytic samples. Model 1 was performed on declined (146) and nondeclined (273) patients; model 2 was performed on declined (144) and nondeclined (267) patients with baseline MMSE scores greater than 8; model 3 was performed on declined (146) patients, nondeclined (273) patients, and those without follow-up MMSE scores who survived for more than 1 year (62); and model 4 was performed on patients who were included in model 3 but who had baseline MMSE scores greater than 8 (267 nondeclined patients, 144 declined patients, and 56 patients with no follow-up). Results are presented in the **Appendix Table**. The floor effect (that is, patients who reached the low end of MMSE scoring at baseline and who were unable or less likely to decline at follow-up) leads to slightly underestimating the risk for dying for the declined group. The follow-up MMSE data on 62 patients that were missing at the 1-year follow-up were not found to bias the estimated risk for dying for the declined group. We note that of the 102 patients with no follow-up MMSE scores, 40 (39.2%) died during the first year after receiving a diagnosis of Alzheimer disease. The 40 patients who died earlier might have declined faster but were not observed during the first year. Thus, follow-up MMSE data on these patients could not be used in this analysis.

Appendix Figure. **Kaplan–Meier survival estimates by cognitive decline.**



Current Author Addresses: Dr. Larson: Center for Health Studies, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101-1448.
Drs. Shadlen and McCormick: Division of Gerontology and Geriatric Medicine, University of Washington School of Medicine, Harborview Medical Center, 325 9th Avenue, Box 359755, Seattle, WA 98104-2499.
Ms. Wang: Division of General Internal Medicine, University of Washington Medical Center, 4225 Roosevelt Way NE, Suite 301, Box 354691, Seattle, WA 98105.
Dr. Bowen: Department of Neurology, University of Washington School of Medicine, 1959 NE Pacific Street, Box 356465, Seattle, WA 98195.
Dr. Teri: Department of Psychosocial and Community Health, University of Washington School of Nursing, 9709 3rd Avenue NE, Suite 507, Seattle, WA 98115-2053.
Dr. Kukull: Department of Epidemiology, University of Washington School of Public Health, 4311 11th Avenue NE, Suite 300, Seattle, WA 98105.

Author Contributions: Conception and design: E.B. Larson, M.-F. Shadlen, L. Wang, J.D. Bowen, L. Teri, W.A. Kukull.
Analysis and interpretation of the data: E.B. Larson, M.-F. Shadlen, L. Wang, W.C. McCormick, L. Teri, W.A. Kukull.
Drafting of the article: E.B. Larson, M.-F. Shadlen, L. Wang, W.C. McCormick.
Critical revision of the article for important intellectual content: E.B. Larson, M.-F. Shadlen, L. Wang, W.C. McCormick, J.D. Bowen, L. Teri, W.A. Kukull.
Final approval of the article: E.B. Larson, M.-F. Shadlen, L. Wang, W.C. McCormick, J.D. Bowen, L. Teri, W.A. Kukull.
Provision of study materials or patients: E.B. Larson, W.C. McCormick, J.D. Bowen, L. Teri, W.A. Kukull.
Statistical expertise: L. Wang.
Obtaining of funding: E.B. Larson, L. Teri, W.A. Kukull.
Administrative, technical, or logistic support: E.B. Larson, W.C. McCormick, L. Teri.
Collection and assembly of data: E.B. Larson, L. Wang, L. Teri, W.A. Kukull.

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Appendix Table. **Hazard Ratios for Death on the Basis of Greater Cognitive Decline at 1 Year of Follow-up***

Variable	Model 1 Hazard Ratio (95% CI)	Model 2 Hazard Ratio (95% CI)	Model 3 Hazard Ratio (95% CI)	Model 4 Hazard Ratio (95% CI)
First year decline in MMSE score				
<5 points	1	1	1	1
≥5 points	1.61 (1.28–2.03)	1.65 (1.31–2.08)	1.60 (1.29–1.99)	1.66 (1.33–2.07)
Baseline MMSE score	0.95 (0.93–0.97)	0.94 (0.92–0.97)	0.94 (0.93–0.96)	0.94 (0.92–0.96)
Age at diagnosis	1.05 (1.03–1.07)	1.05 (1.04–1.07)	1.04 (1.03–1.06)	1.05 (1.03–1.07)
Sex				
Male	1	1	1	1
Female	0.56 (0.45–0.71)	0.58 (0.46–0.73)	0.56 (0.45–0.70)	0.57 (0.46–0.71)
Ethnicity				
White	1	1	1	1
Black	0.64 (0.40–1.02)	0.59 (0.36–0.95)	0.67 (0.44–1.04)	0.63 (0.40–0.99)
Other	0.77 (0.41–1.42)	0.77 (0.42–1.43)	0.71 (0.40–1.28)	0.72 (0.40–1.29)
Ischemic heart disease				
No	1	1	1	1
Yes	1.26 (0.99–1.62)	1.29 (1.01–1.67)	1.26 (0.996–1.59)	1.30 (1.02–1.64)
Congestive heart failure				
No	1	1	1	1
Yes	1.22 (0.86–1.75)	1.18 (0.83–1.70)	1.27 (0.91–1.77)	1.22 (0.87–1.64)
Diabetes				
No	1	1	1	1
Yes	1.97 (1.32–2.95)	1.98 (1.32–2.96)	1.75 (1.22–2.50)	1.69 (1.17–2.45)

* MMSE = Mini-Mental State Examination.

Research evaluation and diagnosis of probable Alzheimer's disease over the last two decades: I

O.L. Lopez, MD; J.T. Becker, PhD; W. Klunk, MD; J. Saxton, PhD; R.L. Hamilton, MD; D.I. Kaufer, MD; R.A. Sweet, MD; C. Cidis Meltzer, MD; S. Wisniewski, PhD; M.I. Kamboh, MD; and S.T. DeKosky, MD

Article abstract—*Objective:* To describe the experience of a research clinic diagnosing AD during the last two decades, with special emphasis on patients who meet the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD, their patterns of clinical presentation, and neuropathologic outcomes. *Background:* Probable AD has a heterogeneous clinical presentation, and can occur in the context of complicating factors. There are few reports, and none with this large of a sample, about the pattern of presentation, the nature of comorbidities, and the sensitivity and specificity of diagnosis. *Results:* The AD Research Center of Pittsburgh examined 1139 patients with probable AD between April 1983 and February 2000. Of these 1139 probable AD patients, 29 (2.5%) had slow progression, 27 (2%) had rapid progression, 70 (6%) had an atypical presentation, and 85 (7%) had coexistent cerebrovascular disease. Confluent periventricular white matter lesions were found in 348 (30.5%) patients with probable AD. The overall sensitivity for the diagnosis of AD was 97% and the specificity 80%. However, the accuracy for the diagnosis of AD varied over the years: from 1983 to 1989, the sensitivity was 94% and specificity 52%, and from 1990 to 2000, the sensitivity was 98% and specificity 88%. *Conclusion:* Although the diagnosis of probable AD has been used to indicate the presence of a homogeneous clinical entity, these patients can vary in presentation, onset, or clinical course. This finding is of particular importance for the understanding of the pathophysiologic basis of the disease, and for the better identification of responders to dementia treatments. Although the sensitivity for the diagnosis of AD remained above 90% over the last two decades, the specificity increased, reflecting progressive improvement in the diagnosis of other dementing disorders.

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The rapid increase in life expectancy in the population over the last two decades and the demographic shifts to occur over the next several decades will result in an epidemic number of adults with neurodegenerative processes that cause dementia. Population studies have found that up to 10% of individuals age 65 or older can have dementia, especially AD.[1] In anticipation of this, in the early 1980s, a significant scientific effort was initiated with the aim of understanding the neurologic, psychiatric, neuropsychological, psychosocial, and neuropathologic characteristics of dementing processes in the adult. The National Institute on Aging funded several centers for the study of AD and related dementias in the United States. Initially, the purpose of these research programs was to evaluate the full spectrum of clinical factors that could relate to the differential diagnosis of the illness and the natural history of the disease. At that time, there was no clear consensus on the specific clinical characteristics or clinical variability of AD, and diagnostic accuracy was considered of critical importance in anticipating possible future treatments. Accurately classified patients and controls followed longitudinally by research clinicians represent the ultimate test for therapies developed in vitro and in experimental animals.

One of the most important advances in the study of AD was the development of research diagnostic clinical criteria (e.g., Diagnostic and Statistical Man-

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From the Alzheimer's Disease Research Center (Drs. Lopez, Becker, Klunk, Saxton, Hamilton, Kaufer, Sweet, Wisniewski, Kamboh, and DeKosky) and the Departments of Psychiatry (Drs. Lopez, Becker, Klunk, Saxton, Kaufer, Sweet, and DeKosky), Neurology (Drs. Lopez, Becker, Kaufer, and DeKosky), Pathology (Neuropathology) (Dr. Hamilton), Radiology (Dr. Meltzer), Epidemiology (Dr. Wisniewski), and Genetics (Dr. Kamboh), University of Pittsburgh School of Medicine, PA.

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Address correspondence and reprint requests to Dr. Oscar L. Lopez, Neuropsychology Research Program, Oxford Building, 3501 Forbes Avenue, Suite 830, Pittsburgh, PA 15213.

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ual of Mental Disorders, third edition [DSM-III],[2] DSM-III-R,[3] DSM-IV,[4] and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA][5]) that increased accuracy of the diagnosis relative to neuropathologic examination.[6-9] These criteria have been the gold standard of diagnostic classification for clinical research, on which molecular biology, genetic, and drug studies have been based. The most frequently used criteria for the diagnosis of AD are those of the NINCDS-ADRDA.[5] These criteria classify AD based on degree of certainty and whether AD is associated with other disease processes. The diagnosis of *probable* AD indicates that in the clinician's view there is no other cause for the presence of dementia other than AD. *Possible* AD indicates that the typical syndrome is present, but there are variations in the onset, presentation, or clinical course, or systemic or other brain disorders sufficient to produce dementia; or when a single, gradually progressive, severe cognitive deficit is identified in the absence of other identifiable cause.

Although the diagnosis of probable AD may imply a homogeneous clinical entity, these patients can vary in presentation, onset, or clinical course.[10-14] However, the frequency of these subgroups, as well as the operationalization of the clinical criteria to classify these patients, have never been described. Therefore, in this report, we describe the neuropsychiatric characteristics of the Pittsburgh Alzheimer's Disease Research Center (ADRC) cohort, with especial emphasis on probable AD and its subgroups. In addition, we examine the accuracy of the clinical diagnosis in a subgroup of patients who had neuropathologic examination.

Materials and methods. We report here the clinical diagnosis as well as the demographic and neuropsychiatric characteristics of 2000 subjects examined at the ADRC of Pittsburgh. The first 316 subjects in the registry were entered through the Alzheimer's Research Program (AG-03705) between April 1, 1983, and October 30, 1985, and the remaining subjects through the ADRC (AG-05133) from November 1, 1985, to December 12, 1999. Each participant, patient and control subject alike, received an extensive neuropsychiatric evaluation including medical history and physical examination, neurologic history and examination, semistructured psychiatric interview, and neuropsychological assessment.

Each individual was interviewed by a psychiatric nurse to identify any physical and cognitive limitations, as well as the caregiving burden to their primary caregiver. Each subject also underwent various laboratory studies, including a standard battery of hematologic studies, blood chemistries, liver and thyroid function tests, vitamin levels, and rapid plasmin reagin (RPR) test. Each participant had a CT scan of the head (before October 1986) or an MRI scan. When clinically indicated, single photon emission tomography of the brain, ^{131}Xenon cerebral blood flow, PET, EEG, and/or CSF studies were completed. Each individual set of results was reviewed by the study team (neurologists, neuropsychologists, and psychiatrists) at a clinical consensus conference. *APOE* genotyping was performed in all available individuals, but their information was not presented at the consensus conference.

Clinical assessment. Neurologic examination. The neurologic examination was performed by both a neurologist and a physician assistant (PA) trained in medical examination of individuals with dementia and the elderly. Each abnormal sign detected by the PA was corroborated by the neurologist. The neurologic examination included assessments of buccolingual and limb praxis, motor impersistence, dressing praxis, cranial nerves, motor tone and abnormal movements, deep tendon reflexes, plantar response, primary sensory testing, stereognosis and graphesthesia, cerebellar testing, release signs, gait abnormalities, and peripheral pulses (including carotid auscultation). The neurologists and the PA completed the New York University (NYU) Scale for Parkinsonism[15] and the Hachinski Rating Scale (HRS).[16]

Neuropsychological examination. The neuropsychological assessment included the Mini-Mental State Examination (MMSE),[17] the Mattis Dementia Rating Scale (MDRS),[18] and the Clinical Dementias Rating (CDR).[19] These global measures were complemented by Copy and Recall of a figure,[20,21] the Benton Visual Form Discrimination Test,[22] Category fluency test,[23] and Digit spans.[24]

Psychiatric examination. The psychiatric evaluations were conducted by geriatric psychiatrists using a semistructured interview,[25] which encompassed the DSM-III-R[3] Axis I disorders. From 1991 on, all subjects were also assessed with the Consortium to Establish a Registry for AD (CERAD) Behavioral Rating Scale.[26] Reliability of each item of the CERAD Behavioral scale ranged from 60% to 85% (substantial to near-perfect agreement) among the psychiatrists. In addition, the Hamilton Depression Rating Scale (HDRS)[27] and the Blessed Dementia Rating Scale for activities of daily living[28] interviews were completed by the psychiatrist on the basis of data from each patient and primary caregiver. Following psychiatric assessments, diagnoses of psychiatric symptoms are currently made according to the DSM-IV.[4] Patients examined before the publication of the DSM-IV were classified according to the DSM-III[2] and DSM-III-R.[3] These diagnoses are reviewed annually on each patient, and modified according to the DSM-IV, when necessary.

Periventricular white matter lesions (PWML). Details of the grading of white matter lesions as well as comparisons between CT and MRI findings have been described previously.[29] For the purpose of our registry entry, the severity of the lesions was classified with respect to the extension (using MRI) or severity (using CT). Patients were classified as having "deep" white matter lesions when they had at least one confluent subcortical periventricular lesion in the MRI or severe radiolucency in at least one area of the brain detected by CT scan.

Inclusion/exclusion criteria. Inclusion criteria. Inclusion criteria included progressive cognitive deficits, age ≥ 40 years, native English speaker, adequate visual and auditory acuity to complete neuropsychological testing, and reliable caregiver capable of providing correct information about the patient's clinical symptoms.

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Exclusion criteria. Exclusion criteria were lifetime history of schizophrenia, manic-depressive disorder, or schizoaffective disorder; history of electroconvulsive therapy; current alcohol or drug abuse/dependence; history of alcohol or drug abuse/dependence within 2 years of the onset of the symptoms of dementia; history of cancer within the previous 5 years; and any significant disease or unstable medical condition that could affect neuropsychological testing (i.e., chronic renal failure, chronic hepatic disease, severe pulmonary disease).

Dementia criteria. The diagnosis of dementia was based on a progressive cognitive deterioration, in the absence of reversible causes of cognitive impairment, and history of normal intellectual function before the onset of cognitive abnormalities. Patients were required to have impairments in two cognitive domains, which did not necessarily include memory. This diagnosis was supported by a MDRS of ≤ 135, a MMSE of ≤ 26, and a CDR of ≥ 0.5. Patients with "normal" scores in global measures of dementia and other neuropsychological testing, but with documented decline in their activities of daily living due to a suspected cognitive deficit, were further examined with more detailed clinical neuropsychological testing.

Diagnostic criteria. For the purpose of this report, we have simplified the cohort classification to six categories: probable AD, possible AD, vascular dementia (VaD), other dementia, not demented, mild cognitive impairment (MCI), and control.

Probable AD. To be diagnosed with probable AD, the patient must have had a gradual cognitive decline without history or evidence of illness that could cause mental impairment other than AD. There could be no focal CNS lesions, based on clinical or neuroimaging criteria. We further classified these patients into three subgroups:

1. *Probable AD with atypical onset or presentation*: These were subjects whose initial clinical symptoms suggested prominent dysfunction in one cognitive domain. For example, patients must have had significant "posterior" deterioration (e.g., Balint's syndrome,[10] visuoconstructional/visuospatial deficits,[11] hemispatial neglect[12]), disproportionate language deficits,[13] or a significant frontal lobe syndrome.[14]

2. *Probable AD with atypical course*: These were subjects whose clinical symptoms a) progressed rapidly (more than 10 points in MMSE score per year) in the absence of other systemic or neurologic causes or b) remained at a plateau for at least 3 years.[30]

3. *Probable AD with cerebrovascular disease (CVD)*: These were subjects who had a) a single "silent" ischemic lesion that could be observed in two cuts of the MRI, or in one cut of the CT scan of the brain; b) clinical symptoms that suggested a TIA or stroke, in the absence of ischemic lesions in neuroradiologic studies, and the cerebrovascular event did not leave any motor sequelae; or c) brief syncopal episodes, with neuroradiologic studies showing a single small ischemic lesion, but with a normal neurologic examination. This group does *not* include patients who experienced brief episodes of aphasia or transient global amnesia, even if neuroradiologic studies did not show ischemic lesions; these patients were classified as possible AD with CVD.

The diagnosis of *possible AD* was based on a history of progressive dementia consistent with AD, but with clinical evidence of some other disease process that might have contributed to the patient's cognitive symptomatology. This group included patients with CVD, head injury, depression, alcoholism, hypothyroidism, vitamin B12 deficiency, and a history of encephalitis. Details of each category are described in the accompanying report.[31]

VaD. These were patients with clinical and/or radiologic evidence of cerebral infarctions contributing to dementia in which concomitant processes other than CVD were excluded, and when the dementia syndrome followed a recognized cerebrovascular event. This group also included patients in whom there was no clear temporal relationship between stroke and dementia, or who had a subtle onset and variable course, but with evidence of relevant CVD (from neuroimaging studies). For those patients with a less clear relationship between stroke and dementia, we required at least two ischemic episodes by history, with a positive neurologic examination or neuroimaging studies. Based on the characteristics of CVD and its relationship to cognitive functions, these patients would have met the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l'Enseignement en Neurosciences criteria for probable VaD,[32] although these criteria were not used at the time of our initial classification. The HRS[16] score was not used as an absolute criterion for diagnosing VaD, because it is not specific to this condition,[33] but a low HRS (e.g., ≤ 4) heavily weighed against the diagnosis of VaD in the consensus conference.

Other dementias. This group included patients with 1) other neurodegenerative dementias, 2) metabolic disorders (e.g., thyroid disease), 3) infectious/transmissible syndromes (e.g., Creutzfeldt–Jakob disease), 4) the dementia syndrome of depression, 5) head trauma encephalopathy, and 6) dementia not otherwise specified.

Not demented subjects. These were patients who were initially diagnosed as demented, but whose symptoms reverted after treatment (e.g., depression, thyroid disease), or patients with history suggesting dementia, but in whom clinical examination did not confirm this presumption. None of these patients took dementia medication (e.g., tacrine, donepezil).

MCI. These were patients with an isolated deficit in recent memory function, or in other cognitive domain, or those who had documented progressive deterioration in at least two cognitive domains, in the absence of other condition that may have caused dementia, but who had not crossed the threshold for dementia. Details of the clinical criteria for MCI and the characteristics of this cohort will be reported in a separate publication.

Controls. These subjects were recruited from the community through newspaper advertisements and by word-of-mouth. In some cases, the spouses and family members of demented patients participated as controls. None of these individuals had memory problems, and all of them had normal performance on neuropsychological testing.

Neuropathologic diagnosis. The neuropathologic diagnosis of AD was based on the CERAD neuropathologic criteria,[34] and these cases were also reviewed for application of the National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of AD.[35]

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Table 1 Number of patients, age, sex, education level, and duration of symptoms

Diagnosis	No. of Patients	Age, y	Sex (%)		Education level, y	Duration of symptoms, y
			Women	Men		
Probable AD	1139	72.8 ± 8.1	786 (70)	343 (30)	12.0 ± 3.0	3.9 ± 2.6
Possible AD	267	73.8 ± 7.3	150 (58)	113 (42)	11.6 ± 2.7	3.8 ± 2.7
Vascular dementia	52	73.4 ± 7.3	27 (52)	25 (48)	11.3 ± 3.2	3.8 ± 2.8
Other dementias	108	66.7 ± 11.1	53 (50)	54 (50)	12.7 ± 3.5	3.4 ± 2.9
Not demented	71	64.9 ± 10.7	40 (58)	30 (42)	14.1 ± 3.5	2.7 ± 2.4
Mild cognitive impairment	110	69.9 ± 9.9	60 (56)	48 (44)	13.8 ± 3.1	2.3 ± 1.7
Controls	253	64.8 ± 9.5	157 (62)	96 (38)	14.2 ± 2.9	NA

Values are mean ± SD or n (%).

NA = not applicable.

Results. The demographic, neuropsychological, neurologic, and psychiatric characteristics of the study sample are shown in tables 1 and 2. The cases with rapid or slow progression, with atypical presentation, or with CVD were compared with 680 probable AD patients without these characteristics, and without confluent PWML (table 3). The cases with slow progression were more likely to be men, had longer duration of symptoms, and had better MMSE, MDRS, CDR, BDRS, and NYU scale scores. Probable AD patients with rapid progression were younger, and had lower MMSE, MDRS, BDRS, and CDR scores. Patients with atypical presentation were younger and better educated (table 4). Patients with CVD were older, had higher HRS scores, and had more ischemic heart disease and hypertension than patients with probable AD without CVD (see table 4).

Probable AD with subcortical white matter lesions. A total of 348 (30.5%) probable AD patients had confluent subcortical white matter lesions. These patients were older, less educated, had higher HRS and NYU scale scores, and had more ischemic heart disease and hypertension than those without such lesions (table 5).

APOE *genotypes and allele frequency.* *APOE* genotypes and allele frequency were examined in 1082 subjects (617 probable AD, 113 possible AD, 13 VaD, 66 other dementia, 33 not demented, 76 MCI, and 164 controls). The percentage of homozygotes for the *APOE**4 allele in each group was probable AD 10%, possible AD 12%, VaD 8%, other dementias 0%, not demented 3%, MCI 8%, and controls 7%. The *APOE**4 allele frequency in each group was probable AD 0.29, possible AD 0.35, VaD 0.19, other dementia 0.15, not demented 0.12, MCI 0.30, and controls 0.17. The frequency of the *APOE**4 allele was similar among the probable AD subgroups (rapid progression 0.27, slow progression 0.26, atypical presentation 0.28, CVD 0.25, PWML 0.27).

The association of AD with the *APOE**4 allele was analyzed with a logistic regression analysis adjusted by age, using the non-*APOE**4 genotypes as reference. The *APOE**4 allele was significantly more frequent in probable AD (relative risk [RR] 2.60, 95% CI 1.75 to 3.86) and possible AD (RR 3.30, 96% CI 1.86 to 5.80) relative to controls. Patients with MCI did not have a higher frequency of the *APOE**4 allele than normal controls (RR 1.35, 95% CI 0.62 to 2.83).

Sensitivity and specificity. A total of 295 patients died and came to autopsy. Relative to the neuropathologic diagnosis, the overall specificity of the clinical diagnosis of AD was 80%, and the sensitivity 97%. However, the sensitivity and specificity of the diagnosis changed over time. From

Table 2 Neuropsychiatric characteristics

Diagnosis	MMSE	MDRS	CDR	BDRS	HDRS	HRS	NYU
Probable AD	16.9 ± 6.1	107.2 ± 22.9	1.3 ± 0.6	6.1 ± 4.2	6.3 ± 4.3	1.5 ± 2.0	11.9 ± 12.6
Possible AD	16.8 ± 5.7	103.6 ± 22.1	1.3 ± 0.6	7.1 ± 4.5	7.7 ± 4.8	4.0 ± 2.7	15.9 ± 14.6
Vascular dementia	18.6 ± 5.8	103.7 ± 21.4	1.3 ± 0.7	7.2 ± 4.6	7.9 ± 4.9	8.6 ± 3.4	26.7 ± 19.3
Other dementia	19.8 ± 6.9	112.9 ± 21.9	1.2 ± 0.7	7.1 ± 4.8	8.3 ± 6.7	3.0 ± 2.4	22.0 ± 19.2
Not demented	27.7 ± 1.9	138.8 ± 6.9	0.58 ± 0.6	1.9 ± 2.2	7.9 ± 5.2	3.1 ± 3.2	4.1 ± 6.2
Mild cognitive impairment	26.0 ± 2.6	134.8 ± 9.0	0.53 ± 0.4	1.9 ± 2.2	5.5 ± 5.2	3.0 ± 2.5	8.5 ± 8.5
Controls	28.7 ± 1.3	141.2 ± 5.0	0.01 ± 0.2	0.09 ± 1.0	2.1 ± 3.6	1.8 ± 1.7	1.9 ± 4.7

Values are mean ± SD.

MMSE = Mini-Mental State Examination; MDRS = Mattis Dementia Rating Scale; CDR = Clinical Dementia Rating; BDRS = Blessed Dementia Rating Scale for activities of daily living; HDRS = Hamilton Depression Rating Scale; HRS = Hachinski Rating Scale; NYU = NYU Scale for Parkinsonism.

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Table 3 Probable AD subgroups

Characteristics	Probable AD	Atypical course: Slow progression	Versus probable AD (t-test/χ^2)	Atypical course: Rapid progression	Versus probable AD (t-test/χ^2)
No. of patients	680	29		27	
Men/women	200/480	14/15	4.71*	10/17	0.72
Age, y	71.7 ± 8.3	73.7 ± 6.2	−1.29	65.9 ± 8.0	3.54‡
Education, y	12.0 ± 2.9	13.2 ± 3.2	−2.31*	11.2 ± 2.2	1.38
Duration, y	3.8 ± 2.5	6.1 ± 5.0	−4.60‡	2.8 ± 1.7	2.06*
Mini-Mental State	17.9 ± 6.0	21.4 ± 4.3	−3.88‡	12.7 ± 8.2	3.62†
Mattis Dementia Rating Scale	107.1 ± 22.7	126.7 ± 8.0	−4.25‡	87.1 ± 34.7	3.76‡
Clinical Dementia Rating	1.3 ± 0.6	0.94 ± 0.2	2.86†	1.7 ± 0.8	−3.56†
Blessed Dementia Rating Scale for ADL	6.0 ± 4.3	4.0 ± 3.0	2.36*	7.6 ± 4.5	−1.89*
Hachisnki Rating Scale	2.4 ± 1.9	1.9 ± 1.8	1.07	2.2 ± 1.7	0.06
Hamilton Depression Rating Scale	6.4 ± 4.3	5.6 ± 4.3	0.84	5.7 ± 4.8	0.70
NYU Scale for Parkinsonism	11.1 ± 12.1	6.3 ± 6.1	2.10†	11.1 ± 11.2	0.01
Ischemic heart disease, n (%)	39 (6)	3 (10)	1.02	2 (7)	0.12
Hypertension, n (%)	162 (24)	9 (31)	0.73	6 (22)	0.04
Diabetes mellitus, n (%)	39 (6)	2 (7)	0.06	2 (7)	0.12

Values are mean ± SD unless otherwise noted.

* $p < 0.05$; † $p \leq 0.01$; ‡ $p \leq 0.001$.

ADL = activities of daily living.

1983 to 1989, the sensitivity was 97% and the specificity was 52%, and from 1990 to 2000, the sensitivity was 98%, and the specificity 88%. Furthermore, sensitivity and specificity of diagnoses improved as a function of multiple annual visits (for additional information, please access the Web version of this article at www.neurology.org). A list of 40 cases where the clinical and pathologic diagnosis disagreed is presented on the *Neurology* Web site. In Cases

Table 4 Probable AD subgroups

Characteristics	Probable AD	Atypical presentation	Versus probable AD (t-test/χ^2)	Probable AD with CVD	Versus probable AD (t-test/χ^2)
No. of patients	680	70		85	
Men/women	200/480	27/43	2.82	30/55	1.18
Age, y	71.7 ± 8.3	68.1 ± 9.3	3.33†	76.6 ± 6.3	−5.05†
Education, y	12.0 ± 2.9	13.3 ± 3.0	−3.57†	11.8 ± 3.3	0.53
Duration, y	3.8 ± 2.5	3.6 ± 2.5	0.42	4.0 ± 2.5	−0.66
Mini-Mental State	17.9 ± 6.0	16.5 ± 7.3	0.69	18.0 ± 5.8	−1.45
Mattis Dementia Rating Scale	107.1 ± 22.7	101.4 ± 29.5	1.73	111.3 ± 16.2	−1.48
Clinical Dementia Rating Scale	1.3 ± 0.6	1.3 ± 0.7	−0.22	1.3 ± 0.6	−0.44
Blessed Dementia Rating Scale for ADL	6.0 ± 4.3	6.1 ± 4.2	−0.25	6.1 ± 3.8	−0.21
Hachisnki Rating Scale	2.4 ± 1.9	2.2 ± 1.8	0.12	3.5 ± 2.3	−5.31†
Hamilton Depression Rating Scale	6.4 ± 4.3	6.8 ± 6.0	−0.67	5.8 ± 3.6	0.92
NYU Scale for Parkinsonism	11.1 ± 12.1	11.0 ± 12.1	0.09	11.3 ± 12.8	−0.40
Ischemic heart disease, n (%)	39 (6)	2 (3)	0.94	11 (13)	6.35*
Hypertension, n (%)	162 (24)	11 (16)	2.29	37 (43.5)	15.0†
Diabetes mellitus, n (%)	39 (6)	4 (6)	0.00	6 (7)	0.22

Values are mean ± SD unless otherwise noted.

* $p < 0.01$; † $p < 0.001$.

ADL = activities of daily living.

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Table 5 Periventricular white matter lesions (WML) in patients with probable AD

Characteristics	With WML	Without WML	χ^2/t-Test
No. of subjects	348	785	
Men/women	101/247	242/543	0.37
Age, y	76.1 ± 6.4	71.5 ± 8.4	−9.11‡
Duration of symptoms, y	4.1 ± 2.7	3.8 ± 2.6	−1.69
Education, y	11.7 ± 3.0	12.1 ± 3.0	1.98*
Mini-Mental State	16.9 ± 5.8	16.8 ± 6.1	0.05
Mattis Dementia Rating	108.4 ± 18.7	106.5 ± 24.6	−1.17
Clinical Dementia Rating	1.3 ± 0.6	1.3 ± 0.6	−1.17
Blessed Dementia Rating Scale for ADL	6.4 ± 4.2	6.0 ± 4.3	−1.48
Hamilton Depression Rating	6.4 ± 4.2	6.3 ± 4.4	0.39
Hachinski Rating Scale	2.8 ± 2.0	2.3 ± 1.9	−4.31‡
NYU Scale for Parkinsonism	13.7 ± 13.2	11.0 ± 11.7	−2.76†
Ischemic heart disease, n (%)	31 (9)	45 (6)	3.88*
Hypertension, n (%)	156 (45)	178 (23)	56.5‡
Diabetes mellitus, n (%)	28 (8)	44 (6)	2.41

Values are mean ± SD unless otherwise noted.

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

ADL = activities of daily living.

13, 14, 15, 20, 21, 22, 23, 24, and 25, the disagreement occurred only at baseline examination (for additional information, please access the Web version of this article at www.neurology.org).

Discussion. The NINCDS-ADRDA criteria require that AD patients with variations in onset, presentation, or clinical course should be classified as possible AD. At that time (circa 1984), it was assumed that these characteristics reflected a second CNS disorder that might alter the AD syndrome, or the presence of other disease processes that could cause dementia. However, it is now evident that there are clear variations in the AD syndrome that do not necessarily reflect the presence of a second CNS disorder. As noted previously, AD can progress rapidly, especially when the onset is early and language deficits are present.[36,37] Conversely, AD patients with focal temporal lobe abnormality (i.e., memory and language deficits) progress at slower rates than typical AD patients.[13,30] These subgroups are particularly important when selecting patients for clinical drug trials. It is possible that an over-representation of slow progressors could modify the outcomes of drug trials.

Other patients can have a disproportionate cognitive deficit either in anterior or posterior cortical areas. Some patients had a greater frontal lobe symptomatology including cognitive deficits[14] and behavioral symptoms (e.g., disinhibition, aggression, irritability, agitation).[38] These patients appear to have a selective frontal cortex vulnerability to AD pathology, which leads to increased loss of neurons,[39] a higher load of neurofibrillary tangles,[14] and dysfunction of specific neurotransmitter systems (e.g., serotonin)[40] in prefrontal areas. By contrast, other patients have a selective vulnerability of occipital–parietal connections, and they experience significant visuospatial/constructional deficits.[10,11]

AD and strokes are the most common CNS disorders in the elderly, and there is an increased risk of developing dementia after stroke.[41] Moreover, some studies suggest that CVD may play a role in the manifestation of AD.[42] Consequently, it is important to determine the clinical implications of the cerebrovascular phenomenon in patients with AD, especially for establishing a clear classification that can be useful for clinicopathologic studies. One of the most important diagnostic problems in classifying AD for research purposes is to determine when the severity of the CVD is such that it can affect the clinical presentation or course. Reliability studies using the NINCDS-ADRDA criteria for AD have shown that the importance of the presence of small "silent" ischemic lesions or history of strokes with complete recovery are major sources of disagreement among clinicians.[6,43,44] However, these lesions can occur in demented and nondemented individuals, and are often associated with age and cerebrovascular risk factors, especially hypertension.[45] Furthermore, these patients are not cognitively different from those without such "silent " lesions.[46] Thus, the current findings and other published data indicate that AD

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patients with mild CVD should be classified as probable AD.

PWML are more frequent in patients with AD than in nondemented individuals,[47] but are thought to be more characteristic of VaD.[48] PWML in patients with AD and nondemented individuals are associated with age and hypertension, and are predictors of symptomatic cerebrovascular disease.[49,50] Although PWML in nondemented individuals have been associated with cognitive impairment in some studies,[51] they do not affect the neuropsychological profile of patients with probable AD.[46,50] Classifying our patients based on the presence of confluent lesions on MRI or moderate/severe radiolucencies on CT[29] follows the notion that there is a threshold effect such that once a certain degree of PWML occurs, the risk of CVD-related dysfunction increases.[29,52] Although this appears to be true in some patients, in others these lesions are clinically asymptomatic. Consequently, we do not classify patients with PWML as probable AD with CVD unless they also have silent ischemic lesions or have manifested a transient cerebrovascular event.

The *APOE** 4 allele frequency was increased in AD,[53-55] and its frequency was similar among the probable AD subgroups. The frequency of the *APOE**4 allele in our normal controls (i.e., 0.17) was slightly higher than that reported in population studies in the United States (approximately 0.09 to 0.14),[53,55] reflecting, perhaps, the increased number of the patients' family members enrolled as controls.[54]

The sensitivity and specificity of the diagnosis of AD and other dementias has changed during the last 20 years. The accuracy of the diagnosis of AD has increased from early reports that found less than 50%[56] to 100%[57] after the research clinical criteria were established. Moreover, use of the NINCDS-ADRDA criteria have been associated consistently with diagnostic accuracy rates of over 80%.[6-9] In our cohort, the sensitivity to AD was high over two decades, perhaps reflecting overdiagnosis; however, the specificity increased from the 1980s to the 1990s. This improvement in specificity reflects, in part, the availability of diagnostic criteria for other dementing illnesses such as VaD,[32,58] frontotemporal dementia,[59] progressive supranuclear palsy,[60] and dementia with Lewy bodies.[61] Indeed, when the NINCDS-ADRDA criteria are used in conjunction with these other diagnostic criteria, we are not only able to better identify the targeted condition (e.g., progressive supranuclear palsy), but AD classification improves, as well.[6]

It is important to note that these results are derived from a referral research clinic where we expect to examine demented subjects that are cognitively and functionally able to participate in annual follow-up examinations, and who have fewer confounding factors. The most important differences between research clinics and community-oriented studies appear to be in the specificity of the diagnostic criteria. Jobst et al.[62] examined a cohort of demented patients referred to a regional dementia clinic, followed annually with detailed neurologic and radiologic examinations, and found 97% sensitivity and 66% specificity for the prospective diagnosis of AD applying the NINCDS-ADRDA criteria. Other community-oriented studies have found both lower sensitivity (e.g., 75% to 85%) and specificity (e.g., 50% to 66%),[63,64] perhaps reflecting the participation of patients with severe systemic or neurologic illnesses that made the diagnosis more difficult. It may also be a consequence of the necessarily restricted clinical examination with few ancillary evaluations (e.g., neuroradiology and neuropsychology), which would have increased sensitivity to the impairment and aided eliminating non-AD cases. As noted here, follow-up examinations significantly improved sensitivity and specificity not only for AD but also for other dementing disorders (for additional information, please access the Web version of this article at www.neurology.org), suggesting that treating neurologists should reevaluate patients at least annually. This becomes increasingly important with the introduction of new medications, and with the changing neurobehavioral profile of the patients as the disease progresses.

The data contained in this report describe the results of 17 years of clinical research evaluation among older individuals. By its very nature, this study is atheoretical, but the data acquired by the ADRC can be used to address hypothesis-driven questions. It should be clear from this report that there has been significant evolution in the clinical diagnosis of AD and related dementias over the last two decades. Probable AD is not a homogeneous entity, and it can have an atypical presentation or clinical course that does not represent a second disease process. Clinicians should use the term possible AD in patients with atypical presentation or clinical course when they do not have access to laboratory or clinical studies that can rule out other disease processes. Although this classification must continue being based on the NINCDS-ADRDA criteria, there is a need for a more refined subclassification of AD for future studies. The clinical variations in AD may turn out to be related to genetic predisposition or resistance associated with different polymorphisms and their interaction with environmental influences. As such, rich clinical cohort studies will provide the ideal sample, and thus, more precise clinical description (i.e., subgrouping) will be needed.

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Research evaluation and diagnosis of probable Alzheimer's disease over the last two decades: I

O.L. Lopez, J.T. Becker, W. Klunk, J. Saxton, R.L. Hamilton, D.I. Kaufer, R.A. Sweet, C. Cidis Meltzer, S. Wisniewski, M.I. Kamboh and S.T. DeKosky

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Dementia with Lewy bodies

Ian McKeith, Jacobo Mintzer, Dag Aarsland, David Burn, Helen Chiu, Jiska Cohen-Mansfield, Dennis Dickson, Bruno Dubois, John E Duda, Howard Feldman, Serge Gauthier, Glenda Halliday, Brian Lawlor, Carol Lippa, Oscar L Lopez, João Carlos Machado, John O'Brien, Jeremy Playfer, and Wayne Reid on behalf of the International Psychogeriatric Association Expert Meeting on DLB

Dementia with Lewy bodies (DLB) is the second commonest cause of neurodegenerative dementia in older people. It is part of the range of clinical presentations that share a neuritic pathology based on abnormal aggregation of the synaptic protein α-synuclein. DLB has many of the clinical and pathological characteristics of the dementia that occurs during the course of Parkinson's disease. Here we review the current state of scientific knowledge on DLB. Accurate identification of patients is important because they have specific symptoms, impairments, and functional disabilities that differ from those of other common types of dementia. Severe neuroleptic sensitivity reactions are associated with significantly increased morbidity and mortality. Treatment with cholinesterase inhibitors is well tolerated by most patients and substantially improves cognitive and neuropsychiatric symptoms. Clear guidance on the management of DLB is urgently needed. Virtually unrecognised 20 years ago, DLB could within this decade be one of the most treatable neurodegenerative disorders of late life.

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Dementia is an increasingly common disorder, which affects 7% of the general population older than 65 years and 30% of those aged over 80 years. Alzheimer's disease and vascular cognitive impairment, either alone or in combination, account for most cases[1] but other causes of dementia are not rare. Initially thought to be uncommon, dementia with Lewy bodies (DLB) is now thought to be the second most common type of degenerative dementia in older people, accounting for 10–15% of cases at autopsy.[2] The importance of diagnosing this disorder lies particularly in its pharmacological management, with good responsiveness to cholinesterase inhibitors[3] but extreme sensitivity to the side-effects of neuroleptic drugs.[4,5] DLB has had several diagnostic labels during the past decade, including diffuse Lewy-body disease,[6] Lewy-body dementia,[7] the Lewy-body variant of Alzheimer's disease,[8] senile dementia of Lewy-body type,[9] and dementia associated with cortical Lewy bodies.[10] Close clinical and pathological similarities are now being recognised between DLB and dementia that occurs during the course of Parkinson's disease (PDD),[11] and there are encouraging reports of successful management of these two clinical disorders that were previously characterised by a poor outcome.[12–14]

In an effort to review and clarify current knowledge, concepts, and methods for further inquiry, a specialist meeting was organised by the International Psychogeriatric Association with the participation of the European Movement Disorder Society. Participants were asked to review relevant literature systematically and discuss it. As a product of this international meeting, we have reviewed the current state of scientific knowledge about DLB and identified key issues requiring clarification and research necessary to advance knowledge in this area. Articles for inclusion were selected by the authors as representing the most relevant and important work and supplemented by the personal knowledge of the specialists who attended the meeting.

Diagnostic concepts

DLB and PDD are clinically defined syndromes; although consensus clinical criteria have been validated for DLB,[2] no formal clinical diagnostic criteria have been proposed or validated for PDD (the subject of a recent comprehensive review in this journal).[11] An arbitrary "1-year rule" has until now been used to separate DLB from PDD; onset of dementia within 12 months of parkinsonism qualifies as DLB and more than 12 months of parkinsonism before dementia as PDD. The limitations of this approach are discussed later.

At autopsy, cases of both disorders have Lewy bodies, which are the characteristic pathological feature of Lewy-body disease, but there are as yet no definite pathological criteria that separate the disorders either from each other or

IGMcK, DB, and JO'B are at the Institute for Ageing and Health, University of Newcastle, Newcastle upon Tyne, UK. JM is at the Medical University of South Carolina, Charleston, SC, USA. DA is at the Rogaland Psychiatric Hospital, Stavanger, Norway. HC is at the Chinese University of Hong Kong, Hong Kong, China. JC-M is at the Research Institute on Aging of the Hebrew Home of Greater Washington and George Washington University, Washington, DC, USA. DD is at the Mayo Clinic Jacksonville, FL, USA. BD is at the Salpêtrière Hospital, Paris, France. JED is at the Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, USA. HF is at the Vancouver Hospital and Health Sciences Center, Vancouver, Canada. SG is at the McGill Centre for Studies in Aging, Quebec, Canada. GH and WR are at the Prince of Wales Medical Research Institute, Sydney, Australia. BL is at the St James' Hospital, Dublin, Ireland. CL is at the Drexel University College of Medicine, Philadelphia, PA, USA. OLL is at the University of Pittsburgh, Pittsburgh, PA, USA. JCM is at the Aurus IEPE, Institute of Research and Education on Aging, Belo Horizonte, Brazil. JP is at the Royal Liverpool Hospital, Liverpool, UK.

Correspondence: Prof Ian G McKeith, Institute for Ageing and Health, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, UK. Tel +44 (0)191 256 3018; fax +44 (0)191 219 5071; email i.g.mckeith@ncl.ac.uk

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Consensus guidelines for the clinical diagnosis of probable and possible DLB[2]

Central features

Progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function. Prominent or persistent memory impairment does not necessarily occur in the early stages but is evident with progression in most cases. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability can be especially prominent.

Core features (two core features essential for a diagnosis of probable, one for possible, DLB)

Fluctuating cognition with pronounced variations in attention and alertness

Recurrent visual hallucinations that are typically well formed and detailed

Spontaneous features of parkinsonism

Supportive features

Repeated falls

Syncope

Transient loss of consciousness

Neuroleptic sensitivity

Systematised delusions

Hallucinations in other modalities

REM sleep behaviour disorder

Depression

Features less likely to be present

History of stroke

Any other physical illness or brain disorder sufficient to interfere with cognitive performance

from Parkinson's disease without dementia. Moreover, autopsy studies of patients with clinically diagnosed DLB and PDD show heterogeneity in terms of distribution and density of Lewy-body pathology, as well as Alzheimer's and vascular pathology.[8,9,15,16] Because of these diagnostic uncertainties and difficulties in clinical ascertainment, routine sources of information such as death certificates and a limited number of population-based studies leave uncertainty about the relative frequencies of DLB and PDD.

Clinical and pathological criteria for DLB

There is some convergence of agreement on the core clinical features of DLB, which are fluctuating cognitive impairment, recurrent visual hallucinations, and parkinsonism.[17] The clinical distinctions between DLB and Alzheimer's disease are increasingly recognised (panel).[2] The presence of Alzheimer's pathology in DLB modifies the clinical presentation, with the lower rate of visual hallucinations and parkinsonism making such cases harder to differentiate clinically.[18] The specificity and sensitivity of the current clinical criteria for DLB reported by various groups[16,17,19–25] need careful interpretation (table) because of different methods and case mixes.[26] In general, specificity is high but sensitivity of case detection is limited. Case validation is compromised by the lack of defined neuropathological criteria for DLB and the presence of Lewy bodies in a large number of cases at autopsy with non-DLB clinical presentations, such as Lewy bodies limited to the amygdala in advanced Alzheimer's disease.[27]

Other than the temporal course of the disease (ie, the 1-year rule), clinical features in DLB and PDD are similar, including fluctuating neuropsychological function[28] and neuropsychiatric features, predominantly visual hallucinations.[29] Within pathological studies of patients with clinically diagnosed DLB and PDD, there is heterogeneity in terms of Alzheimer's and Lewy-body pathology and vascular abnormalities. There do not seem to be obvious neuropathological differences between DLB and PDD, so a descriptive clinicopathological approach to their classification will probably be most productive, with specificity both about clinical terms (DLB or PDD, largely determined by the temporal order of symptoms) and also about pathological findings (Lewy-body disease, Alzheimer's disease, vascular disease). The latter "categories" will need to be further illustrated by details of lesion density and distribution.

Epidemiology

In population-based clinical studies of people aged 65 years or older, the prevalences of DLB and PDD were reported to be 0·7% and 0.3%, respectively, which suggests that each could account for up to 10% of all dementia cases, a proportion consistent with DLB rates of 10–15% from hospital-based autopsy series. A community study of people aged over 85 years found that 5·0% met consensus criteria for DLB (3·3% probable, 1·7% possible) representing 22% of all demented cases,[30] similar to other clinical estimates[31,32] and consistent with estimates of Lewy-body prevalence in a dementia case register followed up to autopsy.[21] One population-based autopsy study found that Lewy bodies were evenly distributed between demented and non-demented individuals, which could be interpreted as evidence of a substantial pool of preclinical cases.[33] No classic epidemiological studies to investigate age and sex variation and potential risk factors for DLB have yet been reported.

Clinical phenomenology of DLB

Cognitive

Cognitive impairment is the presenting feature of DLB in most, but not all, cases. The disorder typically presents with recurrent episodes of confusion on a background of progressive deterioration. Patients with DLB show a combination of cortical and subcortical neuropsychological impairments[34,35] with substantial attentional deficits and prominent frontosubcortical and visuospatial dysfunction[36] that help to differentiate this disorder from Alzheimer's disease.[37,38] Patients with DLB do better than those with Alzheimer's disease on tests of verbal memory but worse on visuospatial performance tasks. This profile can be maintained across the range of severity of disease but can be harder to recognise in the later stages owing to global difficulties. Fluctuations in cognitive function—which may vary over minutes, hours, or days—occur in 50–75% of patients and are associated with shifting degrees of attention and alertness that can be assessed by carers' reports, observers' ratings,[39] or use of computer-based measures of variation in attentional performance.[40]

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Validity and reliability of consensus criteria for DLB[26]

Reference	Number of cases		Diagnostic criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	κ	Comments and recommendations
	DLB	Other							
Mega et al[19]	4	24 AD	Probable	75	79	100	93	F=0·25, H=0·59 P=0·46	Retrospective; suggests 4/6 of H, C, R, B, N, Fl
Litvan et al[20]	14	105 PD, PSP, MSA, CBD, AD	None applied; retrospective clinical diagnosis	18	99	75	89	0·19–0·38	Retrospective; no formal criteria for DLB used; comparison mainly with movement disorder
Holmes et al[21]	9	80 AD, VaD	Probable	22	100	100	91	NA	Retrospective; no specific recommendations; cases with mixed pathology were hardest to diagnose
Luis et al[17]	35	56 AD	Probable	57	90	91	56	F=0·30, H=0·91, P=0·61	Retrospective; suggests H, P, Fl, and rapid progression
Verghese et al[22]	18	94 AD	Probable	61	84	48	90	F=0·57, H=0·87	Retrospective; suggests 3/6 of P, Fl, H, N, D, and F
			Possible	89	28	23	91	P=0·90	
Lopez et al[23]	8	40	··	0	100	0	80		Retrospective; probable DLB not diagnosed once by a team of four raters; no specific recommendations
Hohl et al[24]	5	10 AD	Probable	100	8	83	100	NA	Consensus criteria applied retrospectively; clinician diagnosis without consensus criteria had PPV of 50
			Possible	100	0	NA	NA	NA	
McKeith et al[16]	29	50 AD, VaD	Probable	83	95	96	80	NA	Prospective; false-negative cases associated with comorbid pathology
Lopez et al[25]	13	26 AD	Probable	23	100	100	43		Prospective; met NINCDS–ADRDA criteria for AD, only four met DLB criteria

PPV=positive predictive values; NPV=negative predictive values; AD=Alzheimer's disease; F=falls; H=hallucinations; C=cogwheeling; P=parkinsonism; R=rigidity; B=bradykinesia; N=neuroleptic sensitivity; Fl=fluctuation; NA=not available; PD=Parkinson's disease; PSP=progressive supranuclear palsy; MSA=multiple system atrophy; CBD=corticobasal degeneration; VaD=vascular dementia. *Movement Disorders* © copyright 2003 Movement Disorders Society.

Psychiatric

Psychiatric manifestations are common in DLB—predominantly visual hallucinations, delusions, apathy, and anxiety. They are generally present early in the course of illness and may be the initial reason for referral. They also tend to persist; for example, hallucinations were stable in a placebo-treated DLB group over 20 weeks[13] and in a cohort in which the disorder took its natural course over 52 weeks.[41] The hallucinations are similar to those reported in PDD in that they are vivid, colourful, three-dimensional, and generally mute images of animate objects.[29] Barnes and colleagues[42] suggested that the hallucinations arise from a combination of faulty perceptual processing of environmental stimuli and less detailed recollection of experience, combined with intact image generation. The importance of psychiatric symptoms in the clinical phenomenology of DLB is such that a cluster of hallucinations, delusions, apathy, and depression derived from the neuropsychiatric inventory[43] was used as the primary outcome in the first randomised placebo-controlled study of DLB treatment.[13] Visual hallucinations are associated with greater deficits in cortical acetylcholine[44] and predict better response to cholinesterase inhibitors.[45]

Neurological

Extrapyramidal signs are reported in 25–50% of patients with DLB at diagnosis, and most develop some such signs during the natural course. In up to 25% of autopsy-confirmed cases, however, there may be no record of extrapyramidal signs, which shows that parkinsonism is not necessary for clinical diagnosis of DLB. Indeed, the main reason for "missing" DLB clinically in a prospective clinicopathological study was the absence of extrapyramidal signs.[16] The next most common reason for missing the diagnosis was the suspicion of cerebrovascular disease. Initial suggestions that parkinsonism in DLB is mild have not been supported by studies finding severity equal to that in non-demented patients with Parkinson's disease[46] and similar annual progression rates in motor scores on the unified Parkinson's disease rating scale.[47,48] The pattern of extrapyramidal signs in DLB shows an axial bias—eg, greater postural instability and facial impassivity, with a tendency towards less tremor, consistent with greater "non-dopaminergic" motor involvement. The parkinsonism phenotype of postural instability–gait difficulty[49] is over-represented in DLB, as it also is in PDD, whereas tremor-dominant and postural-instability-gait-difficulty subtypes were evenly distributed in a non-demented group with Parkinson's disease.[50] Extrapyramidal signs in Parkinson's disease, PDD, and DLB may thus be on a continuum, with a shift towards greater non-dopaminergic motor-system involvement through Parkinson's disease to DLB. This idea is consistent with findings that motor features mediated by

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non-dopaminergic pathways (speech, posture, and balance) are more closely associated with incident dementia in Parkinson's disease than tremor, rigidity, and bradykinesia.[51]

Sleep

Rapid-eye-movement (REM) sleep behaviour disorder is a parasomnia manifested by vivid and frightening dreams associated with simple or complex motor behaviour during REM sleep. The disorder is frequently associated with the synucleinopathies, DLB, Parkinson's disease, and multiple system atrophy, but it rarely occurs in amyloidopathies and tauopathies.[52] The neuropsychological pattern of impairment in REM sleep behaviour disorder/dementia is similar to that reported in DLB and qualitatively different from that reported in Alzheimer's disease.[53] Neuropathological studies of REM sleep behaviour disorder associated with a neurodegenerative disorder have shown Lewy-body disease or multiple system atrophy.[54] REM sleep-wakefulness dissociations (REM sleep behaviour disorder, daytime hypersomnolence, hallucinations, cataplexy), characteristic of narcolepsy can explain several features of DLB as well as Parkinson's disease.[55] Sleep disorders could contribute to the fluctuations typical of DLB, and their treatment can improve fluctuations and quality of life.[56]

Autonomic failure

Autonomic abnormalities including orthostatic hypotension and carotid-sinus hypersensitivity are more common in patients with DLB than in those with Alzheimer's disease or in age-matched controls.[57] Clinical presentation of DLB is commonly with "dizziness," presyncope, syncope, and falls,[58,59] and autonomic dysfunction is a risk factor for falls in 65% of these cases, through either orthostatic hypotension or carotid-sinus hypersensitivity. Urinary incontinence has been reported early in the course of DLB compared with Alzheimer's disease.[60]

Disease progression and survival

There is conflicting evidence from comparative studies with Alzheimer's disease about both symptom progression and survival in DLB. Most data have been obtained retrospectively. The most parsimonious explanation from the available findings is that there is no difference in progression between DLB and Alzheimer's disease,[61] but mean values from large studies could conceal disease heterogeneity, and some patients with DLB have a very rapid disease course.[62,63] The conclusion is that either there is no difference between DLB and Alzheimer's disease in survival from onset until death, or that survival is worse in DLB.[64,65] Whether there are any specific features, such as more severe extrapyramidal signs or frequent falls, that are associated with more rapid disease progression or poorer survival is not yet known.

Clinical diagnosis of DLB

DLB can initially present to general practitioners, geriatric psychiatrists, movement-disorder specialists, or emergency services. As with all dementias, accurate clinical diagnosis can only be made after a thorough clinical assessment including a detailed history (from the patient and an informant) and full mental-state, cognitive, and physical (including neurological) examinations.[2] There should be particular emphasis on eliciting the core diagnostic features of fluctuating cognitive impairment, parkinsonism, and recurrent visual hallucinations and the supportive features of falls, depression, other hallucinations, and REM sleep disorder. Diagnosis should be made on the basis of the consensus diagnostic criteria for DLB (panel), which are the most widely accepted and have been the best validated by autopsy. The main differential diagnoses are Alzheimer's disease, vascular dementia, PDD, atypical parkinsonian syndromes (such as progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration), and Creutzfeldt-Jakob disease.

Several retrospective and two prospective studies have examined the predictive accuracy of clinical criteria for probable DLB[16,17,19–25] (table). They show that sensitivity is variable and, although high in one prospective study,[16] was unacceptably low in several other studies. By contrast, specificity is generally high. There is, therefore, a need to develop ways of improving the sensitivity of the diagnosis of DLB without loss of specificity, which may ultimately require a biological test.

Consistent application and greater inter-rater reliability of the consensus criteria would be facilitated by more detailed definitions of the quality, frequency, and severity of core and supportive features. The assessment of fluctuating cognitive impairment poses substantial difficulty to many clinicians, and newly proposed rating scales could be particularly helpful in this regard.[39] The best way to take advantage of supportive diagnostic features (panel) in improving diagnostic accuracy also needs to be identified. Repeated falls, syncope, transient loss of consciousness, and depression are common in older people with cognitive impairment and can serve as "red flags" to a possible diagnosis of DLB. By contrast, neuroleptic sensitivity and REM sleep behaviour disorder can be highly predictive of DLB, but their detection depends on the clinician's having a high index of suspicion and asking appropriate screening questions.

Since PDD is common and typically shares the features of DLB,[11,66] there is much debate about the relation between the two disorders.[67] There are at present no specific operational clinical criteria to diagnose PDD. The criteria in Diseases and Statistical Manual IV are incomplete and descriptive and do not describe several core clinical features associated with dementia in Parkinson's disease. The arbitrary 1-year rule used to separate DLB from PDD is helpful in individual case diagnosis but is increasingly hard to justify from a neurobiological point of view. Current DLB criteria therefore need to be revisited with respect to their relation to PDD; this process would be facilitated by improved operational criteria for PDD. The need for a collaborative research effort by specialists in movement disorders and dementia is apparent and is already being addressed by interdisciplinary task groups.

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Laboratory and neuroimaging investigations

Systemic and pharmacological causes of delirium need to be excluded. The standard EEG may show early slowing, epoch-by-epoch fluctuation, and transient temporal slow-wave activity.[68–70] There are as yet no clinically applicable genotypic or CSF markers to support a diagnosis of DLB.[71–77] There have been, however, sufficient studies to allow the conclusion that neuroimaging investigations can be helpful in supporting the clinical diagnosis. Changes associated with DLB include preservation of hippocampal and medial temporal lobe volume on MRI[78,79] (figure 1) and occipital hypoperfusion on SPECT.[80,81] Other features such as generalised atrophy,[79] white-matter changes,[82] and rates of progression of whole brain atrophy[83] are not helpful in differential diagnosis. Dopamine transporter loss in the caudate and putamen, a marker of nigrostriatal degeneration, can be detected by dopaminergic SPECT[84] and can prove helpful in clinical differential diagnosis. A sensitivity of 83% and specificity of 100% has been reported for the association of an abnormal scan with an autopsy diagnosis of DLB[85] (figure 2).

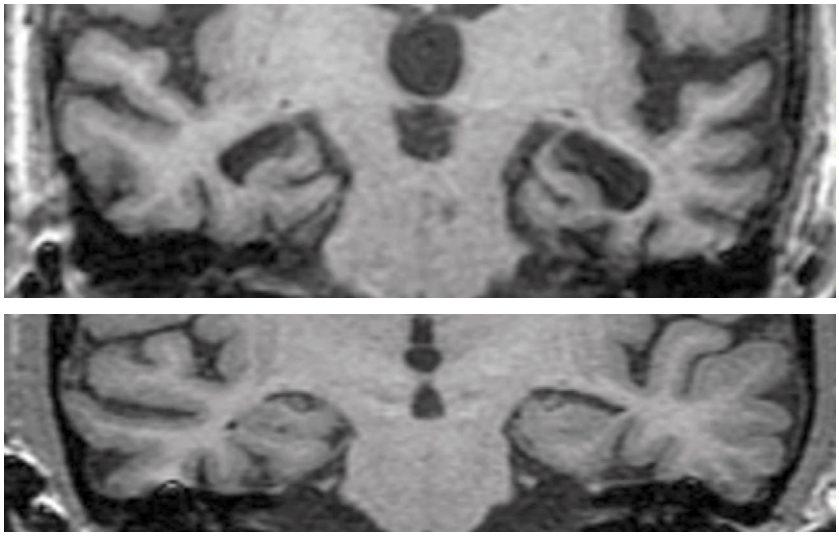

Figure 1. Coronal MRI of patients with Alzheimer's disease and DLB matched for clinical severity of dementia. Medial temporal lobe (particularly hippocampal) atrophy is less pronounced in DLB, consistent with autopsy findings. Images courtesy of Dr Emma Burton.

Pathophysiology of DLB

Consensus criteria for DLB include ubiquitin immunohistochemistry for Lewy-body identification[2,16] and staging into three categories (brainstem-predominant, limbic, or neocortical) depending on the numbers and distribution of Lewy bodies. The recently developed α-synuclein immunohistochemistry is a better marker[86,87] that visualises more Lewy bodies and also shows previously under-recognised neuritic pathology, termed Lewy neurites (figure 3). Use of antibodies to α-synuclein moves the diagnostic rating for many DLB cases from brainstem and limbic groups into the neocortical group. An additional very severe pathological category may therefore now be required. α-synuclein is a normal synaptic protein that has been implicated in vesicle production. In an aggregated and insoluble form it constitutes the main component of the fibrils that are a major constituent of the Lewy bodies in DLB and other synucleinopathies.[15] In most patients with DLB, there are no genetic mutations in the α-synuclein gene or other Parkinson's disease genes. Pathological upregulation of normal, wild-type α-synuclein due to increased mRNA expression is a possible mechanism,[88] or Lewy bodies may form because α-synuclein becomes insoluble or more able to aggregate for some reason.[89] Another possibility is that α-synuclein is abnormally processed, for example by a dysfunctional proteosome system, and that toxic "protofibrils" are therefore produced. Sequestering of these toxic fibrils into Lewy bodies could reflect an effort by the neurons to combat biological stress inside the cell, rather than their simply being neurodegenerative debris. Whether Lewy bodies are "friend or foe" remains to be discovered.

The number of cortical Lewy bodies is not robustly correlated with either the severity or the duration of dementia,[90,91] although associations have been reported with Lewy bodies and plaque density in midfrontal cortex.[92] Lewy neurites and neurotransmitter deficits are suggested as more likely links with clinical symptoms.[91,93] There seems to be no significant cortical pathology that is associated with fluctuating cognition; however, increased numbers of Lewy bodies in the anterior and inferior temporal lobe are associated with the presence and onset of well-formed visual hallucinations.[94,95] These areas are particularly implicated in generation of complex visual images, and their pathological involvement perhaps

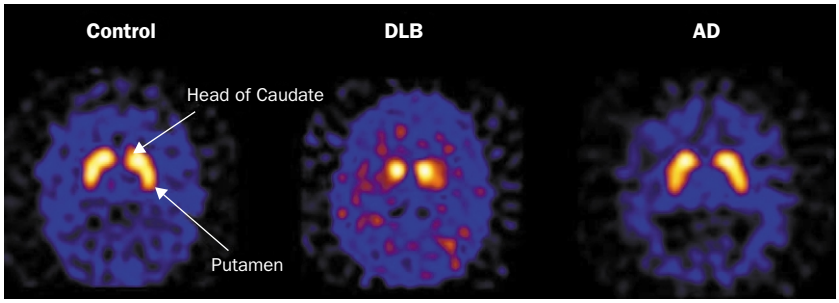

Figure 2. SPECT images of the dopamine transporter at the level of the striatum by use of fluoropropyl-CIT show striking reduction of activity in DLB compared with normal activity in Alzheimer's disease and normal ageing. Images courtesy of Prof J T O'Brien.

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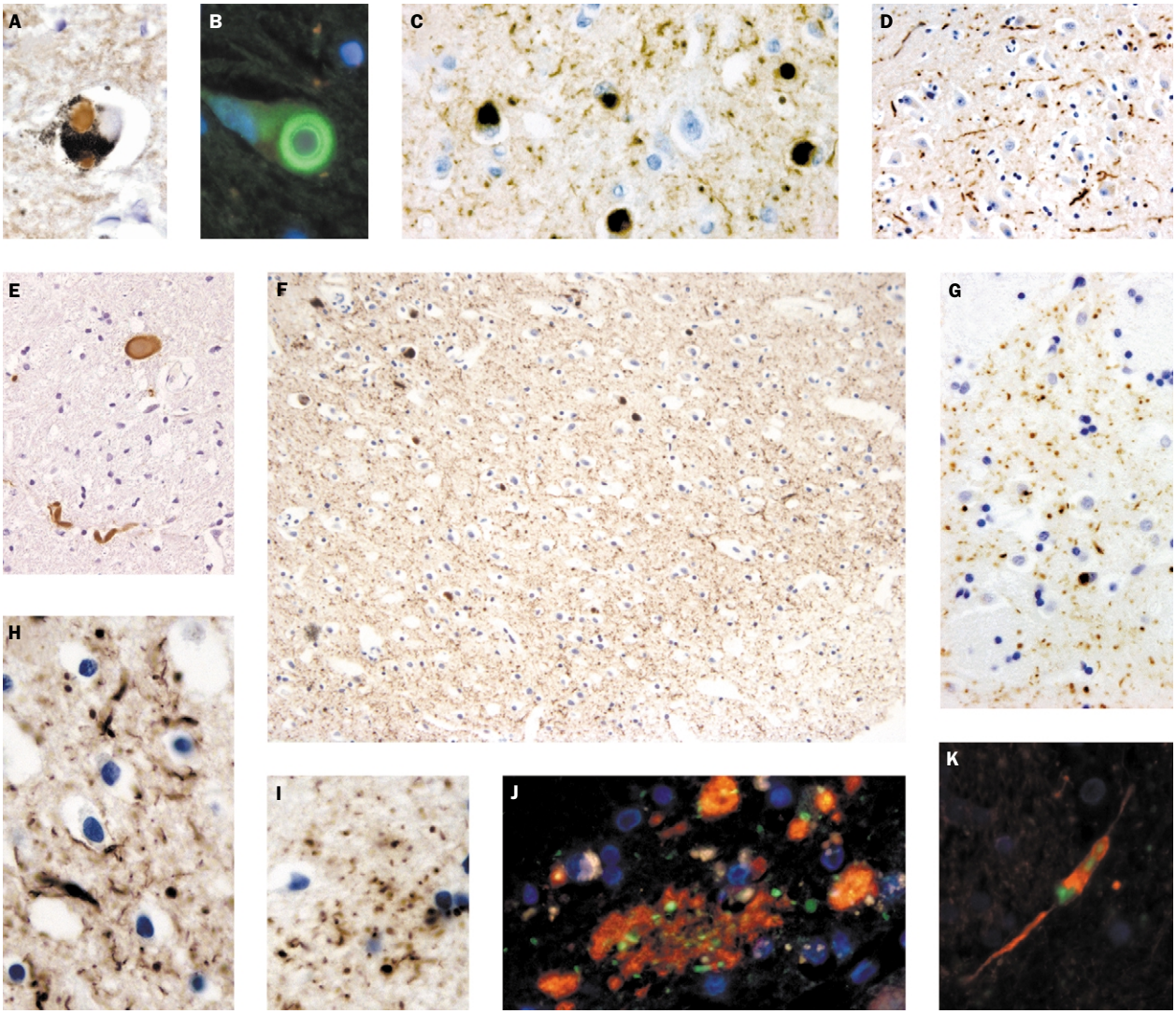

Figure 3. Neuropathology of DLB. Pathological α-synuclein (α-syn) aggregates assume many forms in DLB including typical classical Lewy bodies (LBs) in the pigmented nuclei of the brainstem (A,B), cortical LBs in the neocortex (C) and amygdala, dystrophic or Lewy neurites (LNs) in the CA 2/3 subfield of Ammon's horn (D) and neuroaxonal spheroids (E). The burden of α-syn aggregates in the neocortex (F) can be extreme with cortical LBs in the deeper layers (top left) and LNs throughout the cortical mantle to the pial surface (bottom right). The striatum is also affected (G) with primarily LNs (H) and dot-like aggregates (I). LNs tend to cluster around ß-amyloid plaques (J), which are also common in DLB, and are primarily axonal in location (K). Antibodies: α-syn in A, C-I, and J,K (green); tyrosine hydroxylase in B; β-amyloid in J (red); neurofilaments light chain in K (red). Images courtesy of Dr John E Duda.

contributes to the vivid and complex character of hallucinatory experiences in DLB, contrasting with the very simple visual symptoms (lines and colours) associated with occipital-lobe lesions. Parkinsonism is related to the degree of cell loss and pathology in the nigrostriatal pathway.

Most patients with DLB also have Alzheimer's disease pathology, including cortical amyloid plaques and neurofibrillary tangles. Most have sufficient plaques to meet CERAD criteria for Alzheimer's disease,[8] but only a few meet the tangle-based Braak stages V and VI for Alzheimer's disease. The additional neuritic pathology affects the clinical presentation. DLB patients with few tangles show more core clinical features of DLB, whereas those with many tangles show a pattern more like Alzheimer's disease.[18,89] Lewy bodies also occur in up to two-thirds of patients with early-onset familial Alzheimer's disease caused by mutations of presenilin-1, presenilin-2, or amyloid precursor protein, as well as in sporadic Alzheimer's disease, Down's syndrome, and Pick's disease.[27,96,97] Tau aggregates particularly increase the likelihood of Lewy-body formation in susceptible brain regions, like the amygdala. However, the substantial cortical dysfunction found clinically in patients with limited cortical-cell loss, negligible tangle counts, but numerous cortical Lewy bodies and neurites suggests that they themselves are associated with much functional neuronal impairment. Elucidation of the pathophysiology of DLB will guide future therapeutic strategies.

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Management of DLB

A four-stage approach to the management of DLB has been described: accurate diagnosis; identification of target symptoms with patient and carer; non-pharmacological interventions; and pharmacological interventions.[98] Target symptoms can include extrapyramidal motor features, cognitive impairment, neuropsychiatric features (including hallucinations, depression, sleep disorder, and associated behavioural disturbances), or autonomic dysfunction. Patients, carers, and clinicians can differ in their prioritisation of which symptoms "need" treating, and all must understand the potential for gains in one domain may be at the expense of losses in another.

Non-pharmacological interventions are a humane way of treating people with dementia and have the potential to address most of the areas in which there are management difficulties in DLB. They require a general set of caregiving skills as well as tailoring of interventions to the patient, carer, and environment. A systematic analysis of non-pharmacological approaches to DLB and evaluation of the system changes and costs that are needed to support them in clinical practice have yet to be done.

The evidence base for pharmacological management of DLB is also limited, but there is general agreement that if antiparkinsonian drugs are prescribed, the clinician should aim for the lowest acceptable dose of levodopa monotherapy. The effectiveness of levodopa on motor symptoms in DLB has not been established but is probably less than in uncomplicated Parkinson's disease, possibly because there is additional intrinsic striatal pathology and dysfunction.[99] D2-receptor antagonists, particularly traditional neuroleptic agents, can provoke severe neuroleptic sensitivity reactions in up to 50% of DLB patients with an increase in mortality of two to three times.[4] New atypical antipsychotic drugs used at low dose are safer in this regard, but sensitivity reactions have been documented with most and they should be used with great caution.[100–104]

There is consistent evidence that cholinesterase inhibitors are more effective in DLB than in Alzheimer's disease, for which they were originally developed.[105,106] Fluctuating cognitive impairments, visual hallucinations, apathy, anxiety, and sleep disturbance are significantly improved with cholinesterase inhibitors used in the typical dose range for Alzheimer's disease. In addition to the usual gastrointestinal side-effects associated with this class of drug, increased cholinergic activity may cause hypersalivation and exacerbate postural hypotension and falls in patients with DLB.[107] Cholinesterase inhibitors are deemed by some to be first-line treatment for the cognitive and psychiatric symptoms of DLB, although there have been only two double-blind placebo-controlled studies that addressed their symptomatic effects[3,14] and very limited open-label data on long-term effects.[108] No information is yet available about their use in combination with antiparkinsonian or atypical antipsychotic agents, although these are both common clinical situations.

Disease-modifying strategies developed for either Alzheimer's disease or Parkinson's disease will be candidates for use in DLB but none have been attempted so far. DLB is a particularly attractive target for neuroprotection owing to the presence of significant neuronal dysfunction but no striking cortical neuronal degeneration. In vitro and animal models of α-synuclein aggregation and its relation to amyloid deposition will be useful tools for developing novel disease-modifying therapies for DLB.

Trial designs and regulatory issues

There are no treatments licensed for DLB. Regulatory authorities seem prepared to accept DLB as an indication for regulatory approval of a pharmacological treatment on condition that its existence is widely accepted by experts, that it can be operationally defined by reliable and valid criteria, and that outcomes for studies use validated and standardised outcome measures. The US Food and Drug Administration has considered DLB as an indication and initially has suggested that there be dual primary outcomes, namely global and a specified measure of cognition. Cognitive outcome measures from clinical trials of Alzheimer's disease that are predominantly memory based need not necessarily be used in DLB studies, and more appropriate instruments should be considered. The acceptability of a primary behavioural outcome measure in DLB clinical trials has not yet been clarified. Potential confounding factors for global and functional scales in DLB include the additional disabilities arising from motor disability and, for all outcome measures, the inherent fluctuations of the untreated illness.

Trial designs

Few DLB treatment trials have been reported, partly because the disorder was only recently described, but also because of restricted expertise in clinical diagnosis. The current approach is to address DLB and PDD separately, but the close relation of these disorders and the logistics of recruitment provide the opportunity for both populations of patients to enter into a single clinical trial with a harmonised set of entry criteria. Post-hoc subanalysis could be used to assess for differential responses. Recruitment of patients into such trials will require specialised movement disorder and dementia referral clinics to participate, with an anticipated slower accrual if only patients with DLB are recruited. In view of the small number of randomised controlled trials in either DLB or PDD, the use of placebos is still judged ethical, but we note that cholinesterase inhibitors are already in widespread use in some countries.

Outcome measures

Specific measures of attention and cognitive fluctuation, which are both part of the clinical profile of DLB and PDD, are sensitive to response to treatment intervention.[109] Other key domains of executive functioning, visual perception, and memory systems must also be measured. The most important neuropsychiatric target symptoms include visual hallucinations, delusions, delusional misidentification, apathy, anxiety, and depression. The desired behavioural outcomes might be a reduction in both the intensity and frequency of these key behavioural symptoms with an effect

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Search strategy and selection criteria

This review was based on articles identified by a MEDLINE search with the terms "Lewy body", "dementia", and "Parkinson's disease" as the main keywords or identified from the reference lists of relevant articles, review papers, and book chapters. Articles for citation were chosen for their historical value, importance, ease of access, and timeliness based on the expert knowledge of the delegates.

on non-patient-centred outcomes including improvement in time, workload, and stress for carers. Functional and global assessments will be influenced by the presence of parkinsonism. Scales measuring extrapyramidal motor function can be modified to account for the confounding effects of cognitive impairment on motor performance.[110]

Global awareness of DLB and educational and treatment needs

Most dementia research has been done in North America, Australia, and Europe, but even in these regions, awareness of DLB is only now becoming widespread within specialist care. In countries with less developed dementia services and with greater reliance on primary care, there are substantial difficulties in translating current methods of case detection and diagnosis—eg, administration of cognitive tests to patients who are illiterate or have little education. In most cultures, dementia has been regarded as a normal part of ageing, and patients are brought for help only when behaviour becomes troublesome. Such patients could include those with DLB, and accurate diagnosis is imperative to avoid increased morbidity and mortality from the inappropriate use of neuroleptic agents and to ensure that they are not denied access to cholinesterase inhibitors and other interventions that might be beneficial. The first goal must be to raise awareness. Possible strategies to address these problems in the parts of the world that have the most rapidly expanding elderly populations include combining efforts with international and regional organisations for Parkinson's disease and Alzheimer's disease to include DLB in their educational campaigns, to develop appropriate educational materials, and to disseminate these through accessible internet sites that are linked with existing Lewy-body disease resources.

Conclusions

DLB is one of a group of neurodegenerative disorders that has been characterised as the α-synucleinopathies. The group includes Parkinson's disease with and without dementia and primary autonomic failure. Clinical criteria and assessment scales for the accurate diagnosis of DLB have been developed in the past decade, and these are useful in the differentiation of DLB from other dementia subtypes, particularly Alzheimer's disease and vascular cognitive impairment. But diagnostic accuracy of DLB still needs to be improved. Progress may be difficult given the inevitable pathological heterogeneity that occurs in the ageing brain. Many patients with DLB have substantial additional pathology that modifies the core clinical features and makes those cases difficult to recognise by existing clinical methods. Some modifications to the application of existing diagnostic criteria could help to increase case detection. For example, clinicians assessing elderly patients with cognitive dysfunction should be routinely asking about features that support a DLB diagnosis, such as REM sleep behaviour disorder, repeated falls, or neuroleptic sensitivity. Existing clinical methods and criteria need to be more widely disseminated with the message that patients with DLB can respond well to cholinergic treatment and extremely badly to neuroleptic drugs. A biological diagnostic marker is urgently required. Functional neuroimaging of the dopaminergic system could soon provide such a marker by aiding the distinction between DLB and dementias that lack nigrostriatal dopaminergic degeneration.

A different approach is required to address the distinction between DLB and PDD. These syndromes could be so similar at a biological level that a categorical distinction is inappropriate and the use of a generic term such as Lewy-body disease or α-synucleinopathy for all cases might be preferable. But such terms imply prior knowledge of the underlying pathology and, in the absence of this, diagnosticians might additionally need to use diagnostic terms (DLB, PDD) that describe the individual patient's clinical presentation taking into consideration both the temporal sequence of symptom onset and their relative severity.

No rigorously tested treatment algorithms for DLB have been published, and some basic information is still lacking, for example the responsiveness of parkinsonian features to levodopa. Avoidance of neuroleptic agents is important. Long-term use of cholinesterase inhibitors seems to be helpful for neuropsychiatric and cognitive symptoms, but further clinical trials are needed to clarify how these agents should be used and to identify their side-effect profile in this population. When disease-modifying agents are developed for Parkinson's disease or Alzheimer's disease, they should be tried in DLB and PDD also. Virtually unrecognised 20 years ago, DLB could within this decade be one of the most treatable neurodegenerative disorders of late life.

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Author contributions

All the authors shared responsibility for producing draft reviews of the topic areas chaired by them at the expert meeting. IMcK completed the literature searches and produced a combined draft for final review by all authors. JM proposed the meeting and obtained financial support. All listed participants reviewed materials and presented them at the meeting.

Conflict of interest

IGMcK has received travel sponsorship, honoraria, and research support from Pfizer/Eisai, Novartis, Janssen-Cilag, and Amersham Health. JM has acted as consultant for Eli Lilly, Abbott, AstraZeneca, and Bristol-Myers Squibb and received grants/research support from Eisai America, Inc, Janssen Research Foundation, Novartis, and Pfizer. DA has received travel sponsorship, honoraria, and research support from Pfizer, Novartis, and Janssen-Cilag. JD has received travel support and/or honoraria from Pharmacia, Novartis, and Janssen Pharmaceuticals and research support from Pfizer Pharmaceuticals. HF has received honoraria and research support and has been a paid consultant for Lilly Pharma, Eisai Pfizer, Novartis, and Janssen. SG has acted as consultant to Pfizer, Novartis, and Janssen-Cilag, who are developing drugs useful in DLB. BL has received travel sponsorship, honoraria from Janssen Cilag, Lilly, Pfizer, Astra Zeneca, Wyeth, Organon, Bristol Myers Squibb, and Glaxo Wellcome, and research support from Wyeth. CL is on the speakers' bureau for Pfizer, Novartis, Eisai, OrthoMcNeil, and Janssen (honoraria recipient). JO'B has acted as consultant and/or accepted hospitality and honoraria from Janssen-Cilag, Novartis, Pfizer/Eisai, and Amersham Health. DB, HC, JC-M, DD, BD, GH, OL, JM, JP, and WR have no conflicts of interest to declare.

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Sensitivity and specificity of dopamine transporter imaging with ^{123}I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study

*Ian McKeith, John O'Brien, Zuzana Walker, Klaus Tatsch, Jan Booij, Jacques Darcourt, Alessandro Padovani, Raffaele Giubbini, Ubaldo Bonuccelli, Duccio Volterrani , Clive Holmes, Paul Kemp, Naji Tabet, Ines Meyer, Cornelia Reininger for the DLB Study Group**

Summary

Background Dementia with Lewy bodies (DLB) needs to be distinguished from other types of dementia because of important differences in patient management and outcome. Current clinically based diagnostic criteria for DLB have limited accuracy. Severe nigrostriatal dopaminergic degeneration occurs in DLB, but not in Alzheimer's disease or most other dementia subtypes, offering a potential system for a biological diagnostic marker. The primary aim of this study was to investigate the sensitivity and specificity, in the ante-mortem differentiation of probable DLB from other causes of dementia, of single photon emission computed tomography (SPECT) brain imaging with the ligand ^{123}I-2β-carbometoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (^{123}I-FP-CIT), which binds to the dopamine transporter (DAT) reuptake site. Diagnostic accuracy, positive and negative predictive values, and inter-reader agreement were the secondary endpoints and a subgroup of possible DLB patients was also included.

Methods We did a phase III study in which we used a ^{123}I-FP-CIT SPECT scan to assess 326 patients with clinical diagnoses of probable (n=94) or possible (n=57) DLB or non-DLB dementia (n=147) established by a consensus panel (in 28 patients no diagnosis could be made). Three readers, unaware of the clinical diagnosis, classified the images as normal or abnormal by visual inspection. The study had 90% power to detect the differences between our anticipated sensitivity (0·80) and specificity (0·85) targets and prespecified lower thresholds (sensitivity 0·65, specificity 0·73) using one-sided binomial tests with a significance level of α=0·025.

Findings Abnormal scans had a mean sensitivity of 77·7% for detecting clinical probable DLB, with specificity of 90·4% for excluding non-DLB dementia, which was predominantly due to Alzheimer's disease. A mean value of 85·7% was achieved for overall diagnostic accuracy, 82·4% for positive predictive value, and 87·5% for negative predictive value. Inter-reader agreement for rating scans as normal or abnormal was high (Cohen's κ=0·87). The procedure was well tolerated with few adverse events.

Interpretation A revision of the International Consensus Criteria for DLB has recommended that low DAT uptake in the basal ganglia, as shown by SPECT or PET imaging, be a suggestive feature for diagnosis. Our findings confirm the high correlation between abnormal (low binding) DAT activity measured with ^{123}I-FP-CIT SPECT and a clinical diagnosis of probable DLB. The diagnostic accuracy is sufficiently high for this technique to be clinically useful in distinguishing DLB from Alzheimer's disease.

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*Investigators listed at end of paper

Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK (I McKeith FMedSci, J O'Brien MD); **Department of Mental Health Sciences, University College London, Bloomsbury Campus, London, UK** (Z Walker MD); **Department of Nuclear Medicine, Ludwig Maximilians University Hospital, Munich, Germany** (K Tatsch MD); **Department of Nuclear Medicine, Academic Medical Centre, Amsterdam, Netherlands** (J Booij MD); **Department of Nuclear Medicine, Medical Faculty, University of Nice Sophia-Antipolis, Nice, France** (J Darcourt MD); **Department of Neurology, University Hospital Brescia, Brescia, Italy** (A Padovani MD); **Department of Nuclear Medicine, Spedali Civili di Brescia, Brescia, Italy** (R Giubbini MD); **Department of Neurology** (U Bonuccelli MD) **and Department of Nuclear Medicine, University Hospital of Pisa, Pisa, Italy** (D Volterrani MD); **Memory Assessment and Research Centre, Moorgreen Hospital, Southhampton, UK** (C Holmes MD); **Department of Nuclear Medicine, Southampton General Hospital, Southampton, UK** (P Kemp MD); **Uckfield Community Hospital, Uckfield, UK** (N Tabet MD); **General Electric Healthcare, Clinical Research and Development, Munich, Germany** (C Reininger MD); **and Medicine AG, Munich, Germany** (I Meyer PhD)

Introduction

The importance of early and accurate diagnosis of dementia subtype to inform prognosis and best management has been emphasised by international good practice guidelines[1,2] and is appreciated by patients and their carers. The findings of neuropathological autopsy studies suggest that 50–60% of cases of dementia in people aged 65 years or older are due to Alzheimer's disease, with a further 10–20% each attributable to dementia with Lewy bodies (DLB) or vascular cognitive impairment.[3] Operationalised clinical diagnostic criteria have been agreed for all of these syndromes, but even in specialist research settings they have limited accuracy when compared with neuropathological autopsy findings. The situation in non-specialist clinical settings is likely to be even more imperfect.

The most frequent diagnostic confusion in clinical practice in older patients with dementia is between DLB and Alzheimer's disease.[4] Accurate clinical detection of DLB is particularly important because half of patients with DLB have severe neuroleptic sensitivity to typical and atypical antipsychotics, with a two to three-fold increase in short-term mortality.[5] This increase is over and above the recently recognised risk of neuroleptic-induced cerebrovascular events in all patients with dementia.[6] There is also emerging evidence that some patients with DLB respond especially well to cholinesterase inhibitors.[7]

Diagnostic difficulties have arisen for two main reasons. The first has been a lack of valid and reliable methods to assess the core clinical features by which DLB is usually identified—namely, fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations that are typically well formed and detailed, and spontaneous features of parkinsonism.[8] Second, results of autopsy studies show that patients with DLB who, in addition to subcortical and cortical Lewy bodies,

Correspondence to:
Prof Ian G McKeith,
Institute for Ageing and Health,
Newcastle University,
Newcastle upon Tyne, UK
i.g.mckeith@ncl.ac.uk

carry a great burden of neocortical Alzheimer pathology may not have these clinical features as prominently and will often present with an amnestic syndrome in clear consciousness, more typical of Alzheimer's disease than of DLB.[9] There are, therefore, limitations on the level of accuracy that can be achieved by making diagnoses solely on the grounds of clinical history and examination. As such, there is a clear need for biological markers to assist with accurate ante-mortem diagnosis.

A striking biological difference between DLB and Alzheimer's disease is the severe nigrostriatal degeneration and consequent dopamine transporter (DAT) loss that occurs in DLB, but not to any significant extent in Alzheimer's disease.[10] This difference is most profound in patients with a long history of severe extrapyramidal motor features, but also arises when these features are minimal or absent.[11] Several radioligands have been developed for use in single-photon emission computed tomography (SPECT) to bind in vivo to the striatal DAT or reuptake site. These include an ^{123}I-labelled-cocaine analogue ^{123}I-2β-carbometoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (I-FP-CIT; DaTSCAN, GE Healthcare).[12] The efficacy of this ligand in detecting the loss of nigrostriatal neuron terminals in patients with Parkinson's disease has been shown[13] and it has been approved for use in Europe since 2000 to distinguish between patients with clinically uncertain parkinsonian syndromes and individuals with essential tremor.

Findings of two pilot studies[14,15] have independently shown that ^{123}I-FP-CIT SPECT imaging provides essential information about nigrostriatal dopaminergic neuronal integrity in patients with DLB. In both studies, patients with DLB and Alzheimer's disease were included and both visual and region-of-interest based semi-quantitative assessments of the images were undertaken. There were highly significant differences ($p<0\cdot0001$) in striatal binding between patients with DLB and Alzheimer's disease and between controls and patients with DLB. Significant differences were also seen for the visual assessment. When compared with autopsy diagnosis, the sensitivity and specificity of imaging was 88% and 100%, respectively.[14]

The primary aim of this multicentre study was to determine the sensitivity and specificity of ^{123}I-FP-CIT SPECT imaging in the ante-mortem differentiation of DLB from other causes of dementia. Diagnostic accuracy and positive and negative predictive values of the technique were estimated as secondary outcomes, as was inter-reader agreement for the visual rating of scans. A final aim was to undertake similar analyses on a group of patients clinically diagnosed with possible DLB.

Methods

Participants

Between November, 2003, and August, 2005, we did a phase III, multicentre study in 40 European sites. We included patients aged 55–90 years who met the criteria for dementia detailed in the diagnostic and statistical manual of mental disorders—fourth edition (DSM-IV)[16] and fulfilled at least one of the following: consensus criteria for probable or possible DLB,[8] National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable or possible Alzheimer's disease,[17] or National Institute of Neurological Disorders and Stroke-Association Internationale Pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for probable or possible vascular dementia.[18] A mini-mental state examination (MMSE)[19] score of 10 or more was required to ensure that patients could complete sufficient assessments to provide useful diagnostic information. We defined patients with dementia who had developed parkinsonism more than 1 year before onset of dementia symptoms as having Parkinson's disease with dementia[8] and excluded them from the study. We also excluded patients in any diagnostic group with structural imaging findings indicative of infarction in the region of the basal ganglia, including the internal capsule. We routinely assessed laboratory variables, including vitamin B12, folic acid, glucose, C-reactive protein concentrations, and measures of hepatic, renal, and thyroid function to exclude systemic causes of the neuropsychiatric presentation. We disallowed use of medication known or suspected to interact with the striatal binding of ^{123}I-FP-CIT to the DAT, which included psychopharmaca such as cocaine, amfetamine, mazindol, methylphenidate, benzatropine, bupropion, and sertraline.

The study was done in accordance with the current revision of the Declaration of Helsinki and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation and applicable to national and local laws and regulations. At every participating site, the study protocol and all amendments were approved by an institutional review board or independent ethics committee. All patients and their caregivers gave written informed consent.

Procedures

Clinical diagnosis was established by an independent consensus panel, consisting of three clinicians (experts in the field of DLB), who were provided with a patient profile stemming from quality-assured clinical data from the onsite-investigators' case record forms and copies of onsite original source data, containing full details of the following neuropsychiatric assessments: MMSE,[19] unified Parkinson's disease rating scale (UPDRS) III (motor section),[20] modified Hoehn and Yahr staging,[21] clinical assessment of cognitive fluctuation scale,[22] the Cambridge Cognitive Examination—revised version (CAMCOG-R),[23] Cornell scale for depression in dementia,[24] the investigator's estimation of the patient's intelligence quotient level, neuropsychiatric inventory with caregiver

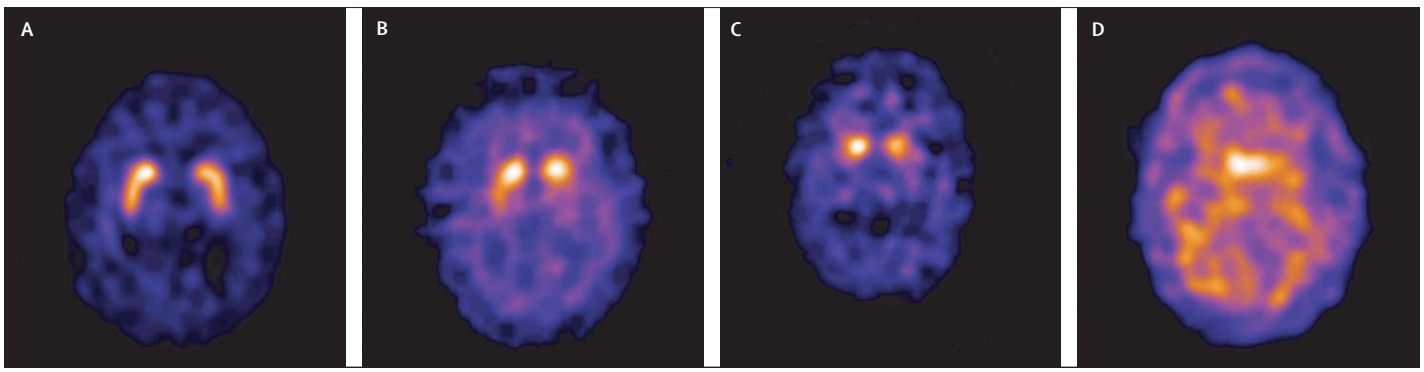

Figure 1: **Normal and abnormal ^{123}I-FP-CIT SPECT images**
A: normal. B: abnormal, type 1. C: abnormal, type 2. D: abnormal, type 3.

distress scale (NPI-D),[25] visual object and space perception (VOSP) battery,[26] and clinical dementia rating (CDR).[27] Results of MRI and CT scans and the onsite investigators' clinical diagnosis before imaging were also available. The consensus panel did not at any stage have access to ^{123}I-FP-CIT SPECT findings and was unaware of the patients' identities and the initials, centre, and names of investigators. Before starting to diagnose cases, we assessed the consensus panel members' performance by presenting them with clinical data for ten non-study cases (five DLB, five Alzheimer's disease; documented in the format described above) for whom autopsy diagnosis was independently available to validate their diagnostic accuracy. All cases were correctly allocated, with 100% concordance between the members of the consensus panel.

The individual panel members reviewed each study case before meeting to agree a final clinical diagnosis of probable DLB, possible DLB, or non-DLB dementia. Patients in the non-DLB category were further allocated to probable or possible Alzheimer's disease, probable or possible vascular dementia, or other (other was to be specified).

Within a few weeks of clinical diagnosis, we acquired SPECT images 3–6 h after a single intravenous injection of ^{123}I-FP-CIT[27] (supplied by GE Healthcare).[28] The recommended dose ranged from 111 MBq to 185 MBq. Images were acquired with 2-headed or 3-headed gamma cameras in a procedure that lasted approximately 40–60 min. Before and 12–24 h after ^{123}I-FP-CIT administration, we gave every patient a thyroid-blocking preparation to stop local uptake of the ligand.

An independent nuclear physician assessed the raw image data and interactively reconstructed all SPECT images on a HERMES workstation (Nuclear Diagnostics, Northfleet, Kent, UK), using HERMES software (version 3.4.4). Additionally, automated, volume-of-interest based semi-quantification of regional DAT striatal binding was undertaken by the same physician using the BRASS neurodiagnostic module of the Hermes 3.4.4 software. Three independent blinded readers (nuclear physicians with expertise in DAT imaging) verified the projection data and assessed these reconstructed images; blinded image assessment was also undertaken on a HERMES workstation with the above software at an independent image review centre (Oslo, Norway). All three readers visually interpreted the SPECT images individually in a random order and one of the physicians verified the correctness of the previously performed quantification procedure. The image analysis, procedures used, and results obtained are described in detail elsewhere.[29] The physicians who assessed the SPECT images were unaware of the patients' personal and clinical information, except for age, since striatal ^{123}I-FP-CIT binding ratios decrease with age.[30] The readers classified the images as normal or abnormal (figure 1). Abnormal scans were subdivided as previously described: asymmetric uptake with normal or almost normal putamen activity in one hemisphere and a more marked change on the other side (type 1); greatly reduced uptake in the putamen on both the right and left sides (type 2); uptake virtually absent (type 3). As can be seen, image D shows little or no evidence of specific binding in caudate and putamen compared with the rest of the cortex.[13] We used only the dichotomous division of normal versus abnormal images for the efficacy assessment.

Statistical analysis

We analysed data with SAS software (version 9.1). For binomially distributed data, we assessed differences among the different diagnostic groups (probable DLB, possible DLB, non-DLB dementia) with respect to patients' characteristics by means of χ^2 tests. We used an analysis of variance (ANOVA) for normally distributed data; if normality could not be established, we used the non-parametric Kruskal-Wallis test.

Our primary analysis was a comparison of the results of visual assessment (normal or abnormal scan) in patients with probable DLB or non-DLB. For this analysis, we calculated: sensitivity—the percentage of times that the image diagnosis was abnormal given that the clinical diagnosis was probable DLB;

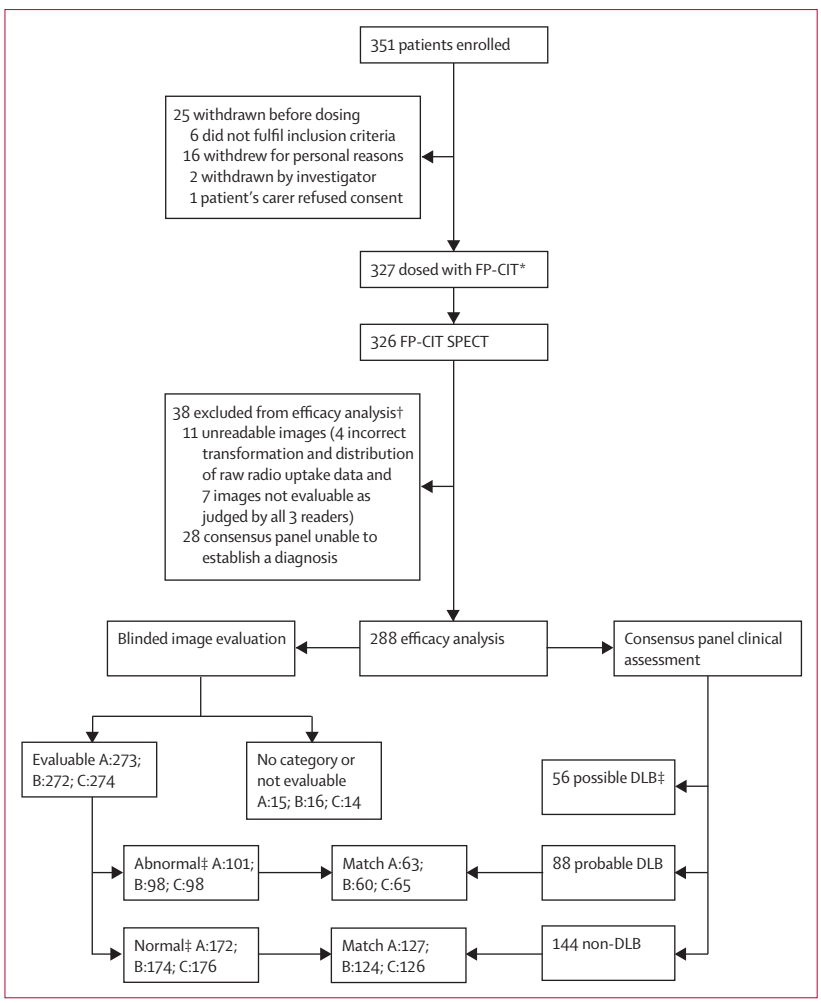

***Figure 2*: Flow chart of patients' disposition**

*One patient who had not been enrolled into the study erroneously received radiotracer. No data were received and no case record form was filled in by the study centre. †Patients could be excluded for more than one reason. A, B and C refer to three independent, masked readers. ‡Patients with a diagnosis of possible DLB were not included in the confirmatory analysis but are included in the numbers of images with normal and abnormal diagnosis. Abnormal includes types 1, 2, and 3. Non-DLB includes possible and probable Alzheimer's disease, vascular dementia, and other forms of dementia.

specificity—the percentage of times that the image diagnosis was normal given that the clinical diagnosis was non-DLB; accuracy—the percentage of times the image diagnosis matched the clinical diagnosis; positive predictive value (PPV)—the percentage of times that the clinical diagnosis was probable DLB given that the image diagnosis was abnormal; and negative predictive value (NPV)—the percentage of times that the clinical diagnosis was non-DLB given that the image diagnosis was normal. We calculated 95% CIs for these estimates with an exact binomial procedure. As part of a secondary analysis we then did similar calculations for patients diagnosed with possible DLB by the consensus panel.

Sample size calculations were based on the hypothesis that the sensitivity and specificity rates of ^{123}I-FP-CIT imaging in the detection of probable DLB and non-DLB patients would be 80% and 85%, respectively (based on an earlier single site study).[15] Using a one-sided, binomial test with a target significance level of 0·025, a total of 218 patients (96 DLB and 122 non-DLB) was needed to achieve 90% power to detect –0·15 (sensitivity) and –0·12 (specificity) difference between these anticipated targets and prespecified thresholds (0·65 for sensitivity, 0·73 for specificity). An over-enrolment of 10% was done to adjust for incorrect clinical categorisation requiring approximately 242 patients to be enrolled. An additional 50 possible DLB cases were enrolled to allow a secondary objective of assessing the performance of imaging in this group and a further 10% were recruited to allow for dropouts and non-evaluable images (total at least 320 subjects).

We ascertained inter-reader agreement for visual assessment (normal or abnormal scan) with Cohen's κ statistic for each pair of independent image readers. Additionally, we calculated a generalised κ coefficient that simultaneously combined the results of all three independent readers. κ values are equal to zero when the agreement does not differ from chance and equal to one when there is perfect agreement.

	Probable DLB (n=94)	Possible DLB (n=57)	Non-DLB (n=147)	No diagnosis (n=28)	p
Male	59 (63%)	36 (63%)	73 (50%)	19 (68%)	0·0810*
Female	35 (37%)	21 (37%)	74 (50%)	9 (32%)	
Age (years)	74·2 (6·6)	74·8 (6·9)	74·9 (7·3)	70·9 (7·9)	0·0296†
UPDRS	28·9 (14·4)	18·5 (11·7)	6·0 (7·6)	17·3 (13·1)	<0·0001†
Hoehn &Yahr	2·51 (1·07)	1·69 (1·05)	0·22 (0·78)	1·41 (1·39)	<0·0001‡
MMSE	20·0 (4·5)	20·9 (4·2)	21·5 (4·4)	23·0 (3·6)	0·0104‡
CDR	1·4 (0·69)	1·2 (0·62)	1·2 (0·69)	1·3 (0·70)	0·0645‡
CAMCOG-R	60·6 (17·6)	63·1 (15·9)	65·4 (16·1)	68·2 (14·4)	0·0280†
Clinical assessment of cognitive fluctuation	6·8 (4·2)	3·0 (4·1)	0·3 (1·2)	3·4 (3·9)	<0·0001‡
NPI-Total	22·7 (17·9)	17·7 (13·3)	10·6 (11·4)	17·1 (14·6)	<0·0001‡
Cornell scale for depression in dementia	6·2 (3·6)	5·7 (3·7)	3·6 (3·0)	6·4 (2·9)	<0·0001‡

Data are mean (SD) or number (%). *χ^2 test. †ANOVA. ‡Kruskal-Wallis test.

***Table 1:* Clinical characteristics of the 326 patients assessed by the consensus panel**

	Sensitivity (95% CI) (n=88)*	Specificity (95% CI) (n=144)*	Accuracy (95% CI) (n=232)*	PPV (95% CI)	NPV (95% CI)
Reader A	77·8 (67·2–86·3)	91·4 (85·4–95·5)	86·4 (81·1–90·6)	84·0 (73·7–91·4)	87·6 (81·1–92·5)
Reader B	75·0 (64·1–84·0)	88·6 (82·1–93·3)	83·6 (78·1–88·3)	78·9 (68·1–87·5)	86·1 (79·4–91·3)
Reader C	80·2 (69·9–88·3)	91·3 (85·3–95·4)	87·2 (82·1–91·3)	84·4 (74·4–91·7)	88·7 (82·3–93·4)
Mean	77·7 (64·1–88·3)	90·4 (82·1–95·5)	85·7 (78·1–91·3)	82·4 (68·1–91·7)	87·5 (79·4–93·4)

*Total number of patients varies slightly by reader, depending on number of evaluable images (readers A and B, n=220; reader C, n=219)

Table 2: **Sensitivity, specificity, accuracy, PPV, and NPV of visual assessment of SPECT images in differentiating between probable DLB and non-DLB**

	Probable DLB (n=88)*	Possible DLB (n=56)*	Probable AD (n=91)*	Possible AD (n=35)*	non-DLB (n=144)*
Reader A	77·8 (67·2–86·3)	41·5 (28·1–55·9)	5·8 (1·9–12·9)	15·6 (5·1–31·9)	8·6 (4·5–14·6)
Reader B	75·0 (64·1–84·0)	38·5 (25·3–53·0)	9·1 (4·0–17·1)	12·1 (3·4–28·2)	11·4 (6·7–17·9)
Reader C	80·2 (69·9–88·3)	34·5 (22·2–48·6)	5·9 (1·9–13·2)	12·1 (3·4–28·2)	8·7 (4·6–14·7)
Mean	77·7 (64·1–88·3)	38·2 (22·2–48·6)	6·9 (1·9–17·1)	13·3 (3·4–31·9)	9·6 (4·5–17·9)

Data are proportion of abnormal ^{123}I-FP-CIT SPECT images (95% CI). AD=Alzheimer's disease. *Number of patients with the respective consensus panel diagnosis. Total number of patients varies slightly by reader, depending on number of evaluable images (reader A, n=273; reader B, n=272; reader C, n=274).

Table 3: **Proportion of abnormal SPECT visual assessment findings in relation to the groups of possible DLB, probable DLB, possible Alzheimer's disease, probable Alzheimer's disease, and non-DLB**

Safety assessment

Patients' safety was assured throughout the whole procedure. Safety assessment included adverse event reporting and evaluation of laboratory variables, vital signs, electrocardiogram, and physical and neurological examinations undertaken at various time points before, during, and after ^{123}I-FP-CIT administration and SPECT imaging.

Role of the funding source

The study was initiated by the principal investigators who designed the protocol in discussions with the sponsor (GE Healthcare) who financially supported the collection, analysis, and interpretation of data, and who were involved in the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 2 shows the flow of the 351 patients through the study. 25 individuals withdrew from the trial before ^{123}I-FP-CIT administration; these individuals are not included in the safety assessment. Of the 326 individuals who received the radiopharmaceutical and who comprised the safety population, 38 were not assessed for efficacy because 11 had unreadable images and 28 were not given a clinical diagnosis by the expert consensus panel (one subject was excluded on both grounds). The on-site clinical diagnoses for the 28 non-evaluable patients were fairly evenly distributed across the three diagnostic groups (probable DLB, n=6; possible DLB, n=9; non-DLB, n=13). Their exclusion is unlikely therefore to have introduced a significant selection bias.

The patients' characteristics are shown in table 1 by subpopulation, according to the diagnoses made by the consensus panel. The mean age of the 326 patients who received ^{123}I-FP-CIT was 74·3 years and 57% were men.

Of the 288 patients included in the efficacy analysis, 88 were diagnosed with probable DLB, 56 with possible DLB, and 144 with non-DLB (of whom 90 had probable Alzheimer's disease, 34 had possible Alzheimer's disease, one had probable vascular dementia, eight had possible vascular dementia, and 11 fulfilled DSM-IV criteria for dementia but subtype diagnosis was unclear). 150 had MRI structural scans and 176 had CT scans as part of the diagnostic procedure.

Table 2 shows the results of the three blinded SPECT readers with respect to the percentages of abnormal SPECT visual assessment findings—probable DLB versus non-DLB patients. The mean sensitivity of SPECT imaging for a clinical diagnosis of probable DLB was 77·7% (95% CI 64·1–88·3) and mean specificity 90·4% (82·1–95·5). We obtained mean values of 85·7% (78·1–91·3) for accuracy, 82·4% (68·1–91·7) for PPV, and 87·5% (79·4–93·4) for NPV.

Table 3 shows the sensitivity of ^{123}I-FP-CIT SPECT visual assessment findings with respect to diagnoses of possible DLB and possible Alzheimer's disease; a mean of 38·2% individuals with possible DLB had abnormal images (range 34·5–41·5) compared with a mean of 13·3% (12·1–15·6) of individuals with possible Alzheimer's disease.

The inter-reader agreement regarding visual assessment (normal or abnormal scan) was very high between the independent readers A and B: 0·82 (95% CI 0·75–0·90); A and C: 0·91 (0·85–0·96); B and C: 0·85 (0·78–0·91). For all three readers simultaneously, Cohen's was 0·87 (0·79–0·94), which also indicates good agreement. Most abnormal scans reported were either type 2 or type 3, with only 4·0–7·0% assessed as type 1.

42 of the 326 patients who received ^{123}I-FP-CIT (13%) had a total of 51 adverse events. Most of these (86%) were

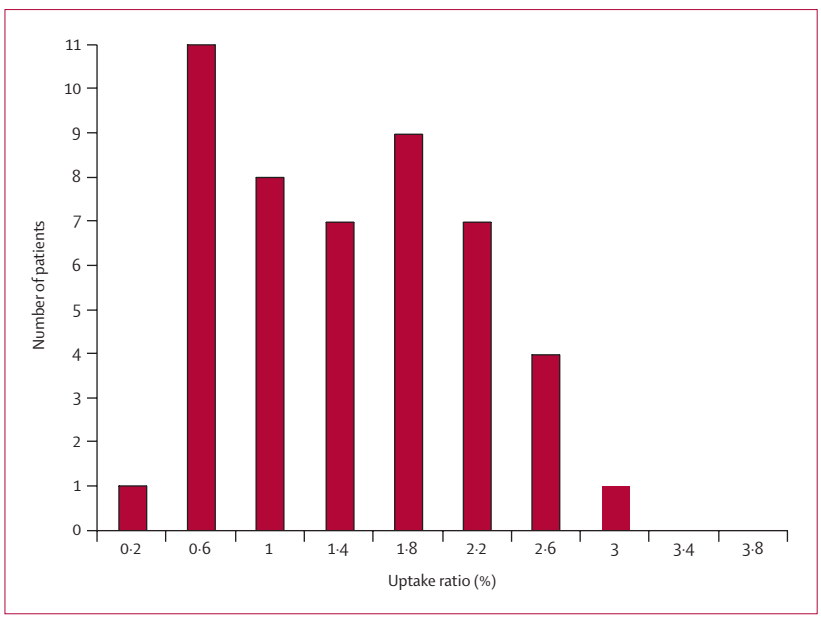

***Figure 3*: Distribution of uptake ratios in patients with a clinical diagnosis of possible DLB**
Uptake ratio was expressed as a ratio of the uptake in individual regions of interest to that of a region of non-specific uptake in occipital cortex. Data for right putamen are shown—a similar pattern was seen in right caudate and right total striatum and in left caudate, left putamen, and left total striatum.

mild in intensity; five (10%) were moderate; and two (4%) were severe. Ten adverse events (20%) were noted in nine patients and were felt to be related to ^{123}I-FP-CIT administration: three (6%) of nausea, two (4%) each of injection-site haemorrhage and injection-site erythema, and one (2%) each of dry mouth, vomiting, and headache. The injection-site related events observed were associated with the route of administration and were not the result of ^{123}I-FP-CIT-related sensitivity reaction. The remaining 41 adverse events (80%) were deemed by the investigator to be related to a cause other than ^{123}I-FP-CIT. No patients withdrew because of adverse events. One death was reported during the study (fractured neck of femur unrelated to the procedure).

Discussion

Our results indicate a high rate of agreement between abnormal striatal DAT binding measured in vivo with ^{123}I-FP-CIT SPECT and a clinical diagnosis of probable DLB (two or more core clinical features present).[8] This finding confirms and further extends findings of earlier single-site studies.[14,15] Given the high specificity of probable DLB clinical diagnosis against the neuropathological diagnosis reported in a review of autopsy controlled studies[31] (mean 92%), it is reassuring to find that the SPECT diagnosis in this study has a similarly high specificity against the consensus clinical diagnosis. The sensitivity of ^{123}I-FP-CIT SPECT imaging is much higher than the reported accuracy rates for clinical consensus criteria against neuropathological findings, which taken collectively find the mean sensitivity of a diagnosis of probable DLB to be only 49% (range 0–83%). The potential gain in diagnostic precision provided by ^{123}I-FP-CIT SPECT is therefore predominantly in sensitivity of case detection, which could be increased from a mean of 49% to the 77·7% reported here.

The clinical diagnosis of possible DLB is even more problematic. The only autopsy study to report on the accuracy of a possible DLB clinical diagnosis[32] noted a specificity of only 28%—ie, most had some other pathology accounting for their presentation. 38% of patients in our study who had a clinical diagnosis of possible DLB also had an abnormal ^{123}I-FP-CIT SPECT image, which is broadly similar to the autopsy rate. The pattern of binding within the possible DLB group seems to comprise a symmetrical bimodal distribution (figure 3) suggesting that it contained a mix of true DLB and non-DLB cases and that SPECT has the potential to discriminate between them. This possibility will need to be established through long-term follow-up of these cases.

The significance of an abnormal scan in 6·9% of patients with probable Alzheimer's disease and 13·3% of patients with possible Alzheimer's disease is unclear. Some patients were probably clinically misclassified by the clinical panel because of a lack of typical DLB features. Images with low striatal binding (false-positive results) have also been reported in a small proportion (5%) of older controls.[15] Conversely, a proportion of patients with apparently typical DLB in this study and others[14,15] have normal scans, analogous to the SWEDD population (subjects without evidence of dopaminergic deficit) identified in clinical trials addressing the progression of Parkinson's disease.[33]

A limitation of our study design is that the gold standard for image validation was a clinical and not a neuropathological diagnosis. However, the clinical consensus panel technique has been shown to be accurate in a prospective diagnostic study with neuropathological confirmation, using the same three-reader system.[34] The sensitivity and specificity of a clinical diagnosis of probable DLB (n=24) in that sample were 83% and 95% and of possible and probable Alzheimer's disease combined (n=19) were 87% and 83%. The feasibility of doing a 40-site multinational study with significant autopsy accrual is highly questionable and would take many years of follow-up to achieve a representative autopsy sample. The consensus panel approach that we used is therefore justifiable and offers a good surrogate for neuropathological diagnosis with no particular biases towards either improving or underestimating the performance of SPECT imaging.

A second potential limitation is that the presence of parkinsonism in DLB cases could have biased the results towards a higher rate of abnormal SPECT in the DLB groups. However, this is a circular argument as parkinsonism is one of the core features by which DLB is

recognised. Analysis of scan performance in those probable DLB cases without significant parkinsonism, defined by a UPDRS score of 15 or less (n=11, 13% of probable DLB group), identified abnormal scans in 64–70% of patients—similar to the performance in the whole group. The cut-off of 15 was chosen because the UPDRS III motor scale contains 14 items and a score of 1 on each of these may be consistent with normal ageing or due to minor confounding issues—eg, physical or cognitive comorbidity. Imaging seems, therefore, to be able to detect dopaminergic degeneration even when it is not clinically manifested as motor parkinsonism, potentially making the technique particularly useful in identifying such cases. Although up to a quarter of patients with Alzheimer's disease can also develop levodopa-resistant parkinsonism, this development usually arises late in the disease course and is not related to the loss of dopaminergic neurons but to striatal tangle pathology.[35] Such patients would not be expected to have severely abnormal DAT binding. Only three patients with Alzheimer's disease had UPDRS scores of 15 or more in this mild-to-moderately demented study population, and in all three the SPECT result was normal, similar to a previous report.[36]

The 50% prevalence of probable and possible DLB cases in our study sample is much higher than the 10–15% typically seen in a dementia assessment clinic but probably reflects the type of population in which ^{123}I-FP-CIT SPECT will typically be used—ie, a group with an increased suspicion and pretest probability of a DLB diagnosis. Most of our non-DLB cases had probable Alzheimer's disease, only 3% had vascular dementia, and no cases of frontotemporal dementia were included. These latter two groups have been shown to have raised rates of abnormal DAT binding and clinicians should bear them in mind when interpreting the significance of an abnormal ^{123}I-FP-CIT SPECT scan.

Is making a clinical diagnosis of DLB important? We feel that it is, because it will prompt the clinician not only to modify pharmacotherapy, but also to assess the patient for additional DLB-specific symptoms that would not generally be considered in non-DLB dementias, such as Alzheimer's disease. These include extrapyramidal motor signs, gait and balance problems, autonomic dysfunction, and specific sleep disorders. The avoidance of neuroleptics in DLB is important because of severe neuroleptic sensitivity reactions,[37] which can induce severe and often irreversible parkinsonism with disturbances in level of consciousness and autonomic stability. There is also emerging evidence that some patients with DLB respond particularly well to cholinesterase inhibitors with improvements in attention, global cognition, and neuropsychiatric features, especially apathy, anxiety, visual hallucinations, and delusions.[7]

There are several other neuroimaging investigations that can help in reaching a diagnosis of DLB but with lower sensitivity and specificity. Examples are preservation of hippocampal[38] and medial temporal lobe volume (sensitivity 38%, specificity 100%) on MRI,[39] atrophy of the putamen,[40] occipital hypoperfusion SPECT (sensitivity 65%, specificity 87%),[41,42] and hypometabolism (PET)[43,44] without occipital atrophy on MRI.[45] Other features, such as the degree of generalised atrophy, rate of progressive brain atrophy, and severity of white matter lesions do not aid in the differential diagnosis of DLB from other dementia subtypes.[46,47] Carbon-11-labelled dihydrotetrabenazine (DTBZ) PET, which examines striatal monoaminergic presynaptic terminal density,[48] and cardiac iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy examining cardiac sympathetic denervation[49] have also been reported as useful in the discrimination of DLB and Alzheimer's disease, but have not yet been applied in large-scale, multicentre clinical trials.

The limited sensitivity of the 1996 clinical consensus criteria for DLB has prompted a recent revision based on new information accumulated since their formulation.[50] The operationalisation of the core features has been improved with the recommendation of specifically designed methods for their detection and quantification. Three new features deemed suggestive of DLB (REM sleep behaviour disorder, severe neuroleptic sensitivity, or low DAT binding in basal ganglia as shown by SPECT or PET imaging) warrant a diagnosis of probable DLB if one or more occurs in conjunction with one core feature. Even in the absence of any core features, these suggestive features should raise suspicion of possible DLB.

Our findings suggest that ^{123}I-FP-CIT SPECT imaging can make a significant contribution to increasing diagnostic accuracy of DLB. An abnormal scan in a patient with dementia and without a history of Parkinson's disease is suggestive of DLB. The test may be used in patients in whom DLB is suspected (possible DLB) to increase diagnostic confidence or to confirm a diagnosis in cases of probable DLB (two or more core features) in which the clinician remains uncertain. The technique is acceptable to patients, and the image reconstruction and the visual analysis are practical and sufficiently robust for use in multiple clinical settings. ^{123}I-FP-CIT SPECT imaging is not helpful in distinguishing DLB and Parkinson's disease with dementia since nigrostriatal dopaminergic degeneration occurs in both disorders as it also does in other parkinsonian syndromes associated with dementia, including progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy. False positive (abnormal, low uptake) FP-CIT SPECT images may be produced if there are vascular lesions in the basal ganglia and, if suspected, these should be sought by CT or MRI.[51] SPECT imaging seems to offer a significant advance in improving our ability to distinguish DLB from Alzheimer's disease and should, in doing so, contribute to better patient management.

The DLB study group

Principal Investigators

Austria—Franz Aichner, OÖ Landesnervenklinik, Linz; Susanne Asenbaum, Universitätshospital Wien, Wien; Gerhard Ransmayr, Allgemeines Krankenhaus Linz, Linz; Michael Rainer, Wien.

France—Jean M Orgogozo, Université Bordeaux, Bordeaux; Florence Pasquier, Hôpital Roger Salengro, Lille; Jacques Touchon, Hôpital Gui de Chauliac, Montpellier; Giovanni Castelnovo, CHU de Nîmes Hôpital Caremeau, Nîmes.

Germany—Johannes Schwarz, Klinik und Poliklinik für Neurologie, Leipzig; Guy Arnold (until Jan 24, 2005) and Eike Spruth (since Jan 25, 2005), Humbold-Universität Berlin, Berlin; Thomas Müller, St Josef-Hospital, Bochum; Inga Zerr, Georg-August Universität Göttingen, Göttingen; Cornelius Weiller (until Feb 15, 2005) and Achim Liepert (since Feb 16, 2005), Universitätsklinikum Eppendorf Klinik und Poliklinik für Neurologie, Hamburg; Reinhard Dengler, Neurologische Klinik mit klinischer Neurophysiologie, Hannover; Peter Urban, Johannes-Gutenberg Universität Mainz Klinik und Poliklinik für Neurologie, Mainz; Wolfgang Oertel, Klinikum der Phillips-Universität Marburg, Marburg; Adrian Danek, Klinikum Großhadern der Ludwig-Maximilians-Universität, München; Rainhard Ehret, Berlin; Per Odin, Neurologische Klinik, Bremerhaven; Alexander Kurz, Psychiatrische Klinik der TU München, München.

Italy—Gilberto Pizzolato (until Dec 31, 2004) and Gianluigi Ricchieri (since Jan 1, 2005), Università di Padova, Padova; Alberto Albanese, Istituto Nazionale Neurologico "Besta", Milano; A Padovani, Spedali Civili di Brescia, Brescia; U Bonuccelli, Università di Pisa.

Norway—Dag Aarsland, Stavanger Universitetssjukehus, Stavanger; Jan Aasly, St Olavs Hospital, Trondheim.

Portugal—Maria M Pareira Costa, HPP Medicina Molecular, Porto.

Sweden—Lars-Olof Wahlund, Karolinska Universitetssjukhuset, Stockholm; Ulla Passant, Universitetssjukhuset, Lund; Elisabet Londos, Universitetssjukhuset, Malmö.

Spain—Eduardo Tolosa Sarro, Hospital Clinic i Provincial, Barcelona; Lorenzo Morlán Gracía, Hospital Universitario de Getafe, Madrid; J Andrés Burguera, Hospital Universitario La Fe, Valencia; Eulegio Gil Neciga, Hospital Virgen del Rocio, Sevilla.

UK—Alan Thomas, Bensham General Hospital, Gateshead; Naji Tabet, Uckfield Community Hospital; E Jane Byrne, Wythenshawe Hospital, Manchester; Peter J Conelly, Murray Royal Hospital, Perth; Peter Bowie, Longley Centre, Sheffield; Derek Brown, Woodlands Centre, Kirkintilloch; Gordon Wilcock, BRACE Centre, Bristol; Clive Holmes, Moorgreen Hospital, Southampton.

Czech Republic—Martin Bojar, Universitiy Hospital Motol, Prague.

Nuclear Physician/Investigator

Austria—Robert Pichler, OÖ Landesnervenklinik, Linz; Michael Schaffarich, Andrea Hofmann, Universitätshospital Wien, Wien; Robert Pichler, OÖ Landesnervenklinik, Linz; Michael Schaffarich, Andrea Hofmann, Universitätshospital Wien, Wien.

France—Michel Zanca, Hôpital Gui de Chauliac, Montpellier; Pierre Olivier Kotzki, Laurent Collombier, CHU de Nîmes Hôpital Caremeau, Nîmes; Michele Allard, Hopital Pellegrin, Bordeaux; Marc Steinling, Hôpital Roger Salengro, Lille.

Germany—Osama Sabri, Swen Hesse, Klinik und Poliklinik für Nuklearmedizin, Leipzig; Dieter L Munz, Dirk Sandrock, Humbold-Universität Berlin, Berlin; Andreas Bockisch, Stefan Müller, Sandra Rosenbaum, Klinik und Poliklinik für Nuklearmedizin, Essen; Johannes Meller, Ute Siefker, Georg-August Universität Göttingen, Göttingen; Susanne Klutmann, Universitätsklinikum Eppendorf, Hamburg; Wolfram Knapp, Georg Berding, Medizinische Hochschule Hannover, Hannover; Martin Bartenstein, Johannes-Gutenberg Universität Mainz, Mainz; Helmut Höffken, Klinik für Nuklearmedizin, Marburg; Alexander Drzezga, Klinikum Rechts der Isar, München; D L Munz, Dirk Sandrock, Humbold-Universität Berlin, Berlin; Wolfram Knapp, Georg Berding, Medizinische Hochschule Hannover, Hannover.

Italy—Franco Bui, Pietro Zucchetta, Maria Cristina Marzola, Servizio di Medicina Nucleare, Padova; Ferruccio Fazio, IRCCS Fondazione San Raffaele del Monte Tabor, Milano; R Giubbini, Spedali Civili di Brescia, Brescia; G Mariani, Duccio Volterrani, Roberto Ceravolo, Università di Pisa, Pisa.

Norway—Attila Kovacs, Nukleærmedisinsk avd, Stavanger; Harald Johnsen, St Olav's Hospital, Trondheim.

Portugal—José Manuel Pereira Oliveira, Hospital Privado da Boavista, Porto.

Sweden—Rimma Daniellson, Karolinska Universitetssjukhuset, Stockholm; Erik Ryding, Douglas Hägerström, Universitessjukhuset, Lund; Ola Thorsen, Universitetssjukhuset MAS, Malmø.

Spain—Francisco Lomeña, Hospital Clinic i Provincial, Barcelona; Carlos Pey, Merche Mitjavilla, Hospital Universitário de Getafe, Madrid; Rosa Perez Velasco, Hospital Universitário La Fe, Valencia; David Garcia Solís, Hospital Universitario Virgen del Rocío, Sevilla.

UK—Jim Lloyd, Royal Victoria Infirmary, Newcastle-upon-Tyne; Sabina Dizdarevic, Royal Sussex County Hospital, Brighton; Mary Prescott, Manchester Royal Infirmary, Manchester; Norman Kennedy, Ninewells Hospital & Medical School, Dundee; Wendy Tindale, Royal Hallamshire Hospital, Sheffield; Gerry Gillen, Western Infirmary, Glasgow; Nigel Bush, Frenchay Hospital, Bristol; Paul Kemp, Southampton General Hospital, Southampton.

Czech Republic—Hana Krizova, University Hospital Motol, Prague.

Contributors

IMcK, JO'B, and ZW were involved in conception and design of the study and were members of the clinical consensus panel. KT, JD, and JB were involved in conception and design of the study and performed the visual and quantitative (JT) reads of the SPECT data. AP, RG, UB, DV, CH, PK, and NT were study investigators. CR was involved in conception and design of the study and IM performed the statistical analysis. IMcK wrote the initial draft of the paper and all authors contributed to its preparation. The final version was read and approved by all authors with IMcK incorporating their additional comments.

Conflicts of interest

IMcK, JO'B, ZW, KT, JB, and JD have received consultancy payments from GE Healthcare. AP, RG, UB, CH, PK, and NT have received reimbursement for study expenses from GE Healthcare. IM and CR were employees of GE Healthcare. All other authors declare that they have no conflicts of interest.

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Prospective validation of Consensus criteria for the diagnosis of dementia with Lewy bodies

I. G. McKeith, C. G. Ballard, R. H. Perry, P. G. Ince, J. T. O'Brien, D. Neill, K. Lowery, E. Jaros, R. Barber, P. Thompson, A. Swann, A. F. Fairbairn and E. K. Perry

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Prospective validation of Consensus criteria for the diagnosis of dementia with Lewy bodies

I.G. McKeith, MD; C.G. Ballard, MD; R.H. Perry, MD; P.G. Ince, MD; J.T. O'Brien, DM; D. Neill, PhD; K. Lowery, BSc; E. Jaros, PhD; R. Barber, MRCPsych; P. Thompson, FRCPsych; A. Swann, MRCPsych; A.F. Fairbairn, FRCPsych; and E.K. Perry, PhD

Article abstract—*Objective:* To determine the validity of a clinical diagnosis of probable or possible dementia with Lewy bodies (DLB) made using International Consensus criteria. *Background:* Validation studies based on retrospective chart reviews of autopsy-confirmed cases have suggested that diagnostic specificity for DLB is acceptable but case detection rates as low as 0.22 have been suggested. *Methods:* We evaluated the first 50 cases reaching neuropathologic autopsy in a cohort to which Consensus clinical diagnostic criteria for DLB, National Institute for Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for AD, and National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for vascular dementia (VaD) had been prospectively applied. *Results:* Twenty-six clinical diagnoses of DLB, 19 of AD, and 5 of VaD were made. At autopsy, 29 DLB cases, 15 AD, 5 VaD, and 1 progressive supranuclear palsy were identified. The sensitivity and specificity of a clinical diagnosis of probable DLB in this sample were 0.83 and 0.95. Of the five cases receiving a false-negative diagnosis of DLB, significant fluctuation was present in four but visual hallucinations and spontaneous motor features of parkinsonism were generally absent. Thirty-one percent of the DLB cases had additional vascular pathology and in two cases this contributed to a misdiagnosis of VaD. No correlations were found between the distribution of Lewy bodies and clinical features. *Conclusion:* The Consensus criteria for DLB performed as well in this prospective study as those for AD and VaD, with a diagnostic sensitivity substantially higher than that reported by previous retrospective studies. DLB occurs in the absence of extrapyramidal features and in the presence of comorbid cerebrovascular disease. Fluctuation is an important diagnostic indicator, reliable measures of which need to be developed further. **Key words:** Dementia—Lewy bodies—Clinical criteria—Sensitivity and specificity.

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Early, accurate clinical diagnosis of dementia with Lewy bodies (DLB) is important[1-7] because it is common, accounting for 15 to 36% of demented cases at autopsy,[8-10] and has a different course,[11] prognosis,[12] and treatment response[13,14] compared with other dementia types. Particularly important management issues include the avoidance of severe neuroleptic sensitivity reactions, achieving the optimal level of antiparkinsonian treatment without exacerbating psychiatric symptoms, and a possible beneficial response to cholinesterase inhibitors.

Three retrospective chart reviews examining the validity of the Consensus criteria for clinical diagnosis of DLB[7] have been published.[5,6,10] Reported sensitivity rates for a clinical diagnosis of probable DLB have varied from 0.22 to 0.75, and specificity from 0.79 to 1.0. Although such retrospective validation studies give a preliminary indication of the perfor-

From the Institute for the Health of the Elderly, Newcastle General Hospital, Newcastle upon Tyne, UK.
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Address correspondence and reprint requests to Dr. Ian McKeith, Professor of Old Age Psychiatry, Wolfson Research Centre, Institute for the Health of the Elderly, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, UK.

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mance of diagnostic criteria, they are potentially confounded by clinical data that were either not recorded in the first instance or were recorded in insufficient detail. Lack of information substantially reduces inter-rater reliability for specific items, and if these are required for diagnosis, will also reduce case detection rates, reflected in low sensitivity figures. For DLB diagnosis, the most problematic item to determine reliably from case notes has been identified as "fluctuation."[4-6] This may, however, be as much a limitation of retrospective chart reviews as of the concept of fluctuation. The necessary test is to apply the clinical diagnostic criteria actively to patients antemortem and then to follow their progress to the time of death and subsequent autopsy. This article reports the findings of such a prospective autopsy validation study of the DLB Consensus criteria. The aim of the study was to assess their sensitivity and specificity in a prospectively assessed cohort, followed to neuropathologic autopsy.

Methods. *Sample.* The Medical Research Council prospective dementia study was established in Newcastle upon Tyne in 1995. Its specific purpose was to evaluate the pathologic characteristics of patients clinically diagnosed as having dementia associated with cortical LB according to the Newcastle criteria[1] for senile dementia of LB type (SDLT),[9] and to compare these with clinically diagnosed AD cases. Patients were recruited via two routes. A specialist outpatient clinic invited potential LB case referrals from psychiatrists, neurologists, and geriatricians covering a wide geographic area (northeast England). The second source, which also provided AD cases, was from consecutive referrals to an old age psychiatry service responsible for assessing dementia presentations from a catchment area population of 100,000 people aged over 65 years living in Tyneside. Cases were eligible for the study if they met relevant diagnostic criteria, were not severely demented (Mini-Mental State Examination [MMSE] score > 8) at baseline, had a reliable informant, and gave appropriately informed consent.

Clinical diagnosis was made after comprehensive multidisciplinary assessment. The DLB Consensus criteria were published during the initial recruitment phase of the study and were substituted for the original Newcastle criteria. All DLB study diagnoses were therefore made using Consensus criteria. National Institute for Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[15] and National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN)[16] criteria were used for the diagnosis of probable or possible AD or vascular dementia (VaD), respectively.

Research assessments at baseline and repeated annually were the Geriatric Mental State (GMS) and History and Etiology (HAS) standardized psychiatric interviews,[17,18] which collect demographic information and inquire into psychiatric and medical history and symptomatic presentation; the Columbia University Scale for the assessment of Psychosis in AD (CUSPAD)[19]; the Cambridge Cognitive Examination (CAMCOG), a standardized and well validated 107-point cognitive assessment schedule[20]; and a neurologic examination including a detailed assessment for focal neurologic signs and the Unified PD Rating Scale (UPDRS) motor section modified for use in demented patients.[21] Next of kin were approached at study entry and asked to indicate their intention to consent to brain autopsy at the time of the subject's death.

Clinical diagnoses were reviewed after death and before neuropathologic diagnosis was available. All clinical data including research assessments and clinical charts were made available to three independent raters (I.G.M., C.G.B., J.T.O.) who listed the clinical diagnoses made and checked that patients had fulfilled criteria. The three raters' decisions were compared and a primary research clinical diagnosis—i.e., that considered most likely—was assigned to each case. Cases of disagreement were resolved by majority verdict. Secondary diagnoses were additionally assigned, using the same procedures, in a hierarchical way to all cases who fulfilled more than one set of criteria.

Neuropathologic evaluation. Brains were dissected fresh for snap frozen tissue sampling and for formaldehyde fixation. Cerebral hemispheres were sliced in the coronal plane every 7.5 mm and the distribution and volume of macroscopic infarcts were mapped on a standardized chart, developed in Newcastle, and confirmed by histology on the coronal slices. Microvascular changes (widening of perivascular spaces, hyaline thickening of arteriolar walls, perivascular pallor of myelin, areas of microinfarction) were evaluated histologically in the basal ganglia; frontal, temporal, parietal, and occipital cortices; deep white matter; hippocampus; amygdala; and midbrain/brainstem. The neuropathologic diagnosis of AD was made using quantitative techniques to determine plaque (von Braunmuhl stain) and tangle (modified palmgren stain) density.[9] The Consortium to Establish a registry for Alzheimer's Disease (CERAD) protocol was also used to evaluate plaques,[22] and Braak staging[23] and Newcastle criteria[9,24] to quantify tangles. The quantitative assessment of LB density followed the Consensus protocol,[7] using ubiquitin,[25] Tau2, Alz50, and AT8 antibodies[26] to detect and distinguish cortical LB. Neuropathologic diagnosis of DLB was made according to the International Consensus criteria and a cortical LB score was assigned following the protocol guidelines[7]; for VaD, diagnosis was made according to NINDS-AIREN criteria.[16] Final neuropathologic diagnosis was agreed in all 50 cases by at least two assessors.

Statistical analysis. The sensitivity, specificity, positive and negative predictive values, and likelihood ratios for each clinical diagnostic group were calculated[27] using pathologic diagnosis as the external validation. Sensitivity is the proportion of true (neuropathologically confirmed) positives correctly identified clinically; specificity is the proportion of true negatives. Positive predictive value (PPV) is the proportion of patients with positive test results who are correctly diagnosed; negative predictive value (NPV) is the proportion of patients with negative test results who are correctly diagnosed. The PPV and NPV can be calculated for any prevalence as follows:

$$\text{PPV} = \frac{\text{Sensitivity} \times \text{prevalence}}{\text{Sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}$$

$$\text{NPV} = \frac{\text{Specificity} \times (1 - \text{prevalence})}{(1 - \text{Sensitivity}) \times \text{prevalence} + \text{specificity} \times (1 - \text{prevalence})}$$

The likelihood ratio represents the probability of making a primary clinical diagnosis (A) if the patient truly has that

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Table 1 Agreement between primary and secondary clinical diagnosis

	Primary clinical diagnosis					
Secondary clinical diagnosis	Probable DLB, n = 24	Possible DLB, n = 2	Probable AD, n = 9	Possible AD, n = 10	Probable VaD, n = 2	Possible VaD, n = 3
Probable DLB, n = 2	N/A	0	0	2	0	0
Possible DLB, n = 7	0	N/A	1	5	0	1
Possible AD, n = 21	17	1	N/A	N/A	1	2
Possible VaD, n = 1	1	1	0	0	0	N/A

DLB = dementia with Lewy bodies; VaD = vascular dementia.

same pathologic diagnosis (A), compared with the probability of receiving diagnosis (A) despite having pathologic diagnosis (B or C).

$$\text{Likelihood ratio} = \frac{\text{Sensitivity}}{(1 - \text{specificity})}$$

Results. Fifty cases were autopsied out of 63 who died during the first 3 years of the study—an autopsy accrual rate of 79%. Twenty-six cases had a primary clinical diagnosis of DLB (25 probable and 1 possible), 19 had a primary diagnosis of AD (9 probable and 10 possible), and in 5 cases, VaD was the primary diagnosis (2 probable and 3 possible).

Thirty-one cases received secondary clinical diagnoses—21 possible AD, 2 probable DLB, 7 possible DLB, and 1 possible VaD. The relationships between primary and secondary clinical diagnoses are shown in table 1 and confirm previous reports that the majority of DLB cases also meet criteria for other dementia subtypes, particularly possible AD.[5]

At autopsy, 29 neuropathologic diagnoses of DLB were made, 15 of AD, and 5 of VaD. One case had atypical pathologic features of progressive supranuclear palsy (PSP). The pathologic groups were similar for mean (SD) age at death: DLB, 78.3 (5.5) years; AD, 83.4 (4.7) years; and VaD, 79.7 (7.0) years. Sex distributions were also similar: percentage of women in DLB was 58%; in AD, 68%; and in VaD, 60%. VaD cases presented earlier in their illness after first onset of symptoms, at a mean (SD) of 1.3 (0.6) years, compared with DLB at 3.6 (2.4) years and AD at 3.3 (1.8) years. The prevalence of core clinical diagnostic features of DLB (significant fluctuation, persistent visual hallucinations, spontaneous parkinsonism) in the autopsy-confirmed DLB cases were 85%, 85%, and 87%, respectively.

Neuropathologically, of the 29 autopsy-positive DLB cases, 69% had Consensus criteria LB scores > 6 (neocortical category), 24% had LB scores of 3 to 6 (limbic category), and 7% had scores of 2 or less (brainstem category). Patients in these these groups were not distinguishable by any specific pattern of demographic or clinical features. Using semiquantitative senile plaque estimates, 54% were classified as CERAD definite AD cases, 33% as probable AD, and 12% did not fulfill minimum CERAD criteria for AD. Braak staging was: Stage 0, four cases; Stage 1, four cases; Stage 2, 12 cases; Stage 3, four cases; Stage 4, four cases; Stage 5, one case; and Stage 6, no cases. Only one DLB case, therefore, had isocortical AD using the Braak method, and only two cases (7%) had sufficient neocortical neurofibrillary tangles for a diagnosis of AD using Newcastle criteria.[24]

Twenty of the 29 DLB cases (69%) had no significant vascular pathology. Six (21%) had "incidental" small focal ischemic lesions predominantly in white matter or basal ganglia, and 3 (10%) had a moderate degree of vascular pathology consisting of small infarcts (<15 mL) combined with arteriosclerosis or congophilic angiopathy. In only one case were these vascular lesions considered sufficient, by themselves, to produce a dementing syndrome.

Clinicopathologic correlation and diagnostic accuracy. Table 2 shows the sensitivity, specificity, PPV, NPV, and likelihood ratios for each of the primary clinical diagnostic groups. Twenty-four pathologically confirmed DLB cases were correctly identified by primary clinical diagnoses of probable DLB according to the Consensus criteria, returning a diagnostic sensitivity and specificity of 0.83 and 0.95. For all diagnoses of probable or possible DLB combined, specificity fell to 0.91. Corresponding figures for a clinical diagnosis of probable or possible AD were 0.87 and 0.83, and for probable and possible VaD, 0.40 and 0.93.

Three additional DLB autopsy cases were correctly identified by their secondary diagnosis (two probable, one possible), potentially increasing overall sensitivity of detection to 27/29 = 0.93. Six incorrect secondary diagnoses of DLB were made (all as possible cases), reducing specificity to 0.76 if secondary diagnoses are included in the analysis.

Misclassified cases. Eleven of the 50 primary clinical diagnoses were not substantiated at autopsy (22%). Table 3 reports the pathologic findings in the two clinical false positive and five false negative DLB cases.

False positive DLB diagnoses. Two false positive clinical diagnoses of DLB were made. Case A (see table 4) was a woman who at age 81 suddenly started to experience recurrent complex visual hallucinations of people in her house, also seeing colored flags and distorted images in mirrors and windows. These fluctuated, being present for several weeks at a time. At age 83, she was hospitalized with an unexplained acute confusional state, following which the hallucinations became more persistent. Her cognitive impairment was always mild (MMSE 20/30 only 6 months before death) and did not show significant fluctuations. CT brain scan was normal. Hachinski Ischemic Score (HIS) was 2. There were no extrapyramidal features but she became confused and very sedated with haloperidol. The clinical diagnosis of possible DLB was based on the presence of mild cognitive impairment and prominent visual hallucinations. Nonprogression of dementia and lack of cognitive fluctuation were atypical features. At au-

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Table 2 *Sensitivity, specificity, and predictive values of primary clinical diagnoses compared with neuropathologic diagnosis*

	Pathologic diagnosis								
Primary clinical diagnosis	DLB, n = 29	AD, n = 15	VaD, n = 5	PSP	Sensitivity	Specificity	PPV	NPV	Likelihood ratio
Probable DLB, n = 25	24	1	0	0	0.83	0.95	0.96	0.80	17.3
Possible DLB, n = 1	0	0	0	1					
Probable + possible DLB, n = 26	24	1	0	1	0.83	0.91	0.92	0.79	8.7
Probable AD, n = 9	0	7	2	0	0.78	0.94	0.78	0.94	12.0
Possible AD, n = 10	3	6	1	0					
Probable + possible AD, n = 19	3	13	3	0	0.87	0.83	0.68	0.94	5.0
Probable VaD, n = 2	0	0	2	0	0.40	1.00	1.00	1.00	—
Possible VaD, n = 3	2	1	0	0					
Probable + possible VaD, n = 5	2	1	2	0	0.40	0.93	0.40	0.93	5.7

DLB = dementia with Lewy bodies; VaD = vascular dementia; PSP = progressive supranuclear palsy; PPV = positive predictive value; NPV = negative predictive value.

topsy she had tau-positive neuronal inclusions suggesting PSP but with an atypical distribution and mild vascular pathology, but no LB.

The other clinical false positive diagnosis (of probable DLB) was Case B, a 77-year-old man with severe bronchiectasis and chronic obstructive airway disease who had multiple hospitalizations because of recurrent confusional episodes that were usually diagnosed as secondary to recurrent chest infections. He was too deaf for formal assessment but appeared to have mild and only slowly progressive cognitive impairment. When confused he responded to prominent visual hallucinations of people, animals, and flowers in his house. MRI brain scan showed marked hippocampal atrophy. HIS was 3. There was mild generalized limb rigidity, resting and action tremor, and unsteady gait that was aggravated by thioridazine. A clinical diagnosis of probable DLB was made because the confusion and hallucinations sometimes appeared to occur independently of recurrent chest infections. At autopsy he had plaque-predominant AD and some additional minor vascular pathology.

False negative DLB diagnoses. Five pathologically confirmed DLB cases received other primary clinical diagnoses (two as possible VaD—Cases C and G in table 4, and three as possible AD—Cases D, E, and F). Two of these five cases (D and F) had secondary diagnoses of probable DLB and one (Case E) of possible DLB.

Case C. This 87-year-old man had a 1-year history of recurrent confusional states and fluctuating levels of orientation and consciousness that were presumed to be secondary to recurrent urinary infections, although urine cultures were consistently negative. CT brain scan showed mild, generalized atrophy only. Later, he had a definite stroke with a residual left hemiparesis, followed by a series of transient ischemic attacks. CT was not repeated. HIS was 13. The fluctuating confusional episodes, which were marked in first 1 to 2 years of his illness, diminished after the stroke. Hallucinations and extrapyramidal features were never recorded. He was diagnosed with possible VaD.

Case G. This 88-year-old woman experienced rapid cognitive decline over 6 months. Mild day-to-day fluctuation was noted but no hallucinations or extrapyramidal features were present. She had asymmetric tendon reflexes L > R and CT brain scan showed small areas of infarction in the basal ganglia in addition to moderate generalized atrophy. HIS was 7. A SPECT blood flow scan showed low cortical uptake and a right anterior parietal defect. She was diagnosed with possible VaD.

Case D. Case D had a rapid onset of fluctuating confusion at age 84 with repeated unexplained falls and visual hallucinations where she imagined seeing relatives in her house and cats and dogs in the pattern on her carpet. She also heard a baby crying. These stopped abruptly after 5 months although paranoid delusions about poisoning and theft persisted. CT brain scan showed generalized atrophy and periventricular ischemia. HIS was 6. She became oversedated with mild limb rigidity on 1 mg risperidone daily but had no spontaneous extrapyramidal features. Late-stage episodic losses of consciousness were diagnosed as TIAs despite absence of focal neurologic signs. Although she met probable DLB criteria early in her illness, this was considered as a secondary diagnosis because core symptoms did not persist.

Case E. This man had a history of having an anterior cerebral aneurysm clipped at age 70 after frontal headache and collapse. He had a myocardial infarction and developed secondary renal impairment at age 72. There was fluctuating confusion of sudden onset at age 78 in which he was intermittently disorientated with socially disinhibited behavior, but he also had lucid periods. CT brain scan

Table 3 *Agreement between secondary clinical diagnosis and neuropathologic diagnosis*

	Pathologic diagnosis		
Secondary clinical diagnosis	DLB	AD	VaD
Probable DLB, n = 2	2	0	0
Possible DLB, n = 7	1	6	0
Possible AD, n = 21*	18	1	1
Possible VaD, n = 1	1	0	0

* 1 = Atypical tau disorder (progressive supranuclear palsy); DLB = dementia with Lewy bodies; VaD = vascular dementia.

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Table 4 *Neuropathologic features of clinically misclassified dementia with Lewy bodies (DLB) cases*

Case	Primary (1) and secondary (2) clinical diagnosis and core clinical features			CERAD diagnosis,* rank			Braak stage†	Newcastle AD criteria	AD type	Vascular features (all insufficient on their own to cause dementia)	Cortical LB score	Neuro-pathologic diagnosis
	Fluctuation	Hallucinations	EPF	1st	2nd	3rd						
Clinical false positive DLB cases (n = 2)												
A	1) Possible DLB 2) Possible AD 0	++	0	11	2		1	−		Small infarcts in putamen and globus pallidus external segment and cerebellum		Atypical tau disorder (atypical PSP)
B	1) Probable DLB 2) Possible AD +	+	+	2	7f		5	+	Atypical—plaque predominant, medial temporal and subcortical tangles	Small vessel pathology (perivascular space enlargement and diffuse white matter pallor) and small infarcts in frontal lobe white matter and cerebellum		AD atypical
Clinical false negative DLB cases (n = 5)												
C	1) Possible VaD 2) Possible AD +	−	−	6c	7a	3	0	−		Small old parieto-occipital infarct, larger recent fronto-parietal and occipital infarcts, and vascular amyloid in occipital lobe	9	DLB, neocortical category
D	1) Possible AD 2) Probable DLB +	+	−	2	6d		5	+	Typical—neocortical plaques and tangles and subcortical tangles	Moderate vascular thickening and increased perivascular spaces in putamen and mild arteriosclerosis in white matter vessels	7	DLB, neocortical category
E	1) Possible AD 2) Possible DLB ++	−	−	7f	6b	4a	3	−		Mild diffuse congophilic angiopathy, small left parietal infarct and superficial hemosiderosis	0	DLB, brainstem category
F	1) Possible AD 2) Probable DLB −	+	+	6c	2		2	−	Mild—plaque predominant and medial temporal tangles	None of note	9	DLB, neocortical category
G	1) Possible VaD 2) Possible AD +	−	−	6d	7f		2	−		Ischemic focus in hippocampus (CA1) and prominent arteriosclerosis in striatum with vascular tortuosity and perivascular enlargement	4	DLB, limbic category

* Consortium to Establish a Registry for AD (CERAD) diagnosis: 2 = definite AD; 3 = probable AD; 4a = possible AD; 5a = definite PD with or without dementia and with LB at any site; 6b = PD-related changes with LB in substantia nigra and/or other subcortical structures (brainstem DLB); 6c = PD-related changes with LB in neocortex (neocortical DLB); 6d = PD-related changes with LB in amygdala and/or entorhinal cortex (limbic DLB); 7a = vascular disease with infarcts only; 7f = vascular disease, other than infarcts, lacunae, Binswanger's disease, and hemorrhage; 11 = progressive supranuclear palsy (PSP).

† Braak stages of AD: 1+2 = transentorhinal; 3+4 = limbic; 5+6 = isocortical.

EPF = extrapyramidal features.

showed the surgical clip and some right frontal atrophy only. HIS was 4. He met possible DLB criteria but possible AD was the primary diagnosis, the atypical features being attributed to frontal damage following surgery.

Case F. This man was first assessed at age 77 after 5 years of progressive cognitive decline that started with sudden onset of periodic confusion, daytime drowsiness, and visual hallucinations. HIS was 2. In his final year, poor mobility and falls were attributed to parkinsonism but were nonresponsive to levodopa. Although he met probable DLB criteria, the diagnosis of possible AD was preferred because cognitive fluctuation was not marked and the hallucinations were thought to be possibly due to cataracts and digoxin toxicity.

Discussion. Using Consensus criteria for the diagnosis of DLB, 24 of 29 autopsy-confirmed cases were correctly identified antemortem—a sensitivity rate of 0.83. Two false positive clinical diagnoses of DLB were made (one probable, one possible), producing an

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overall diagnostic specificity of 0.91 in this sample. Three additional LB cases were given secondary clinical diagnoses of DLB (two possible and one probable), potentially increasing sensitivity to 0.93, although at the cost of reduced specificity (0.76). These figures compare favorably with the corresponding sensitivity and specificity rates for NINCDS-ADRDA diagnoses of AD (0.87, 0.83) and NINDS-AIREN diagnoses of VaD (0.40, 1.00) made within this same study and similar to those reported elsewhere.[28,29]

The group of patients studied was heavily biased toward including patients with DLB, who accounted for 52% of the clinical and 58% of the pathologic sample. This weighting was intentional as the primary objective was to test how the Consensus criteria performed in the positive identification of cases. We anticipated, therefore, that we might tend to overdiagnose DLB clinically, and were surprised to find the opposite, with only 2/26 (8%) false positive diagnoses but 5/29 (17%) of autopsy-confirmed cases remaining undetected.

The over-representation of DLB cases (the prevalence of autopsy-confirmed DLB in patients attending our routine dementia assessment service is typically only 15 to 20%) requires an adjustment to be made so that PPV and NPV rates can be generalized to clinical practice. Positive and negative predictive values are dependent on the prevalence of the disease in the sampling frame and can be calculated for any known prevalence—see Statistical methods for details.

Assuming a DLB prevalence of 15%, the estimated PPV for a primary diagnosis of probable DLB is 0.75 and NPV is 0.96. In other words, 75% of cases clinically assessed as probable DLB in our routine dementia assessment service are likely to be correctly diagnosed, as are 96% of those considered not to have DLB. For all DLB primary diagnoses (probable + possible), PPV = 0.61, NPV = 0.97. The corresponding figures for a DLB prevalence of 20% are probable DLB, 0.80, 0.95; and for probable and possible DLB combined, 0.69, 0.95. A similar calculation to adjust AD prevalence rates from the 30% in this research sample to the 60% usually reported in our typical clinic population produces estimates for a diagnosis of probable AD of PPV = 0.95, NPV = 0.73, and for probable and possible AD combined, PPV = 0.88, NPV = 0.81.

Five DLB pathology cases were given incorrect primary clinical diagnoses—three of possible AD and two of possible VaD. The clinical findings were characterized by a lack of spontaneous extrapyramidal features in four of the five and by the absence of visual hallucinations in three or a failure of these to persist over time in one case (Case D). We have previously commented on the importance of clinicians being prepared to diagnose DLB in the absence of parkinsonism,[30] as literature review of nine recent studies finds it never to occur in up to 20% of cases.[12] Review also finds visual hallucinations to be present at any point throughout the illness in only 46% (range 13 to 80%). Therefore, although both of these core features are useful "signposts" alerting clinicians to the possibility of DLB, they cannot be relied upon to detect approximately one fifth of cases. In Case E, the presence of an etiologic factor (previous intracranial surgery) possibly accounted for the atypical, fluctuating clinical presentation. He had superficial cerebral hemosiderosis due to an anterior communicating artery aneurysm and brainstem LB in this case may represent epiphenomenal LB.[31]

All three cases incorrectly assigned as having possible AD were additionally given secondary diagnoses of DLB, indicating that the assessors had recognized suggestive clinical features but had difficulty in correctly interpreting their significance in relation to other signs and symptoms. Neither of the two cases misdiagnosed with possible VaD was offered a secondary diagnosis of DLB, even though both met possible criteria. Additional vascular pathology was present in 9 of the 29 cases (31%) classified neuropathologically as having DLB; in 6 cases (21%), the lesions were "incidental" small, focal areas of ischemia, predominantly in white matter or basal ganglia, of the type commonly reported in the brains of cognitively unimpaired older people. They had no effect on accuracy of DLB diagnosis.

In the three remaining cases (10%), the vascular pathology was more extensive and in two was associated with a clinical misdiagnosis of possible VaD. Review of Case C shows that fluctuating, confusional episodes preceded the patient's later stroke by at least a year and the incorrect clinical diagnosis was partly a consequence of attempting to find a unitary explanation for all symptoms, rather than opting for a "mixed pathology" category. In Case G, a combination of sudden onset, asymmetric tendon reflexes (recorded on only one occasion) and brain scan findings (CT and SPECT) indicative of cerebrovascular disease contributed to the selection of a primary vascular diagnosis. Barber et al.[32] have shown that periventricular lesions and white matter hyperintensities on MRI occur in similar proportions of DLB and AD patients, both being significantly more prevalent than in aged controls and less than in VaD. Minor brain imaging abnormalities, which are often interpreted as evidence of cerebrovascular disease, should not automatically exclude a DLB diagnosis—they are consistent with it and may indicate additional vascular pathology. The decision-making process appears analogous with that for interpreting imaging findings when diagnosing AD.

In four of the five autopsy DLB cases not clinically diagnosed as such, significant cognitive fluctuation was recorded in the records, confirming that this is a key symptom in detecting the syndrome.[7,9] Mega et al.[5] have suggested that well-defined operationalized criteria for distinguishing the fluctuations that characterize DLB are lacking. They suggested that fluctuations of 5 or more points on the MMSE over three administrations in a 6-month period could meet this

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criterion, although within that particular study this criterion did not achieve satisfactory inter-rater reliability. Because our subjects were assessed only annually, we could not directly test this hypothesis. The report of the Second International Workshop on DLB[33] recommends that a variety of complementary techniques be developed to improve the assessment of cognitive fluctuation. These include the use of questionnaires and diary keeping by a reliable informant, which provide a more comprehensive evaluation of different aspects of function, which may fluctuate. The administration of specific psychometric procedures, including computer-based tasks, which are sensitive to very short-term variations in attentional performance may also help to discriminate DLB from AD.[34]

Three previously published, retrospective chart reviews examining the validity of the Consensus criteria have already been mentioned.[5,6,10] Although each used slightly different neuropathologic methods, all three approximated closely to the Consensus guidelines and technical variations are unlikely to have contributed greatly to any discrepant findings. Twenty-five percent of LB pathology cases from a community-based dementia case register in London[10] had additional vascular pathology, similar to the 31% that we found. Our experience is that patients with mixed pathology pose greater problems in accurate clinical diagnosis than "pure" pathologic cases. Chart review identified only two of nine DLB autopsy cases without additional vascular pathology in the London series (sensitivity = 0.22) with no false positive clinical diagnoses (specificity = 1.0). Inspection of the data presented in that article shows that two of these nine cases did not receive a clinical diagnosis of DLB because of a >1 year history of motor PD before the onset of neuropsychiatric features. Although the Consensus statement does stipulate this arbitrary 1-year cutoff, its primary function was to distinguish marker points along the spectrum of LB disease rather than to discriminate from other pathologies. If these two motor onset cases are included, sensitivity increases to 0.44. Two further cases were excluded because of "stroke disease as evidenced by brain imaging," although precise details of the imaging changes are not given. Minor periventricular lucencies or white matter hyperintensities would be consistent with a primary diagnosis of DLB.[32] Another group[6] has suggested that four clinical features have utility in discriminating DLB and AD cases: unspecified hallucinations, unspecified extrapyramidal features, fluctuating course, and rapid progression. The presence of only one of these symptoms had high sensitivity (0.91) but low specificity (0.62) and was therefore analogous with the Consensus "possible" DLB category. Two, three, or more features were associated with improved specificity, but as this reached unity, sensitivity fell to 0.43.

In the most recent study to examine these issues,[35] clinical abstracts from 18 autopsy-confirmed DLB and 76 other non-LB demented cases were reviewed. Inter-rater reliability was acceptable for all key diagnostic items, ranging from 0.57 for fluctuation to 0.90 for extrapyramidal features. Consensus criteria for probable DLB had sensitivity of 0.61 and specificity of 0.84. Diagnostic accuracy improved further (0.78, 0.85) when the analysis was confined to patients with mild or moderate disease or when DLB cases also fulfilling pathologic criteria for AD were excluded (0.78, 0.81).

Several other groups of investigators have presented limited data in abstract form about clinicopathologic correlations in patients clinically diagnosed as having DLB by Consensus criteria. In the Oxford Project To Investigate Memory and Aging (OPTIMA) project,[36] 26 of 102 (25%) of a consecutive series of demented cases were found to have nigral LB. At study entry the sensitivity value of the Consensus criteria was 0.58; specificity, 0.89; PPV, 0.89; and NPV, 0.86. Patients clinically diagnosed with possible DLB were no more likely to have LB at autopsy than were other diagnostic groups, reflecting our own experience that possible DLB as currently defined is a nonspecific label. A discriminant function analysis including 12 items found seven factors that were able to correctly distinguish 85% of autopsy-proven DLB cases from an AD group.[37] These were neuroleptic sensitivity, nonvisual hallucinations, clouding of consciousness, syncope, spontaneous parkinsonian features, fluctuations, and gender. One study[38] found the Consensus criteria to be highly sensitive (0.89) but the false positive diagnosis rate was also high (71%).

This prospective evaluation of the Consensus criteria for the clinical diagnosis of DLB made few false positive diagnoses. Even when diagnostic accuracy rates are corrected to take account of the high proportion of DLB cases in this series, the estimated PPV for probable DLB in a typical dementia clinic population is 0.75 to 0.80. This is similar to the PPV of 0.75 recently reported in a study sample that had a 19% prevalence of DLB cases,[35] suggesting that the core features of DLB, particularly items relating to fluctuation, can be identified when the appropriate clinical methods detailed in the Consensus article are actively applied. Seventeen percent of autopsy-confirmed cases in our sample remained undetected, even when the index of suspicion for DLB was high within a research study. Lack of extrapyramidal features and visual hallucinations were the usual reasons for misdiagnosis, which was more likely to occur in the presence of additional vascular pathology. This suggests that in routine clinical practice a significant proportion of DLB cases are continuing to go undiagnosed. Fluctuating cognition appears to be a more frequent and specific diagnostic feature than either visual hallucinations or parkinsonism. The Second International Workshop on DLB[33] recommended that the Consensus criteria should continue to be used in their current format, the only modification being the addition of REM sleep behavior disorder and depression to the list of additional features

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"supportive" of a diagnosis of DLB. Standardized methods for identifying fluctuation need to be established and diagnostic accuracy may be additionally improved by the use of appropriate investigations. Medial temporal lobe atrophy on MRI is significantly less in DLB than in AD[38] and reduced dopamine transporter activity in the striatum[39] may be visualized by FP-CIT SPECT in DLB but not AD.[40] Future clinicopathologic validation studies should incorporate such diagnostic investigations applied to a suitably heterogenous case mix, including a greater proportion with possible DLB and patients presenting with motor features of PD. Neuropathologic identification of DLB cases should be augmented by the use of antibodies to α-synuclein, which are emerging as the most sensitive markers of LB disease.[41] A final important observation is that there is a high prevalence of mixed pathology, even in a highly selected cohort of demented subjects such as these, serving as a reminder that Occams's razor does not always serve the clinician well. Future developments in clinical classification of the dementias should take account of this.

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Unilateral pallidotomy in PD

A controlled study of cognitive and behavioral effects

B. Schmand, PhD; R.M.A. de Bie, MD; M. Koning-Haanstra, MSc; J.S. de Smet, MSc; J.D. Speelman, MD; and A.H. van Zomeren, PhD, for the Netherlands Pallidotomy Study (NEPAS) group

Article abstract—*Objective:* To investigate whether unilateral pallidotomy affects cognitive and behavioral functioning. *Methods:* At baseline and after 6 months we assessed neuropsychological functioning in 35 patients with advanced PD. After baseline examination, patients were randomized to pallidotomy within 1 month (6 left-sided, 13 right-sided) or to pallidotomy after follow-up assessment 6 months later (n = 16; control group). We performed neuropsychological tests of language, visuospatial function, memory, attention, and executive functions. Self ratings and proxy ratings of memory problems and dysexecutive symptoms were also collected. *Results:* No significant differences over time were found between pallidotomy and control groups, with the exception of a decrease of verbal fluency in the left-sided pallidotomy group. *Conclusions:* Unilateral pallidotomy is relatively safe with respect to cognition and behavior. Left-sided pallidotomy may lead to minor deterioration in verbal fluency. The sample size of this study is too small, however, to rule out the possibility of infrequent but clinically important side effects. **Key words:** PD—Stereotactic surgery, pallidotomy—Cognition disorders—Neuropsychological tests.

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Patients with advanced PD frequently have levodopa-induced dyskinesias and rapid, seemingly unpredictable oscillations in their motor state despite optimal pharmacologic treatment. Pallidotomy is a further treatment option in such cases. In the last decade, several cohort studies investigating the efficacy of posteroventral pallidotomy in advanced PD have been published.[1] The safety of the procedure with respect to cognition and behavior has only recently been studied with appropriate neuropsychological tests. Little or no cognitive or behavioral effects have been reported.[2-12]

Most of these were open studies without a control group. This is a methodologic flaw because it does not control for practice effects of neuropsychological testing, which may lead to better performance at follow-up. Absence of test score decline in a treated group, therefore, does not necessarily imply that there are no harmful effects. Only two studies have used control groups. However, these were self-selected groups, introducing possible bias such as a shorter disease duration in the control patients.[7,9] In many studies, follow-up examinations were not scheduled at fixed intervals; this renders the results difficult to interpret.[2,5,10,11] Finally, few studies appro-priately distinguished between left and right pallidotomy in the statistical analysis of the psychological test results.[3,6,10-12] Failure of the remaining studies to do so may have attenuated the capacity to detect lateralized cognitive changes.

We studied the efficacy and possible side effects of unilateral pallidotomy in a randomized controlled

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From Academic Medical Center (Drs. Schmand, de Bie, and Speelman), Department of Neurology, University of Amsterdam; University Hospital (M. Koning-Haanstra and Dr. van Zomeren), Department of Neurology, Groningen; and Twee Steden Hospital (J. de Smet), Department of Medical Psychology, Tilburg, the Netherlands.

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Address correspondence and reprint requests to Dr. B. Schmand, Department of Neurology, H2-222, Academic Medical Center, P.O. Box 22700, 1100 DE Amsterdam, the Netherlands; e-mail: b.schmand@amc.uva.nl

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Prospective validation of Consensus criteria for the diagnosis of dementia with Lewy bodies

I. G. McKeith, C. G. Ballard, R. H. Perry, P. G. Ince, J. T. O'Brien, D. Neill, K. Lowery, E. Jaros, R. Barber, P. Thompson, A. Swann, A. F. Fairbairn and E. K. Perry

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Diagnosis and management of dementia with Lewy bodies

Third report of the DLB consortium

I.G. McKeith, MD, FMedSci; D.W. Dickson, MD; J. Lowe, DM; M. Emre, MD; J.T. O'Brien, DM; H. Feldman, MDCM; J. Cummings, MD; J.E. Duda, MD; C. Lippa, MD; E.K. Perry, DSc; D. Aarsland, MD; H. Arai, MD; C.G. Ballard, MD; B. Boeve, MD; D.J. Burn, FRCP; D. Costa, MD; T. Del Ser, MD, PhD; B. Dubois, MD; D. Galasko, MD; S. Gauthier, MD, FRCPC; C.G. Goetz, MD; E. Gomez-Tortosa, MD, PhD; G. Halliday, PhD; L.A. Hansen, MD; J. Hardy, PhD; T. Iwatsubo, MD; R.N. Kalaria, FRCPath; D. Kaufer, MD; R.A. Kenny, MD; A. Korczyn, MD; K. Kosaka, MD; V.M.-Y. Lee, PhD, MBA; A. Lees, MD; I. Litvan, MD; E. Londos, MD, PhD; O.L. Lopez, MD; S. Minoshima, MD, PhD; Y. Mizuno, MD; J.A. Molina, MD; E.B. Mukaetova-Ladinska, MD, PhD; F. Pasquier, MD, PhD; R.H. Perry, DSc; J.B. Schulz, MD; J.Q. Trojanowski, MD, PhD; and M. Yamada, MD, PhD, for the Consortium on DLB*

Abstract—The dementia with Lewy bodies (DLB) Consortium has revised criteria for the clinical and pathologic diagnosis of DLB incorporating new information about the core clinical features and suggesting improved methods to assess them. REM sleep behavior disorder, severe neuroleptic sensitivity, and reduced striatal dopamine transporter activity on functional neuroimaging are given greater diagnostic weighting as features suggestive of a DLB diagnosis. The 1-year rule distinguishing between DLB and Parkinson disease with dementia may be difficult to apply in clinical settings and in such cases the term most appropriate to each individual patient should be used. Generic terms such as Lewy body (LB) disease are often helpful. The authors propose a new scheme for the pathologic assessment of LBs and Lewy neurites (LN) using alpha-synuclein immunohistochemistry and semiquantitative grading of lesion density, with the pattern of regional involvement being more important than total LB count. The new criteria take into account both Lewy-related and Alzheimer disease (AD)-type pathology to allocate a probability that these are associated with the clinical DLB syndrome. Finally, the authors suggest patient management guidelines including the need for accurate diagnosis, a target symptom approach, and use of appropriate outcome measures. There is limited evidence about specific interventions but available data suggest only a partial response of motor symptoms to levodopa: severe sensitivity to typical and atypical antipsychotics in ~50%, and improvements in attention, visual hallucinations, and sleep disorders with cholinesterase inhibitors.

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Clinical diagnostic criteria for DLB. Since the publication of Consensus criteria for clinical and pathologic diagnosis of dementia with Lewy bodies (DLB),[1,2] new information indicates that clinical criteria for probable DLB have acceptable specificity, but suboptimal sensitivity.[3,4] Reasons identified include difficulties in recognition of the core feature fluctuation[5,6] and a low rate of all core features (fluctuation, visual hallucinations, parkinsonism) in the presence of neocortical, neurofibrillary tangle (NFT) pathology.[7-9] The criteria have therefore been modified (table 1) to incorporate additional items indicative of LB pathology. Distinction is made between clinical features or investigations that are *suggestive* of DLB, i.e., have been demonstrated to be significantly more frequent than in

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Address correspondence and reprint requests to Professor I.G. McKeith, Institute for Ageing and Health, Wolfson Research Centre, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, UK; e-mail: i.g.mckeith@ncl.ac.uk

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Table 1 *Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)*

1. *Central feature* (essential for a diagnosis of possible or probable DLB)

   Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.

2. *Core* features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)

   Fluctuating cognition with pronounced variations in attention and alertness

   Recurrent visual hallucinations that are typically well formed and detailed

   Spontaneous features of parkinsonism

3. *Suggestive features* (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)

   REM sleep behavior disorder

   Severe neuroleptic sensitivity

   Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

4. *Supportive features* (commonly present but not proven to have diagnostic specificity)

   Repeated falls and syncope

   Transient, unexplained loss of consciousness

   Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence

   Hallucinations in other modalities

   Systematized delusions

   Depression

   Relative preservation of medial temporal lobe structures on CT/MRI scan

   Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity

   Abnormal (low uptake) MIBG myocardial scintigraphy

   Prominent slow wave activity on EEG with temporal lobe transient sharp waves

5. A diagnosis of DLB is *less likely*

   In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging

   In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture

   If parkinsonism only appears for the first time at a stage of severe dementia

6. *Temporal sequence* of symptoms

   DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy.

other dementing disorders, and *supportive* features, which commonly occur but with lower specificity. Clinicians should adopt a high index of suspicion, screening all patients with dementia for possible DLB (one core or one suggestive feature) paying particular attention to the early clinical presentation.[7,10] The widespread use of improved assessment tools and methods of investigation should further improve diagnostic accuracy.

Progressive disabling mental impairment is a mandatory requirement for the diagnosis of DLB. This statement[1] remains true although it is apparent that disability in DLB derives not only from cognitive impairment but also from neuropsychiatric, motoric, sleep, and autonomic dysfunction. The cognitive profile of DLB comprises both cortical and subcortical impairments with substantial attentional deficits and prominent executive and visuospatial dysfunction.[11,12] A "double discrimination" can help differentiate DLB from Alzheimer disease (AD), with relative preservation of confrontation naming and short and medium term recall as well as recognition, and greater impairment on verbal fluency, visual perception and performance tasks.[13-15] Patients with DLB with neocortical neurofibrillary tangles (NFTs) often lack this profile, showing pronounced memory deficits more characteristic of AD. Composite global cognitive assessment tools such as the Mini-Mental State Examination (MMSE) cannot be relied upon to distinguish DLB from other common dementia syndromes and some patients who meet criteria for DLB will score in the normal range.

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DLB and dementia associated with Parkinson disease (PDD). Many patients with PD develop dementia, typically 10 years or more after onset of motor symptoms.[16,17] Other than age at onset, temporal course, and possibly levodopa responsivity,[18,19] no major differences between DLB and PDD have been found in any variable examined including cognitive profile,[20] attentional performance,[21] neuropsychiatric features,[22] sleep disorders,[23] autonomic dysfunction,[24] type and severity of parkinsonism,[25] neuroleptic sensitivity,[26] and responsiveness to cholinesterase inhibitors.[27,28] The relative contributions of LB formation and synuclein pathology, AD-type pathology, neuron loss, or neurochemical deficits as determinants of dementia in PD remain unresolved although recent studies suggest that Lewy-related pathology is more strongly associated than AD-type changes.[29-31]

The distinction between DLB and PDD as two distinct clinical phenotypes based solely on the temporal sequence of appearance of symptoms has been criticized by those who regard the different clinical presentations as simply representing different points on a common spectrum of LB disease, itself underpinned by abnormalities in alpha-synuclein metabolism. This unitary approach to classification may be preferable for molecular and genetic studies and for developing therapeutics. Descriptive labels that include consideration of the temporal course are preferred for clinical, operational definitions. DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism and PDD should be used to describe dementia that occurs in the context of well-established PD. The appropriate term will depend upon the clinical situation and generic terms such as LB disease are often helpful. In research studies in which distinction is made between DLB and PDD, the 1-year rule between the onset of dementia and parkinsonism for DLB should be used. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings including pathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy.

Core features. Although no major amendments to the three core features of DLB are proposed, improved methods for their clinical assessment are recommended for use in diagnosis and measurement of symptom severity.

Fluctuation. It is the evaluation of fluctuation that causes the greatest difficulty in clinical practice.[32] Inter-rater reliability is said to be low[5,6] although reports have generally been based upon review of pre-existing case records and notes, rather than direct rating of patients. Questions such as "are there episodes when his/her thinking seems quite clear and then becomes muddled?" were previously suggested as useful probes, but two recent studies[33,34] found 75% of both AD and DLB carers to respond positively. More detailed questioning and qualitative analysis of carers' replies is therefore needed. The Clinician Assessment of Fluctuation scale[35] requires an experienced clinician to judge the severity and frequency of "fluctuating confusion" or "impaired consciousness" over the previous month. The semi-structured One Day Fluctuation Assessment scale[35] can be administered by less experienced raters and generates a cut-off score to distinguish DLB from AD or vascular dementia (VaD). The Mayo Fluctuations Composite Scale[34] requires three or more "yes" responses from caregivers to structured questions about the presence of daytime drowsiness and lethargy, daytime sleep >2 hours, staring into space for long periods, or episodes of disorganized speech, as suggestive of DLB rather than AD. Recording variations in attentional performance using a computer based test system offers an independent method of measuring fluctuation, which is also sensitive to drug treatment effects.[36] Which of these various available methods is most appropriate will depend upon the setting and the level of expertise available. It is recommended that at least one formal measure of fluctuation is used when applying DLB diagnostic criteria and that staff are appropriately trained in its use.

Visual hallucinations. Recurrent, complex visual hallucinations (VH) continue to be one of the most useful signposts to a clinical diagnosis of DLB. They are generally present early in the course of illness with characteristics as described in the original report.[1] Informant-based assessment tools such as the Neuropsychiatric Inventory (NPI)[37] are helpful both for screening for VH and assessing their severity and frequency but do not always distinguish them from hallucinations in other sensory modalities. Caregivers tend to under-report VH and patients with mild to moderate cognitive impairment can contribute useful information about their presence and quality.[38] Patients with DLB with VH show more profound visuoperceptual dysfunction compared to those without hallucinations.[39,40] Increased numbers of LB in the anterior and inferior temporal lobe and amygdala at autopsy are associated with the presence and onset of VH,[41] each of these areas being implicated in the generation of complex visual images. Brain perfusion imaging demonstrates reduced occipital uptake[42,43] in areas identified as primary and secondary visual cortex.[44] VH are associated with greater deficits in cortical acetylcholine[45,46] and their presence may predict a good response to cholinergic therapy.[47]

Parkinsonism. The severity of extrapyramidal motor features in DLB is generally similar to that of age-matched patients with PD with or without dementia[26] with an average 10% annual progression rate.[48] There is an axial tendency with greater postural instability, gait difficulty, and facial immobility[49] than in non-demented patients with PD. Rest tremor is less common. The assessment of motor features may be complicated by the presence of cognitive impairment. A simple, five-item subscale of the Unified PD Rating Scale (UPDRS)[50,51] contains only those items that can reliably be assessed in DLB

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independent of severity of dementia (tremor at rest, action tremor, body bradykinesia, facial expression, rigidity). Levodopa responsiveness in DLB[18,19] is almost certainly less than in uncomplicated PD, possibly because of intrinsic striatal degeneration[52] and the fact that a significant proportion of the parkinsonian symptoms may be non-dopaminergic in origin.

Suggestive features. If one or more of these is present, in addition to one or more core features, a diagnosis of probable DLB should be made. Possible DLB can be diagnosed if one or more suggestive features is present in a patient with dementia even in the absence of any core features. Suggestive features therefore have a similar diagnostic weighting as core clinical features but are not in the light of current knowledge considered sufficient, even in combination, to warrant a diagnosis of probable DLB in the absence of any core feature.

REM sleep behavior disorder. REM sleep behavior disorder (RBD) is manifested by vivid and often frightening dreams during REM sleep, but without muscle atonia. Patients therefore appear to "act out their dreams" vocalizing, flailing limbs, and moving around the bed sometimes violently. Vivid visual images are often reported, although the patient may have little recall of these episodes. The history is obtained from the bed partner, who may report many years of this sleep disorder prior to the onset of dementia and parkinsonism.[53] RBD is frequently associated with an underlying synucleinopathy—PD, DLB, or multiple system atrophy (MSA)—and only rarely with other neurodegenerative disorders.[54] Associated sleep disorders in DLB including excessive daytime drowsiness may also contribute to the fluctuating pattern. Screening questions about the presence of day and night time sleep disturbance should always be asked, facilitated by the use of sleep questionnaires, particularly those that query bed partners about a history of repeated episodes of "acting out dreams."[23] The diagnosis of RBD may be confirmed by polysomnography.

Severe neuroleptic sensitivity. Deliberate pharmacologic challenge with D2 receptor blocking agents should not be used as a diagnostic strategy for DLB because of the high morbidity and mortality associated with neuroleptic sensitivity reactions,[55] which are characterized by the acute onset or exacerbation of parkinsonism and impaired consciousness.[56] Approximately 50% of patients with DLB receiving typical or atypical antipsychotic agents do not react so adversely and a history of neuroleptic tolerance does not therefore exclude a diagnosis of DLB. A positive history of severe neuroleptic sensitivity is, by contrast, strongly suggestive of DLB.

Dopamine transporter imaging. Functional imaging of the dopamine transporter (DAT) defines integrity of the nigrostriatal dopaminergic system and currently has its main clinical application in assisting diagnosis of patients with tremor of uncertain etiology.[57] Imaging with specific ligands for DAT, e.g., FP-CIT, beta-CIT, IPT, TRODAT, provides a marker for presynaptic neuronal degeneration. DAT imaging is abnormal in idiopathic PD, MSA, and progressive supranuclear palsy (PSP). Low striatal DAT activity also occurs in DLB but is normal in AD,[58] making DAT scanning particularly useful in distinguishing between the two disorders.[59,60]

Supportive features. These are features (see table 1) that are commonly present in DLB but lack sufficient diagnostic specificity to be categorized as core or suggestive. Routine enquiry should be made about such symptoms since patients and carers may not consider them related to the dementing process. Severe autonomic dysfunction may occur early in disease, producing orthostatic hypotension, neurocardiovascular instability, urinary incontinence, constipation, and impotence, as well as eating and swallowing difficulties.[61-63] Autonomic dysfunction may also contribute to repeated falls and syncope and the transient losses of consciousness that are seen in some patients with DLB.[64] Systematized delusions, hallucinations in other modalities, and depression may all occur during the course of DLB and if they are prominent early, they can lead to diagnostic confusion with late onset psychosis, delusional depression, or other primary psychiatric diagnoses.[10,65]

Exclusion features. Careful exclusion of other systemic or neurologic disorders that may explain the clinical presentation is essential. Particular difficulty exists in relation to attributing clinical significance to evidence of cerebrovascular disease, since pathologic and imaging studies suggest that white matter lesions (periventricular and deep white matter), microvascular changes, and lacunes may be present in up to 30% of autopsy confirmed DLB cases.[66,67] A diagnosis of DLB with cerebrovascular disease may sometimes be the most appropriate.

Special investigations. A recent review concluded that there are as yet no clinically applicable genotypic or CSF markers to support a diagnosis of DLB.[3,68] The role of DAT transporter scanning has already been discussed. Other imaging investigations can also be helpful, including preservation of hippocampal and medial temporal lobe volume on MRI,[69,70] atrophy of the putamen,[71] and occipital hypoperfusion (SPECT) and hypometabolism (PET)[42,43,72-74] without occipital atrophy on MRI.[75] Other features such as the degree of generalized atrophy, rate of progressive brain atrophy, and severity of white matter lesions do not aid in differential diagnosis from other dementia subtypes.[76,77] Scintigraphy with [I-123] metaiodobenzyl guanidine (MIBG),[78] which enables the quantification of postganglionic sympathetic cardiac innervation, is reduced in DLB and has been suggested to have high sensitivity and specificity in the differential diagnosis from AD.[79] Confirmatory studies with larger patient numbers are required. The standard EEG may show early slowing, epoch by epoch fluctuation, and transient temporal slow wave activity.[3]

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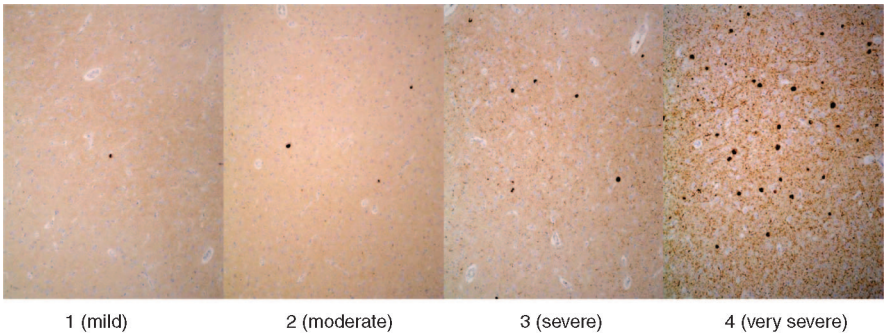

Figure. Staging of alpha-synuclein pathology in dementia with Lewy bodies (DLB). Alpha-synuclein immunostaining in cerebral cortex of DLB cases illustrating increasing severity of Lewy bodies (LBs) and LB pathology scored as stages 1 to 4. Stage 1 = sparse LBs or Lewy neurites (LNs); Stage 2 = >1 LB per high power field and sparse LNs; Stage 3 = ≥4 LBs and scattered LNs in low power field; Stage 4 = numerous LBs and LNs. Images courtesy of Dr. E. Jaros. 5 μm thick sections, pretreated with pressure cooker for 1 minute in EDTA pH8; Vector Elite Kit, Novocastra mouse monoclonal alpha-synuclein antibody (clone KM51), 1:30 dilution, DAB final reaction product.

Pathologic assessment and diagnostic criteria for DLB. *Dementia with Lewy bodies as a pathologic diagnostic category.* DLB was originally defined as a clinicopathologic entity with a specific constellation of clinical features, and a descriptive approach was proposed for assessing neuropathology.[1] The only neuropathologic requirement for DLB was the presence of LBs somewhere in the brain of a patient with a clinical history of dementia. Other pathologic features, e.g., senile plaques and neuron loss, could occur, but they were not inclusive or exclusive to the diagnosis. In many but not all cases the neuropathologic findings conform to those previously described as limbic or diffuse LB disease.[80,81] This liberal definition has the advantage of being widely inclusive, bringing many neuropathologic cases into consideration for DLB; however, as increasingly sensitive methods for detecting LBs have been developed, as many as 60% of AD cases may be considered to meet pathologic criteria for DLB using the 1996 criteria. Virtually none of these patients will have had the DLB clinical syndrome as described above, especially those cases with extensive NFTs[8,9] or those with one or more LBs in the amygdala but without significant Lewy-related pathology in other brain regions.[82] The inclusion of such cases as pathologically confirmed DLB has contributed to a view that the clinical criteria have suboptimal sensitivity.[4]

New recommendations are proposed that take into account both the extent of Lewy-related pathology and AD-type pathology in assessing the degree of certainty that the neuropathologic findings explain the DLB clinical syndrome. The scheme proposed should provide increased diagnostic specificity, since cases in which LBs are detected in the setting of extensive AD-type pathology that is likely to obscure the clinical features of the DLB syndrome are now classified as having a "low likelihood" of DLB.

Identification of Lewy bodies and Lewy-related pathology. LBs and Lewy neurites (LN) are pathologic aggregations of alpha-synuclein. They are also associated with intermediate filaments, chaperone proteins, and elements of the ubiquitin-proteasome system, indicating a role of the aggresomal response, but these features are not specific for LBs and are found in other neuronal inclusions.[83,84]

While hematoxylin and eosin (H&E) histologic staining may be adequate for detection of brainstem type LBs, it is not sufficient for cortical LBs and it is incapable of detecting LNs. Ubiquitin immunohistochemistry, which unequivocally stains LBs and LNs, can only be recommended in cases with minimal concurrent AD-type pathology, since ubiquitin is also present in NFTs, which can be easily confused with LBs. Rather than ubiquitin immunohistochemistry, it is now more appropriate to use immunohistochemical staining for alpha-synuclein, since this has been shown to be the most sensitive and specific method currently available for detecting LBs and Lewy-related pathology. We also recommend a semiquantitative grading of lesion density rather than the counting methods previously proposed (see figure).

Brain sampling and evaluation of Lewy-related pathology. The scheme previously proposed[1] for characterization of regional involvement of the brain with respect to LB pathology, i.e., brainstem, limbic, and diffuse cortical types, as well as the recommended tissue sampling procedures, remains unchanged. The previous Consortium protocol advised counting LB density in five cortical regions with a summed score for the overall LB rating. Given the poor inter-rater reliability of counting of LBs, the new recommendations propose a semiquantitative grading of severity of Lewy-related pathology into mild, moderate, severe, and very severe, along lines similar to those used to grade SP and NFTs by the CERAD protocol.

Brain sampling and evaluation of AD-type pathology in DLB. At the time of the original statement there was considerable uncertainty about the significance of coexisting AD-type pathology[85] and the most widely used method for evaluating AD-type pathology was the CERAD protocol.[86] Subsequently, a working group of the NIA-Reagan Institute expanded upon the CERAD protocol, which used a plaque-based diagnostic algorithm, by adding assessments of topographic stages of neurofibrillary pathology.[87] As well as adding NFTs to the diagnostic algorithm, the NIA-Reagan criteria admit that the

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Table 2 *Assignment of Lewy body type based upon pattern of Lewy-related pathology in brainstem, limbic, and neocortical regions*

Lewy body type pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
	IX-X	LC	SN	nbM	Amygdala	Transentorhinal	Cingulate	Temporal	Frontal	Parietal
Brainstem-predominant	1-3	1-3	1-3	0-2	0-2	0-1	0-1	0	0	0
Limbic (transitional)	1-3	1-3	1-3	2-3	2-3	1-3	1-3	0-2	0-1	0
Diffuse neocortical	1-3	1-3	1-3	2-3	3-4	2-4	2-4	2-3	1-3	0-2

Brain regions are as defined anatomically in the original Consensus report.[1]

IX = 9th cranial nerve nucleus; X = 10th cranial nerve nucleus; LC = locus ceruleus; SN = substantia nigra; nbM = nucleus basalis of Meynert.

fit between clinical and pathologic features is imperfect and that the best that can be accomplished at present is a probability statement about the likelihood that the neuropathologic findings account for dementia. This approach has been adopted in the proposed DLB criteria which assess the likelihood that the neuropathologic findings predict the clinical syndrome of DLB. The likelihood that the observed neuropathology explains the DLB clinical syndrome is *directly related to the severity of Lewy-related pathology, and inversely related to the severity of concurrent AD-type pathology*. This approach is based on studies that demonstrate that clinical diagnostic accuracy for DLB is higher in patients with low burdens of AD-type pathology.[7,8,88] This revision is prompted by the body of literature that deals with clinicopathologic correlations in DLB and the desire to implement more rigorous and specific neuropathologic criteria than currently exist. The proposal obviously requires further research to test its validity. The proposal can be summarized as follows.

- Cases should be assigned a likelihood that the dementia can be attributed to AD pathology using the NIA-Reagan criteria, which employs the CERAD method for assessing neuritic plaques[86] and a topographic staging method for neurofibrillary degeneration comparable to that proposed by Braak and Braak.[89]
- Lewy body type pathology should be assigned according to the previous guidelines in the original Consensus report.[1] Semiquantitative grading of Lewy body severity should be adopted rather than counting LB in various brain regions.
- The following scoring system for LB is recommended (figure):

  0 = None

  1 = Mild (sparse LBs or LNs)

  2 = Moderate (more than one LB in a low power field and sparse LNs)

  3 = Severe (four or more LBs and scattered LNs in a low power field)

  4 = Very severe (numerous LBs and numerous LNs)

While brainstem nuclei are affected in virtually every case of LB disease, the severity of brainstem pathology is highly variable. Similarly, there is a range of severity of involvement in the various limbic and neocortical regions; thus, for most areas a range of severity is acceptable. The pattern of regional involvement is more important than total LB count. Table 2 presents a scheme for assigning LB disease type by assessing the regional pattern of Lewy-related pathology using CERAD-like scoring for LB.

Table 3 shows criteria for allocating a probability that neuropathologic findings will be associated with a DLB clinical syndrome taking account of both AD and LB type pathology.

As in the NIA-Reagan criteria, SP types should be subclassified as diffuse and neuritic but for diagnostic purposes, only neuritic plaques should be considered.

Specification for the assessment of vascular pathology in DLB was made in the original consensus statement document and in the absence of further significant research findings it is recommended to continue using this approach.

Neuropathologic research strategies. A scheme to stage Lewy-related pathology in the brain has been proposed for PD.[90] The validity of staging and its relevance to DLB remains to be determined by its application to brains of prospectively studied individuals with a range of cognitive and extrapyramidal dysfunction. Similarly, while considerable research has been reported on Lewy-related pathology in the amygdala and periamygdaloid cortex using immunostaining for alpha-synuclein, additional studies are warranted in prospectively studied cohorts in order to understand possible clinical correlates of this pathology in DLB as well as in AD, where this may be the only brain region with alpha-synuclein pathology.[91,92] Critical to this issue is the clinical significance, if any, of this pattern of alpha-synuclein pathology. As such, the presence or absence of LB in the amygdala should be documented in all cases of dementia reaching neuropathologic autopsy. Determining the presence of alpha-synuclein pathology in the amygdala in other dementias is a related research objective.

It is clear from several case studies that familial cases of DLB occur[93,94] and that LBs are commonly

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Table 3 Assessment of the likelihood that the pathologic findings are associated with a DLB clinical syndrome

	Alzheimer type pathology		
	NIA-Reagan Low (Braak stage 0–II)	NIA-Reagan Intermediate (Braak stage III–IV)	NIA-Reagan High (Braak stage V–VI)
Lewy body type pathology			
Brainstem-predominant	Low	Low	Low
Limbic (transitional)	High	Intermediate	Low
Diffuse neocortical	High	High	Intermediate

DLB = dementia with Lewy bodies; NIA = National Institute on Aging.

seen in familial cases of AD.[95] There are recent reports that triplication of the alpha-synuclein gene (SNCA) can cause DLB, PD, and PDD whereas gene duplication is associated only with motor PD, suggesting a gene dose effect.[96] However, SCNA multiplication is not found in most patients with LB disease.[97] Continued clinical, pathologic, and genetic evaluation of familial cases of DLB and AD is therefore an important and potential highly informative area for continued research.

Clinical management. Patient management in DLB is complex and includes early detection, investigation, diagnosis, and treatment of cognitive impairment; assessment and management of neuropsychiatric and behavioral symptoms; treatment of the movement disorder; and monitoring and management of autonomic dysfunction and sleep disorders.[98] The evidence base for making recommendations about the management of DLB is limited and what follows is based upon consensus opinion of clinicians experienced in treating DLB.

Nonpharmacologic interventions. Nonpharmacologic interventions have the potential to ameliorate many of the symptoms and functional impairments associated with DLB, but none has yet been systematically evaluated. Cognitive dysfunction and associated symptoms such as VH can for example be exacerbated by low levels of arousal and attention and strategies to increase these by social interaction and environmental novelty may reduce their presence and impact.

Pharmacologic treatments. Motor parkinsonism. Levodopa can be used for the motor disorder of both DLB and PDD.[18,19] Medication should generally be introduced at low doses and increased slowly to the minimum required to minimize disability without exacerbating psychiatric symptoms. Anticholinergics should be avoided.

Neuropsychiatric symptoms. Visual hallucinations are the most commonly experienced psychiatric symptom and are often accompanied by delusions, anxiety, and behavioral disturbance. When pharmacologic intervention is required the options include cholinesterase inhibitors (CHEIs) or atypical antipsychotic medications. Open label studies have demonstrated the effectiveness of all three generally available CHEIs in DLB and PDD but placebo controlled trial data are only available to date for rivastigmine.[27,28] The reported reduction in symptom frequency and intensity of VH appears to be mediated at least in part by improved attentional function and the presence of VH is associated with greater cognitive improvement.[47] Side effects of hypersalivation, lacrimation, and urinary frequency may occur, in addition to the usual gastrointestinal symptoms, and a dose dependent exacerbation of extrapyramidal motor features may occur in a minority. If CHEIs are ineffective or if more acute symptom control of behavior is required, it may be difficult to avoid a cautious trial of an atypical antipsychotic. The clinician should warn both the carer and patient of the possibility of a severe sensitivity reaction.[26] Typical antipsychotics should be avoided.[55] Novel atypicals with potentially more favorable pharmacologic properties, such as quetiapine, clozapine, and aripiprazole, may have theoretical advantages over traditional agents in LB disease[99-101] but controlled clinical trial data are needed.

Depression is common in both DLB and PDD and there have been no systematic studies of its management. At the present time SSRI and SNRIs are probably preferred pharmacologic treatment. Tricyclic antidepressants and those with anticholinergic properties should generally be avoided. Apathy is also common and may improve with CHEIs.[27] Sleep disorders are frequently seen in LB disease and may be an early feature. RBD can be treated with clonazepam 0.25 mg at bedtime, melatonin 3 mg at bedtime, or quetiapine 12.5 mg at bedtime and titrated slowly monitoring for both efficacy and side effects.[53] CHEIs may be helpful for disturbed sleep.[102]

Cognitive symptoms. CHEIs may be of benefit for the fluctuating cognitive impairments with impact on global function and activities of daily living.[103] The effect size in DLB is reported as being generally larger than seen with the same drugs when used in AD.[104] Only limited data on long-term effects are available[105] and there are none about possible disease-modifying effects.

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Author affiliations

From the Institute for Ageing and Health (Drs. McKeith, O'Brien, E.K. Perry, Burn, Kalaria, Kenny, Mukaetova-Ladinska, and R.H. Perry), University of Newcastle upon Tyne, UK; Department of Neuropathology (Dr. Dickson), Mayo Clinic Jacksonville, FL; Division of Pathology (Dr. Lowe), School of Molecular Medical Sciences, University of Nottingham, UK; Department of Neurology (Dr. Emre), Istanbul University, Istanbul Faculty of Medicine, Turkey; UBC Division of Neurology (Dr. Feldman), University of British Columbia, Vancouver, Canada; Department of Neurology (Dr. Cummings), UCLA Medical School Alzheimer's Disease Center, Los Angeles, CA; Parkinson's Disease Research, Education and Clinical Center (Dr. Duda), Philadelphia VAMC, PA; Memory Disorders Program (Dr. Lippa), Drexel University School of Medicine, Philadelphia, PA; Section of Geriatric Psychiatry (Dr. Aarsland), Stavanger University Hospital, Norway; Department of Geriatric & Respiratory Medicine (Dr. Arai), Tohoku University School of Medicine, Miyagi, Japan; Wolfson Centre for Age-Related Diseases (Dr. Ballard), London, UK; Department of Neurology (Dr. Boeve), Mayo Clinic, Rochester, MN; Institute of Nuclear Medicine (Dr. Costa), HPP Medicina Molecular, SA, Porto, Portugal; Section of Neurology (Dr. del Ser), Hospital Severo Ochoa, Madrid, Spain; Hopital La Salpêtrière (Dr. Dubois), Paris, France; Depts. of Neuroscience (Dr. Galasko) and Pathology (Dr. Hansen), University of California San Diego, La Jolla; MCSA Alzheimer's Disease Research Unit (Dr. Gauthier), McGill Centre for Studies in Aging, Quebec, Canada; Department of Neurological Sciences (Dr. Goetz), Rush University Medical Center, Chicago, IL; Fundación Jiménez Diaz (Dr. Gómez-Tortosa), Servicio de Neurología, Madrid, Spain; Prince of Wales Medical Research Institute (Dr. Halliday), Sydney, Australia; Laboratory of Neurogenetics (Dr. Hardy), National Institute on Aging, Bethesda, MD; Department of Neuropathology & Neuroscience (Dr. Iwatsubo), University of Tokyo, Japan; Dept. of Neurology CB 7025 (Dr. Kaufer), University of North Carolina School of Medicine, Chapel Hill; Department of Neurology (Dr. Korczyn), Tel-Aviv University, Israel; Department of Psychiatry (Dr. Kosaka), Fukushimera Hospital, Toyohashi, Japan; Center for Neurodegenerative Disease Research (Drs. Lee and Trojanowski), University of Pennsylvania School of Medicine, Philadelphia; Reta Lila Weston Institute of Neurological Studies (Dr. Lees), Royal Free & UCL Medical School, London, UK; Department of Neurology (Dr. Litvan), Movement Disorder Program, University of Louisville School of Medicine, KY; Department of Clinical Sciences (Dr. Londos), University Hospital, Malmoe, Sweden; Neuropsychology Research Program (Dr. Lopez), University of Pittsburgh Medical College, PA; Department of Radiology (Dr. Minoshima), University of Washington, Seattle; Department of Neurology (Dr. Mizuno), Juntendo University School of Medicine, Tokyo, Japan; Servicio de Neurologia (Dr. Molina), Hospital 12 de Octubre, Madrid, Spain; Clinique Neurologique (Dr. Pasquier), Centre Hospitalier et Universitaire, Lille, France; Department of Neurodegeneration and Restorative Research Center of Neurological Medicine (Dr. Schulz), University of Göttingen, Germany; and Department of Neurology & Neurobiology of Ageing (Dr. Yamada), Kanazawa University Graduate School of Medical Science, Kanazawa, Japan.

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Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium

I. G. McKeith, D. W. Dickson, J. Lowe, M. Emre, J. T. O'Brien, H. Feldman, J. Cummings, J. E. Duda, C. Lippa, E. K. Perry, D. Aarsland, H. Arai, C. G. Ballard, B. Boeve, D. J. Burn, D. Costa, T. Del Ser, B. Dubois, D. Galasko, S. Gauthier, C. G. Goetz, E. Gomez-Tortosa, G. Halliday, L. A. Hansen, J. Hardy, T. Iwatsubo, R. N. Kalaria, D. Kaufer, R. A. Kenny, A. Korczyn, K. Kosaka, V.M.Y. Lee, A. Lees, I. Litvan, E. Londos, O. L. Lopez, S. Minoshima, Y. Mizuno, J. A. Molina, E. B. Mukaetova-Ladinska, F. Pasquier, R. H. Perry, J. B. Schulz, J. Q. Trojanowski, M. Yamada and for the Consortium on DLB

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Article abstract—Clinical criteria for the diagnosis of Alzheimer's disease include insidious onset and progressive impairment of memory and other cognitive functions. There are no motor, sensory, or coordination deficits early in the disease. The diagnosis cannot be determined by laboratory tests. These tests are important primarily in identifying other possible causes of dementia that must be excluded before the diagnosis of Alzheimer's disease may be made with confidence. Neuropsychological tests provide confirmatory evidence of the diagnosis of dementia and help to assess the course and response to therapy. The criteria proposed are intended to serve as a guide for the diagnosis of probable, possible, and definite Alzheimer's disease; these criteria will be revised as more definitive information becomes available.

Clinical diagnosis of Alzheimer's disease:

Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

Alzheimer's disease is a brain disorder characterized by a progressive dementia that occurs in middle or late life. The pathologic characteristics are degeneration of specific nerve cells, presence of neuritic plaques, and neurofibrillary tangles. Alterations in transmitter-specific markers include forebrain cholinergic systems, and, in some cases, noradrenergic and somatostatinergic systems that innervate the telencephalon.

A Work Group on the Diagnosis of Alzheimer's Disease was established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA). The group intended to establish and to describe clinical criteria for the diagnosis of Alzheimer's disease of particular importance for research protocols and to describe approaches that would be useful for assessing the natural history of the disease. The need to refine clinical diagnostic criteria has been emphasized because 20% or more of cases with the clinical diagnosis of Alzheimer's disease are found at autopsy to have other conditions and not Alzheimer's disease. Moreover, therapeutic trials can be meaningfully compared only if uniform criteria are used for diagnosis and response to treatment.

The need for this report was suggested by the National Advisory Council of the NINCDS. The report has been reviewed by workshop participants, representatives of the National Advisory Neurological and Communicative Disorders and Stroke Council, representatives of the ADRDA, and designated reviewers representing professional societies concerned with the diagnosis of Alzheimer's disease. (For list of professional societies and designated reviewers, see page 943.)

The report was developed by subgroups that addressed medical history, clinical examination, neuropsychological testing, and laboratory assessments; the report was then discussed in plenary session. Based on a consensus of the participants, criteria were developed to serve as a clinical basis for diagnosis. These criteria should be useful also for comparative studies of patients in different kinds of investigations, including case control studies, therapeutic trials, evaluation of new diagnostic laboratory tests, and clinicopathologic correlations.

The criteria are not yet fully operational because of insufficient knowledge about the disease. The criteria are compatible with definitions in the current Diagnostic and Statistical Manual of Mental Disorders (DSM III) and in the International Classification of Diseases. These criteria must be regarded as tentative and subject to change. Additional longitudinal studies, confirmed by autopsy, are necessary to establish the validity of these criteria in com-

*For Work Group Participants and Affiliations, see page 943.

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Address correspondence and reprint requests to Dr. Stadlan, 7550 Wisconsin Avenue, Federal Building, Room 700, Bethesda, MD 20205.

Table 1. Criteria for clinical diagnosis of Alzheimer's disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test,[1] Blessed Dementia Scale,[2] or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and

histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

familial occurrence;

onset before age of 65;

presence of trisomy-21; and

coexistence of other relevant conditions such as Parkinson's disease.

parison with other criteria such as DSM III.

Criteria for dementia syndrome. Dementia is the decline of memory and other cognitive functions in comparison with the patient's previous level of function as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests. A diagnosis of dementia cannot be made when consciousness is impaired by delirium, drowsiness, stupor, or coma or when other clinical abnormalities prevent adequate evaluation of mental status. Dementia is a diagnosis based on behavior and cannot be determined by computerized tomography, electroencephalography, or other laboratory instruments, although specific causes of dementia may be identified by these means.

Criteria for Alzheimer's disease. Alzheimer's disease is a progressive, dementing disorder, usually of middle or late life. The clinical criteria for the diagnosis of PROBABLE, POSSIBLE, and DEFINITE Alzheimer's disease are outlined in table 1. A clinical diagnosis of probable Alzheimer's disease can be made with confidence if there is a typical insidious onset of dementia with progression and if there are no other systemic or brain diseases that could account for the progressive memory and other cognitive deficits. Among the disorders that must be excluded are manic-depressive disorder, Parkinson's

disease, multi-infarct dementia, and drug intoxication; less commonly encountered disorders that may cause dementia include thyroid disease, pernicious anemia, luetic brain disease and other chronic infections of the nervous system, subdural hematoma, occult hydrocephalus, Huntington's disease, Creutzfeldt-Jakob disease, and brain tumors.

A diagnosis of definite Alzheimer's disease requires histopathologic confirmation. A clinical diagnosis of possible Alzheimer's disease may be made in the presence of other significant diseases, particularly if, on clinical judgment, Alzheimer's disease is considered the more likely cause of the progressive dementia. The clinical diagnosis of possible rather than probable Alzheimer's disease may be used if the presentation or course is somewhat aberrant. The information needed to apply these criteria is obtained by standard methods of examination: the medical history; neurologic, psychiatric, and clinical examinations; neuropsychological tests; and laboratory studies.

Medical history. A medical history should be taken from the patient and from an informant who is well acquainted with the affected individual. This approach is essential to establish a history of progressive deterioration and for identifying tasks that the patient can no longer perform adequately. A diary maintained by an observer may be very helpful in documenting changes in various functions. The history discloses abnormalities including impaired memory and other cognitive functions, impaired activities of daily living, alterations in mood, often delusions and illusions, and sometimes hallucinations. Common complaints of patients or families include forgetfulness about appointments or errands; inability to find the way to an accustomed destination; inability to use money and instruments of daily living such as a telephone; deterioration in work or homemaking performance; difficulty adapting to changes in the workplace; difficulties in dressing, reading, and writing; and inability to recognize previously familiar individuals.

Clinical examination. The clinical examination provides data to fulfill inclusionary and exclusionary criteria for the diagnosis of Alzheimer's disease and to document symptoms such as delusions or depression that identify subgroups of patients important both for research studies and for patient care. Mental status testing, an essential component of the clinical examination, includes specific assessment of orientation, registration, attention, calculation, recent recall, naming, repeating, understanding, reading, writing, and ability to draw or copy. Because cognitive impairment may occur in depressive syndromes, it is important to inquire about affective state and depressive symptoms, such as disturbed sleep and weight loss, before diagnosing Alzheimer's disease. Inquiry specifically about the presence of delusions and hallucinations is needed to identify subgroups. Both symptoms may be experienced in a variety of neuropsychiatric disorders, which may or may not have known organic substrates.

Quantitative aids to the clinical examination include the Mini-Mental State Examination[1] for cognitive screening; the Blessed Dementia Scale[2] for clinical symptoms and social function; the Hamilton Depression Scale[3] for severity of depression; the Present State Examination[4] for anxiety, depression, delusions, and hallucinations; and the Hachinski Scale[5,6] for estimating the likelihood of multi-infarct dementia. A complete psychiatric evaluation is needed to exclude the various psychiatric disorders.

Complete examination of sensory and motor systems (including cranial nerves, tone, reflexes, coordination, gait, and proprioception) is needed to exclude other neurologic disorders. In early stages, patients are alert and free of other neurologic changes related to the dementia except for the occasional presence of snout reflex, jaw jerk, rigidity, or myoclonus, all of which may be encountered in nondemented elderly people. As the disease progresses, some patients become apathetic or show irritability, agitation, paranoid ideas, sleep disorders, or incontinence. In the very advanced stages, patients may become mute and lose all ability to communicate.

Neuropsychological testing. Neuropsychological tests may provide additional information for the diagnosis of dementia. Because there are no normative population standards for many of these tests, abnormal performance can be determined only by comparison with a normal control group matched for age, sex, and local education. A score falling in the lowest fifth percentile of an individual's normal control group may be designated as "abnormal." One or more abnormal scores will identify an individual for research purposes who is highly likely to be cognitively impaired. Progressive worsening can be established by comparison with the patient's previous performance on these tests. Although there is continued debate about the tests that best measure these functions, the Work Group did make some suggestions (table 2).

Similar series of tests can be used to assess less severely affected patients by increasing the complexity of the neuropsychological tests. Further modification in the test procedure may be needed to detect impairment in highly intelligent patients. Confirmation of the dementia syndrome by neuropsychological tests should be based on measurable abnormalities in two or more aspects of cognition.

In longitudinal assessment, many patients with Alzheimer's disease show progressive loss of recent memory followed by disorders of language, praxis, or visual perception. In some patients with Alzheimer's disease, however, the first symptoms are difficulty in finding words, impaired visual perception, or apraxia, with memory impairment and other symptoms and signs appearing later.

Although neuropsychological tests are presently used primarily to provide confirmatory evidence for

Table 2. Neuropsychological evaluation

The major cognitive processes that are impaired in Alzheimer's disease, with examples of the kinds of tests used to assess these functions, include:

orientation to place and time, graded by a test such as the Mini-Mental State Examination[1];

memory evaluated by tests such as a free-recall test[7] of concrete nouns, a 3-4 paired-associate learning test (verbal and nonverbal) by use of a recognition paradigm, the Recognition Span Test,[8] and the Brown-Peterson Distractor Test[9,10] (stopping the task when the patient fails or begins to produce the distractor instead of the stimulus trigrams);

language skills tested by examination of verbal fluency of the semantic or category type, with the examiner writing responses, and by other tests such as the Boston Naming Test[11] (preferably one of the abbreviated forms), the Boston Diagnostic Aphasia Examination,[12] the Western Aphasia Test,[13] and the Token Test[14-16] with Reporter's Test[17];

praxis evaluated by tests[18] such as those in which the patient copies a drawing (cube, daisy, clock, or house) or performs the block design subtest of the Wechsler Adult Intelligence Scale[19];

attention monitored by tests such as a reaction-time task[20] or by the Continuous-Performance Test[21];

visual perception studied by use of a variety of tasks, such as the Gollin Incomplete-Pictures Test[22] and the Hooper Test[23];

problem-solving skills determined by tests such as the Wisconsin Card Sorting Test[24,25] or The Poisoned Food Problem Task of Arenberg[26,27]; and

social function, activities of daily living,[28,29] and instrumental activity of daily living,[30] assessed by methods similar to those described in the Philadelphia Geriatrics Center Forms.[31]

the diagnosis of dementia, these tests are valuable for determining patterns of impairment, for assessing changes in impairment over time and after drug treatment or rehabilitation, and for establishing correlations of abnormal performance with laboratory and neuropathologic examinations.

Laboratory assessments. Clinical assessment and neuropsychological tests provide information to meet the criteria for clinically probable Alzheimer's disease. At present, there are no specific diagnostic laboratory tests for Alzheimer's disease, but some tests can enhance diagnostic accuracy by identifying other causes of the dementia syndrome. Moreover, as suggested by the Work Group, the laboratory approaches described below used quantitatively in longitudinal studies should help to clarify the natural history of Alzheimer's disease, possibly provide information needed in subtyping the disease, and permit measurement of efficacy of therapeutic interventions. Some of these techniques, particularly positron emission tomography, are strictly investigative tools and not readily available outside of research institutions.

Electrophysiologic methods. The EEG of some patients with Alzheimer's disease shows increased slow-wave activity that may become more pronounced with progression of the disease. Evoked potentials (EP) are brain waves associated with sensory or other events that may be auditory, somatosensory, or visual. Endogenous or cognitive potentials, such as P300, are thought to reflect speed of cognition. The latency of P300 is altered with age, and there appears to be an increased latency of P300 potentials in 50 to 80% of patients with Alzheimer's disease compared with age-matched control subjects. These changes occur in different dementias and are not specific to Alzheimer's disease. The P300 wave, however, is normal in depressive syndromes and may therefore be useful in differentiating the dementia of Alzheimer's disease from the dementia of depressive syndromes, particularly when adequate normal data become available.

Computerized tomography. CT is useful in the diagnosis of Alzheimer's disease because it permits the exclusion of other disorders such as subdural hematoma, brain tumor, hydrocephalus, and dementia associated with vascular disease. The technique can delineate gyri and sulci and quantitate tissue densities, ventricular size, CSF volume, and brain mass. In Alzheimer's disease, the volume of the ventricular system and the width of the third ventricle are increased, gyri are narrowed, and sulci are widened; however, these general patterns may not be particularly useful as diagnostic criteria in individual cases. Furthermore, available data do not indicate how well a qualitative observation correlates with the magnitude of cognitive abnormality or with evidence of progression of disease. There is a pressing need for quantitative CT studies of Alzheimer's disease patients during the course of disease and for correlation of CT images with clinical signs, neuropsychological test results, and autopsy findings.

Regional cerebral blood flow. Measurement of regional cerebral blood flow (rCBF), including ^{133}xenon clearance, may help differentiate Alzheimer's disease and dementia associated with cerebrovascular disease. In multi-infarct dementia (MID), early changes include decreased autoregulation; in the later stages of MID, rCBF and oxygen consumption are decreased. In patients who have Alzheimer's disease, rCBF and cerebral metabolic rate are decreased; but A-V differences, carbon dioxide responses, and autoregulation are preserved.

Positron emission tomography. Positron emission tomography (PET) is a research technique that allows quantitative assessment of the rate of glucose utilization, oxygen consumption, and rCBF. With some isotopes, these characteristics can be assessed during neuropsychological testing; moreover, ^{11}C-markers may permit the use of retest paradigms. Early reports suggest that rCBF determined by PET may be reduced in areas of encephalomalacia. In contrast, most patients with Alzheimer's disease show cerebral hypometabolism when compared with

age-matched controls. These changes correlate with disease severity and may be correlated with neuropsychological test performance. For example, speech impairment may be correlated with decreased activity in the left hemisphere, whereas impaired performance on spatial tasks may be more closely correlated with impaired activity in the right hemisphere. Different approaches may be necessary for delineating presynaptic and postsynaptic markers of transmitter systems, as recently achieved with PET images of the dopamine system. Since PET reveals a significant variation even among normal subjects, any changes may have to be severe to be detected. The value of PET studies in determining the stage of disease, in documenting progression, and in assessing the effects of treatment is unknown.

Magnetic resonance imaging. The proton nuclear magnetic resonance (NMR) image, or magnetic resonance imaging (MRI), reveals the demarcation of gray and white matter of the brain and has therefore proved useful in studies of demyelinating disorders. Although the method has not been applied systematically to the study of dementia, it has potential for differentiating between Alzheimer's disease, multi-infarct dementia, and low-pressure hydrocephalus. Information should soon be available about the usefulness of MRI in the diagnosis of Alzheimer's disease.

Examination of body fluids and nonneural tissues. In the diagnosis of Alzheimer's disease, studies of blood and CSF are helpful in excluding chronic infections, such as cryptococcal meningitis and syphilis, and other disorders. To date, definitive diagnostic information about Alzheimer's disease from blood or CSF has not been sought consistently, but CSF should be studied to demonstrate neurotransmitters, metabolites, and synthesizing and degradative enzymes. Other techniques, such as sophisticated radioimmunoassays with specific antibodies, may be useful for detecting markers of the disease, such as constituents associated with the development of neurofibrillary tangles and neuritic plaques. Specific abnormalities have not been detected in nonneural tissues.

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Work Group Participants and Affiliations

Guy McKhann, MD, Johns Hopkins University Medical School, Chairman; Francois Boller, MD, PhD, University of Pittsburgh; Nelson Butters, PhD, VA Medical Center and University of California School of Medicine, San Diego; Suzanne Corkin, PhD, Massachusetts Institute of Technology; Thomas Crook, PhD, Center for Studies of the Mental Health of the Aging, National Institute of Mental Health; David Drachman, MD, University of Massachusetts Medical Center; Steven Ferris, PhD, New York University; Marshall Folstein, MD, Johns Hopkins University Medical School; John H. Growdon, MD, Massachusetts General Hospital; Leonard Heston, MD, University of Minnesota Medical Center; Michael Huckman, MD, Rush-Presbyterian-St. Luke's Medical Center; Lissy F. Jarvik, MD, PhD, UCLA and West LA-VA Medical Center, Brentwood; Robert Katzman, MD, Albert Einstein College of Medicine; Nancy E. Miller, PhD, Center for Studies of the Mental Health of the Aging, National Institute of Mental Health; Edwin Olsen, MD, Veterans Administration Central Office, Washington, DC; Donald Price, MD, Johns Hopkins University Medical School; Stanley I. Rapoport, MD, National Institute on Aging; Arnold Starr, MD, University of California Medical Center, Irvine; Juan Taveras, MD, Massachusetts General Hospital; Eugene J. Oliver, PhD, National Institute of Neurological and Communicative Disorders and Stroke; Lawrence Rubinstein, PhD, National Institute of Neurological and Communicative Disorders and Stroke; Mr. William Weiss, National Institute of Neurological and Communicative Disorders and Stroke; Emanuel M. Stadlan, MD, National Institute of Neurological and Communicative Disorders and Stroke, Executive Secretary of the Work Group.

Professional Societies and Designated Reviewers

American Psychological Association: James L. Fozard, PhD, Veterans Administration Central Office.

American Neurological Association: David Drachman, MD, University of Massachusetts Medical Center; Robert Katzman, MD, Albert Einstein College of Medicine; Herbert Karp, MD, Emory University School of Medicine and Wesley Woods Center, Atlanta.

International Neuropsychological Society: Alfred W. Kaszniak, PhD, University of Arizona.

American Academy of Neurology: David Drachman, MD, University of Massachusetts Medical Center; Robert Katzman, MD, Albert Einstein College of Medicine; Stuart A. Schneck, PhD, University of Colorado.

American Psychiatric Association: Lissy F. Jarvik, MD, PhD, University of California, Los Angeles and West LA-VA Medical Center, Brentwood; Peter V. Rabins, MD, Johns Hopkins Hospital; Charles E. Wells, MD, Vanderbilt University Medical Center; Jerome Yesavage, MD, Veterans Administration Hospital, Palo Alto.

American Geriatrics Society: John Blass, MD, Burke Rehabilitation Center and Cornell University Medical College; Charles E. Wells, MD, Vanderbilt University Medical Center.

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SPECIAL ARTICLE

Clinical and Pathological Diagnosis of Frontotemporal Dementia

Report of the Work Group on Frontotemporal Dementia and Pick's Disease

Guy M. McKhann, MD; Marilyn S. Albert, PhD; Murray Grossman, MD, PhD; Bruce Miller, MD; Dennis Dickson, MD; John Q. Trojanowski, MD, PhD;

An international group of clinical and basic scientists participated in the Frontotemporal Dementia and Pick's Disease Criteria Conference at the National Institutes of Health in Bethesda, Md, on July 7, 2000, to reassess clinical and neuropathological criteria for the diagnosis of frontotemporal dementia (FTD). Previous criteria for FTD have primarily been designed for research purposes. The goal of this meeting was to propose guidelines that would enable clinicians (particularly neurologists, psychiatrists, and neuropsychologists) to recognize patients with FTD and, if appropriate, to expedite their referral to a diagnostic center. In addition, recommendations for the neuropathological criteria of FTD were reviewed, relative to classical neuropathology and modern molecular biology. *Arch Neurol. 2001;58:1803-1809*

The perception of the major causes of dementia has evolved over time. Not too long ago, most physicians and the general public thought that dementia was primarily related to vascular processes (reflected in the term *hardening of the arteries*). More recently, the emphasis has shifted to Alzheimer disease (AD), to such an extent that many general physicians mistake different types of dementia for AD.

Frontotemporal dementia is one of the neurodegenerative disorders commonly mistaken for AD. Because it often affects people in midlife, it is also frequently mistaken for primary psychiatric disorders. Pathologically, it includes a heterogeneous group of sporadic and familial neuropsychiatric diseases.

Arnold Pick,[1-3] in a series of articles based on gross examination of the brain, reported cases of dementia with severe circumscribed atrophy of the frontotemporal regions. He noted that the transition between the atrophic and preserved regions was abrupt. Several years later, Alois Alzheimer[4] described the cellular pathology of intraneuronal inclusions (later known as *Pick bodies*) and ballooned cortical neurons. The definition of the clinical entity of what became known as *Pick disease* was presented in a series of articles in the 1920s.[5-7] This concept of Pick disease emphasized the importance of Pick bodies and ballooned neurons in the pathological diagnosis and the clinical distinction of this disorder from AD. This conceptualization was subsequently expanded on by several groups.[8-10] Since that time, there has been continuing controversy concerning whether the identifiable cellular changes of Pick bodies and ballooned neurons are a requirement for diagnosis.

In the 1980s and 1990s, several research groups recognized that there were many patients with clinical features similar to those of patients with Pick disease who had neither the classical lobar atrophy nor the characteristic cellular changes. These disorders came to be known by several different names, including FTD, frontal lobe degeneration of the non-Alzheimer type, frontotemporal lobar degeneration (FTLD), dementia lacking distinct histopathological features, primary progressive aphasia, and semantic dementia.[11-24]

From the Department of Neurology, Johns Hopkins University School of Medicine, and Zanvyl Krieger Mind/Brain Institute, Baltimore, Md (Dr McKhann); Departments of Pathology (Dr Trojanowski) and Neurology (Dr Grossman), University of Pennsylvania, Philadelphia; Department of Neurology, University of California at San Francisco (Dr Miller); Department of Pathology, Mayo Clinic Jacksonville, Jacksonville, Fla (Dr Dickson); and Departments of Psychiatry and Neurology, Harvard Medical School, Boston, Mass (Dr Albert). A list of the members of the Work Group on Frontotemporal Dementia and Pick's Disease appears at the end of this article.

An important recent expansion of the field was the identification of biochemical abnormalities and genetic mutations associated with these disorders.[25-29] In addition, in recent years, there has been the recognition that some patients with behavioral changes associated with frontal lobe dysfunction may also have clinical and pathological evidence of a simultaneous progressive motor neuron disease (MND). This link between MND and dementia was suggested by several authors in the 1980s.[30-32] The term *FTD with MND* was subsequently proposed.[33] Recently, a possible genetic marker for such cases has been localized to chromosome 9.[34]

To facilitate the systematic study of this group of patients, several sets of research criteria have also been published in recent years.[35-37] These research criteria have been focused on the need to have subgroups of patients for study during life and accurate pathological diagnosis on autopsy. In addition, there have been an increasing number of studies examining the reliability and validity of these criteria.[38-40]

RECOMMENDATIONS ON CLINICAL CRITERIA FOR FTD

The concept of Pick disease has been expanded beyond Pick's original observations, clinically and pathologically. With this expansion have come several terms, as mentioned in the introduction, that imply neuropsychological findings that tend to require specialized research training for identification, or imply underlying pathologic conditions. To aid the general physician, we recommend that, from a clinical perspective, these cases be referred to collectively as *FTD*. We recognize that this term includes groups of patients whose pathological conditions and genetic mechanisms are heterogeneous. However, the association of these distinct pathological and genetic entities cannot, at least at present, be correlated with distinct clinical syndromes.

DEMOGRAPHICS OF FTD

Frontotemporal dementia occurs primarily between the ages of 35 and 75 years. The disease affects both sexes approximately equally. A substantial proportion of patients (20%-40%) have a clear-cut family history of FTD. Variations in rates of family history among clinical centers most likely reflect ascertainment differences, such as the ethnic concentration in a catchment area, the research interests of the investigators, and other related issues.

CORE CLINICAL PHENOTYPES OF FTD

Patients with FTD present with 2 patterns: gradual and progressive changes in behavior, or gradual and progressive language dysfunction.

Behavioral Presentation of FTD

The most common presentation of FTD is an early change in social and personal conduct, characterized by difficulty in modulating behavior to the social demands of a situation. This is often associated with a lack of inhibition, resulting in impulsive or inappropriate behavior, for example, swearing at inappropriate times, outbursts of frustration, or lack of social tact. Progression of the disease may lead to poor financial judgment or impulsive acts (such as grabbing food off of someone else's plate, shoplifting, or impulsive buying). At the extreme, the impulsivity can be self-destructive, such as when patients try to get out of a moving car because something of interest has caught their attention. In some individuals, inappropriate sexual behavior occurs. There may also be repetitive or compulsive behaviors. This may include a preoccupation with repeating specific personal acts (eg, rereading the same book) or repeating specific physical actions (eg, walking to the same location repeatedly). Dietary habits and personal hygiene may also change. Overeating is common, as well as food fads in which only certain foods are eaten. There is a loss of concern for one's personal appearance, and patients may be increasingly unkempt early in the disease. All of this occurs in the setting of the patient's showing little insight into or personal concern for his or her actions. Although there are complaints of memory disturbance—and on formal memory testing these patients often, indeed, show abnormalities—they do not have a true amnestic syndrome. They are able to keep track of day-to-day events and to be oriented.

Language Presentation of FTD

Early and progressive change in language function is the alternate presentation of FTD. This occurs in the setting of relative preservation of other cognitive domains, such as memory. Many of these patients present with troubles in the expression of language, marked by problems using the correct word, including the naming of persons and things or expressing oneself. Difficulties in reading and writing then develop. In this subgroup of patients with FTD, understanding of word meaning is well preserved. With progression of disease, less and less language is used, until the patient may be virtually mute. Another subgroup of these patients presents with severe problems naming and understanding word meaning. This becomes progressively worse, and their speech has less substantive content as the disease progresses. Although the changes in language may be the initial presentation of the illness, as the disease progresses, behavioral changes may occur. In the research community, the terms *primary progressive aphasia* and *semantic dementia*, as mentioned in the introduction, are often used to characterize these patients, depending on the specific nature of the language disturbance.

IMAGING AND LABORATORY DATA IN FTD

Structural imaging studies, with computed tomography or magnetic resonance imaging, may show atrophy of the anterior temporal and frontal lobes, while single-photon emission computed tomography, positron emission tomography, and perfusion magnetic resonance imaging typically demonstrate decreased perfusion of the frontal and temporal lobes. In some cases, these alterations show a striking asymmetry. More widespread at-

rophy or perfusion deficits, for example involving parietal lobes, are more compatible with AD. The findings on the electroencephalogram are usually normal in the early stage of FTD, but this does not mean that the behavioral manifestations are primarily the result of a psychiatric illness.

EXCLUDING OTHER POTENTIAL CAUSES OF DEMENTIA

The diagnosis of FTD can only be considered when other potential medical causes have been ruled out. These include other central nervous system conditions that cause progressive deficits in cognition and behavior (eg, cerebrovascular disease, Parkinson disease, and Huntington disease), systemic conditions that are known to cause dementia (eg, hypothyroidism and human immunodeficiency virus infection), or persisting effects of substance abuse (eg, alcohol use).

COMPARISON OF FTD AND AD

Unlike the incidence of AD, which increases markedly with age, it is rare to have the onset of FTD after age 75. Moreover, the early appearance of behavioral symptoms, common in FTD, is unusual in AD. Unlike patients with FTD, patients with early AD tend to maintain socially appropriate behavior. Despite their memory deficits, they preserve their social graces and are usually adept at covering up their memory difficulty. As AD progresses, patients may act inappropriately in financial and other situations requiring judgment; this is primarily related to their cognitive problems, rather than to impulsiveness or a lack of concern for social norms. Furthermore, the apathy of a patient with AD is likely to occur in situations that are confusing and overwhelming, whereas the apathy of a patient with FTD is more pervasive, more often reflects an indifference about others, and is sometimes a generalized lack of initiative.

In addition, patients with AD have an early and profound difficulty learning and retaining new information. As the disease progresses, memory for new and old information is lost. In contrast, memory loss is less prominent in most patients with FTD who are mildly impaired, although memory difficulties often worsen as the disease progresses.[41] For example, many patients with FTD who are mildly impaired are oriented and able to keep track of recent events, but may be variable in performance on memory testing because of lack of concern or effort in the testing situation.

In FTD, the progressive language dysfunction already described can occur as an isolated cognitive entity with or without associated behavioral disturbance. In contrast, when language dysfunction occurs in AD, it is almost always associated with some degree of memory abnormality. In FTD, spatial difficulties are rare in patients with mild or moderate impairment, while spatial difficulty is generally seen in AD by the time that patients are moderately impaired.

Notably, patients with FTD are more likely than patients with AD to have motor abnormalities. A subset of patients with FTD develops symptoms suggestive of MND, as noted in the introduction. These symptoms include weakness and muscle wasting. Symptoms of parkinsonism, such as rigidity, are seen in both disorders.

Furthermore, in FTD and AD, early in the course there is difficulty with cognitive flexibility and tasks that require shifting between one mental set and another. Therefore, an assessment of these functions will not easily differentiate these patients. However, when patients with AD and FTD have progressed to an advanced stage, they often appear similar, and what may distinguish them from one another is the course they took to reach this advanced stage of brain dysfunction.

Mutations in 3 genes are known to be causative in AD, and at least one gene (*APOE*) has been identified as a risk factor for AD. None of these genetic mechanisms are involved in the development of FTD.

CLINICAL CRITERIA FOR FTD

Based on the foregoing, the recommended clinical criteria for diagnosing FTD are

(1) The development of behavioral or cognitive deficits manifested by either
- (*a*) early and progressive change in personality, characterized by difficulty in modulating behavior, often resulting in inappropriate responses or activities or
- (*b*) early and progressive change in language, characterized by problems with expression of language or severe naming difficulty and problems with word meaning.

(2) The deficits outlined in 1a or 1b cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
(3) The course is characterized by a gradual onset and continuing decline in function.
(4) The deficits outlined in 1a or 1b are not due to other nervous system conditions (eg, cerebrovascular disease), systemic conditions (eg, hypothyroidism), or substance-induced conditions.
(5) The deficits do not occur exclusively during a delirium.
(6) The disturbance is not better accounted for by a psychiatric diagnosis (eg, depression).

SUMMARY OF CLINICAL CRITERIA FOR FTD

It is important to recognize patients with FTD early in their course and to refer them to neurologic and psychiatric physicians who are experienced in their management. This referral is important because the clinical course and treatment of these patients are different from those of patients with AD. For example, patients with FTD have different behavioral manifestations early in the disease and may have a longer clinical course. In addition, when behavioral symptoms predominate, patients with FTD who develop clinical manifestations in midlife may initially be confused with patients with atypical late life depression, or, when the onset is in younger persons, it may

be confused with mental disorders such as schizophrenia, mood disorder, addiction, or antisocial personality disorder.

There have been remarkable advances in the understanding of the underlying pathophysiology and genetic mechanisms of FTD that allow counseling of patients and their families in ways that were not possible in the past. In addition, research groups interested in FTD are exploring new therapeutic approaches.

RECOMMENDATIONS ON NEUROPATHOLOGICAL EVALUATION AND CLASSIFICATION OF FRONTOTEMPORAL DEGENERATIVE DISORDERS

The clinical syndromes described thus far are associated with several neuropathological abnormalities, which will be further described herein. However, specific sets of pathological findings have, to date, not been associated with specific clinical manifestations. Nevertheless, the constellation of neurodegenerative and other abnormalities—detected by histochemical, immunohistochemical, biochemical, molecular biological, and other methods used for the analysis of the postmortem brain from a patient with a well-documented FTD—usually enables neuropathological diagnosis of the underlying disease.

Therefore, at the autopsy of a patient with a well-documented FTD (with or without parkinsonism, motor deficits, or other less common associated impairments), the systematic examination of the postmortem brain recommended herein will facilitate detection of neurodegenerative and other lesions, estimation of the regional distribution and abundance of these abnormalities, and formulation of 1 or more neuropathological diagnoses to account for the clinical manifestation. Although these methods frequently enable a specific neuropathological diagnosis, this is not always possible because of extensive gaps in the current understanding of frontotemporal degenerative disorders and the mechanisms leading to the onset and progression of these disorders. In this discussion, the term *FTD* will be used for the clinical syndrome already described, while *FTLD* or the other terms subsequently defined will be used to describe neuropathological findings.

NEUROPATHOLOGICAL EVALUATION OF FRONTOTEMPORAL DEGENERATIVE DISORDERS

Gross examination of the postmortem brain from a patient with FTD usually reveals frontal or temporal lobar atrophy or both, but the distribution and severity of brain atrophy are not specific for a particular neurodegenerative disorder. Subsequent microscopic examination using contemporary histochemical and immunohistochemical methods may reveal brain lesions diagnostic of other well-recognized disorders, such as AD or Lewy body disease.[42,43] In this section, we discuss disorders other than these well-recognized ones that also present with frontal or temporal lobar atrophy. The brain regions to examine and the preferred methods of tissue staining are described in previous reports on criteria for the neuropathological diagnosis of frontotemporal degenerative disorders,[21,23,24,35,38] as well as in reports on diagnostic criteria for neurodegenerative disorders that must be excluded.[42,43] In addition to traditional histochemical methods for diagnosis of AD pathological conditions (eg, Bielschowsky silver stain or thioflavin-S fluorescent microscopy), sensitive methods for detecting tau abnormalities, such as the Gallyas silver stain or immunohistochemical studies with tau antibodies, are essential for the neuropathological evaluation of FTD. Immunohistochemical testing for ubiquitin is also important in the routine evaluation of frontotemporal degenerative disorders, because some of the characteristic lesions are negative for tau yet positive for ubiquitin. Immunohistochemistry is also the most sensitive method for detecting other pathological conditions that are supportive or exclusive of the diagnosis. For example, ballooned or achromatic neurons that are found in several of the disorders associated with FTD are best appreciated with immunostaining for neurofilaments or α-B-crystallin. Although Lewy bodies can be detected with ubiquitin immunostaining, immunostaining for synuclein is a more specific method to exclude this diagnosis. Routine application of immunohistochemical methods has fostered a modern neuropathological classification of neurodegenerative disorders. Two main categories of neurodegenerative diseases, tauopathies and synucleinopathies, are based on this principle.[29,44,45]

ANCILLARY METHODS OF EVALUATION

Although not a part of routine diagnostic evaluation, several specialized techniques (eg, morphometric and neurochemical analyses) may shed additional insight into frontotemporal degenerative disorders.[28] In addition, electron microscopic analysis of the nature of the filaments that accumulate within neurons and glia provides additional means of differentiating various frontotemporal degenerative disorders.[46] These methods are encouraged but are not required for diagnosis. On the other hand, biochemical analyses of tau protein abnormalities have proven to be useful in the rational classification of these disorders[47] and are recommended. Fractionation of tau protein differentiates disorders with and without measurable amounts of insoluble tau. Further characterization of this abnormal insoluble tau differentiates cases with a predominance of tau with 3 microtubule-binding repeats, 4 microtubule-binding repeats, or a combination of both.[47,48] Recent investigation has also suggested that some frontotemporal degenerative disorders have selective loss or marked reduction of all tau proteins in the soluble fraction in the setting of normal levels of tau messenger RNA.[49] These results need to be confirmed but suggest that analysis of soluble tau may also be useful in characterizing frontotemporal degenerative disorders.

RECOMMENDATIONS FOR CLASSIFICATION OF FTD

As emphasized in the most recent iteration of recommended consensus criteria for the postmortem diagnosis of AD,[43] only probabilistic statements can be made about the causal relationships between neuropathologi-

cal findings and clinical manifestations, because it is unclear how neurodegenerative diseases cause dysfunction and death of brain cells or specific neuropsychiatric symptoms. Therefore, because the clinical manifestations of FTD cannot accurately predict the nature of the underlying neurodegenerative disease—and because some of the diagnostic terms previously used for different clinical variants of FTD have been misunderstood to imply a specific neuropathological diagnosis—it is recommended that clinical terms for specific clinical variants of FTD be abandoned. Furthermore, the correlation of neuropathological findings with FTD in a patient does not prove a cause-and-effect relationship, because more than 1 brain abnormality may contribute to the manifestations of dementia. Finally, the neuropathological findings alone cannot establish that a patient had FTD in the absence of documented clinical information. It is hoped that contemporary studies will further our understanding of the anatomical and pathological substrates of the clinical signs.

With these caveats in mind, the classification of FTD recommended herein requires exclusion of other central nervous system diseases that could account for the clinical syndrome, and demonstration of a plausible correlation between the neuropathological findings and clinical evidence of FTD. The recommended classification of neurodegenerative disorders associated with FTD, which follows, comprises 5 distinct neuropathological categories. For each of the categories, wording inclusive of disorders not yet identified has been added to reflect uncertainties about poorly characterized disorders that may be shown in the future to belong in one of these categories.

(1) When the predominant neuropathological abnormalities are tau-positive inclusions (with associated neuron loss and gliosis) and insoluble tau has a predominance of tau with 3 microtubule-binding repeats, the most likely diagnoses are

- (*a*) Pick disease,
- (*b*) frontotemporal dementia with parkinsonism linked to chromosome 17,[50] or
- (*c*) other as yet unidentified familial and sporadic frontotemporal disorders.

(2) When the predominant neuropathological abnormalities are tau-positive inclusions (with associated neuron loss and gliosis) and insoluble tau has a predominance of 4 microtubule-binding repeats, the most likely diagnoses are

- (*a*) corticobasal degeneration,
- (*b*) progressive supranuclear palsy,
- (*c*) frontotemporal dementia with parkinsonism linked to chromosome 17,[29,44,46,48] or
- (*d*) other as yet unidentified familial and sporadic frontotemporal disorders.

(3) When the predominant neuropathological abnormalities are tau-positive inclusions (with associated neuron loss and gliosis) and insoluble tau has a predominance of 3 and 4 microtubule-binding repeats, the most likely diagnoses are

- (*a*) neurofibrillary tangle dementia,
- (*b*) frontotemporal dementia with parkinsonism linked to chromosome 17,[29,44,46,48] or
- (*c*) other as yet unidentified familial and sporadic frontotemporal disorders.

(4) When the predominant neuropathological abnormalities are frontotemporal neuronal loss and gliosis without tau- or ubiquitin-positive inclusions and without detectable amounts of insoluble tau, the most likely diagnoses are

- (*a*) frontotemporal lobar degeneration (also known as *dementia lacking distinct histopathological features*)[20,21,28] or
- (*b*) other as yet unidentified familial and sporadic frontotemporal disorders.

(5) When the predominant neuropathological abnormalities are frontotemporal neuronal loss and gliosis with ubiquitin-positive, tau-negative inclusions and without detectable amounts of insoluble tau, with MND or without MND but with MND-type inclusions, the most likely diagnoses are

- (*a*) frontotemporal lobar degeneration with MND,
- (*b*) frontotemporal lobar degeneration with MND-type inclusions but without MND, or
- (*c*) other as yet unidentified familial and sporadic frontotemporal disorders.

NEUROPATHOLOGICAL DIAGNOSTIC ALGORITHM FOR FRONTOTEMPORAL DEGENERATIVE DISORDERS

Although the recommended classification is based on biochemical and neuropathological methods, a practical approach to the diagnosis of degenerative dementias is also needed. A comprehensive but simple algorithm has been proposed by Lowe.[51] This algorithm, as it relates to diagnosis of frontotemporal degenerative disorders, is used in the following approach.

After excluding AD and Lewy body disease with methods that are recommended for these diagnoses,[42,43] a pathologist should examine cortex, hippocampus, basal ganglia, and brainstem for neurofibrillary tangles using tau immunostaining or the Gallyas silver method. In evaluating brainstem and basal ganglia sections for Lewy bodies with ubiquitin or synuclein immunostaining, the finding of glial cytoplasmic inclusions characteristic of multiple system atrophy confirms this diagnosis; however, multiple system atrophy is an uncommon cause of frontotemporal degeneration.[52] If Gallyas or tau staining reveals round, well-circumscribed cytoplasmic inclusions in small nonpyramidal neurons in the upper cortical layers of the frontal and temporal cortex—as well as the amygdala, basal ganglia, and brainstem monoaminergic nuclei—then Pick disease is a diagnostic consideration.[53] Similar methods may reveal neurofibrillary tangles, and if they are numerous and limited to the medial temporal lobe, this suggests a diagnosis of tangle-only dementia,[54] although a distinction from argyrophilic grain disease[55] may be difficult. If tangles are more widespread in the subcortical regions (globus pallidus, subthalamic nucleus, substantia nigra, and pons), which are vulnerable in progressive supranuclear palsy,[56] then this diagnosis needs to be considered. Neurofibrillary abnormalities in an overlapping distribution suggestive of progressive supranuclear palsy, but with cortical astro-

Work Group on FTD and Pick's Disease

Meeting Chairs

Harvard Medical School, Boston, Mass: Marilyn S. Albert, PhD. *University of Pennsylvania, Philadelphia:* Murray Grossman, MD, PhD. *University of California, San Francisco:* Bruce Miller, MD.

Meeting Organizational and Logistical Support

Southeastern Pennsylvania Chapter of the Alzheimer's Association, Philadelphia: Helen-Ann Comstock, BA, Lisa Radin, BA. *National Institute on Aging, Bethesda, Md:* Creighton Phelps, PhD.

Meeting Chairs of the Clinical and Neuropathology Work Groups

Johns Hopkins University, Baltimore, Md: Guy M. McKhann, MD. *University of Pennsylvania:* John Q. Trojanowski, MD, PhD, respectively.

Members and Contributors to the Summary

University of Toronto, Toronto, Ontario: Catherine Bergeron, MD, FRCPC. *Lund University Hospital, Lund, Sweden:* Arne Brun, MD. *USC Alzheimer's Disease Research Center, Los Angeles, Calif:* Tiffany Chow, MD. *University of Pennsylvania:* H. Branch Coslett, MD, Virginia M-Y. Lee, PhD. *French Institute of Health & Medical Research, Lille, France:* Andre Delacourte, PhD. *University of California, Los Angeles:* Daniel Geschwind, MD, PhD. *Mayo Clinic Jacksonville, Jacksonville, Fla:* Neill R. Graff-Radford, MD, Michael Hutton, MD. *National Institute of Neurological Disorders and Stroke, Bethesda:* Jordan Grafman, PhD. *Harvard Medical School:* John H. Growdon, MD. *Lund University:* Lars Gustafson, MD. *Erasmus University, Rotterdam, the Netherlands:* Peter Heutink, MD. *Cambridge University, Cambridge, England:* John Hodges, MD. *MCP Hahnemann University, Philadelphia:* Carol F. Lippa, MD. *Henry Jackson Foundation, Bethesda:* Irene Litvan, MD. *The Royal Infirmary, Manchester, England:* David Neary, MD, Julie S. Snowden, MD. *University College, London, England:* Martin Rossor, MA, MD, FRCP. *Department of Veterans Affairs, Olympia, Wash:* Gerard Schellenberg, PhD. *Dijkzigt Hospital, Rotterdam:* John van Swieten, MD. *Columbia University, New York, NY:* Jean Paul Vonsattel, MD.

cytic plaques and ballooned or achromatic neurons, suggest a diagnosis of corticobasal degeneration.[57] If Gallyas and tau staining fail to reveal significant neuronal and glial lesions, then ubiquitin immunostaining is needed to evaluate frontotemporal and hippocampal abnormalities. If cortical and hippocampal dentate neurons have ubiquitin-positive, tau-negative round or filiform inclusions, which are often found in brains that also harbor histologic evidence of MND, then a diagnosis of FTLD with MND-type inclusions is warranted, even if there is no evidence of MND.[51] If all of the above measures fail to reveal distinctive histopathological conditions and if a diagnosis of prion disease has been excluded by immunohistochemical or genetic methods, FTLD (also known as *dementia lacking distinct histopathological features*) is a reasonable diagnosis.

CONCLUSIONS

The recommendations summarized herein reflect the shared views of the meeting participants based on an iterative process that builds on previous efforts to improve the criteria and procedures for the accurate diagnosis of these dementias.[21,23,24,35,38] Moreover, the participants also recommended continuation of this iterative process, so that the recommendations can be validated and refined. In addition, they urged increased efforts to develop inexpensive biochemical and molecular diagnostic methods for the accurate and timely diagnosis of FTD in different settings. Finally, the participants concluded the meeting with the optimistic predictions that rapid advances in research on FTD and other neurodegenerative diseases will facilitate efforts to improve methods for the early and accurate diagnosis of FTD, and that clinical and basic research on these dementias will hasten discovery of more effective strategies to treat them.

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Corresponding author and reprints: Guy M. McKhann, MD, Department of Neurology, Zanvyl Krieger Mind/Brain Institute, Johns Hopkins University, 338 Krieger Hall, 3400 N Charles St, Baltimore, MD 21218-2685 (e-mail: guy.mckhann@jhu.edu).

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Stiff-man syndrome treated with intrathecal baclofen

Richard D. Penn, MD, and Eugene A. Mangieri, MD

Stiff-man syndrome is a rare, progressive motor disorder causing disabling muscle rigidity and spasms, which is often associated with insulin-dependent diabetes mellitus. In patients with this syndrome, Solimena et al[1,2] documented the presence of autoantibodies against glutamic acid decarboxylase (GAD), an enzyme selectively concentrated in pancreatic beta cells and CNS neurons secreting the major inhibitory neurotransmitter γ-aminobutyric acid (GABA). Although plasmapheresis has been tried,[3] diazepam remains the most effective treatment; it acts on the GABA receptors, making them more sensitive to GABA.[4] Unfortunately, as the disease progresses, diazepam becomes less effective and severe spasms occur. Baclofen is a direct GABA-B agonist that does not require GABA secretion to activate its receptor. Thus, baclofen would logically be a useful medication for treating stiff-man syndrome if it could be provided in sufficiently high concentration to the spinal cord receptors. We have treated severe spasticity of spinal origin with intrathecal baclofen and found that it significantly reduces spasms and rigidity when oral medications failed.[5] We now report similar success with two patients with stiff-man syndrome.

Patient 1. A 42-year old man reported 7 years of progressive rigidity and spasms that began in his trunk musculature and gradually involved both legs and made walking difficult. Diazepam had afforded initial relief, but as the disease progressed, he became disabled and unable to work at his job as a machinist. Pain became worse as the intensity and frequency of spasms increased. He gradually elevated his diazepam dose to 140 mg/d, without significant improvement. At age 34, he developed diabetes mellitus and was placed on insulin. His only neurologic abnormalities were demonstrated on motor examination. He had increased muscle tone in his axial muscles, with a pronounced lumbar lordosis. Mild sensory stimulation or volitional movements would set off severe spasms in his back and legs. His reflexes were normal and a Babinski sign was not present.

A lumbar puncture was performed and 75 μg baclofen (Ciba-Geigy, Basel, Switzerland) was injected. One hour later, his rigidity and spasms completely disappeared and he was able to walk normally. By 8 hours, the effect was decreasing, and by 24 hours he returned to baseline. A programmable drug pump and catheter (SynchroMed, Medtronic, Inc., Minneapolis, MN) going to the lumbar subarachnoid space was implanted, and his spasms were completely controlled with baclofen 120 μg/d. Over the next 2½ years, the dose of intrathecal baclofen was gradually increased to 1,200 μg/d to suppress his spasms; diazepam has been reduced to 20 mg/d, but is still necessary in low dose. He has had an episode of meningitis requiring antibiotics and replacement of the pump and catheter system, and twice the catheter has dislocated from the subarachnoid space and needed replacement. Each time he stopped receiving intrathecal baclofen his spasms recurred.

Patient 2. A 63-year-old woman was diagnosed with stiff-man syndrome in 1988. At that time, she had a one-year history of progressive spasms in her back and legs and difficulty with gait, and she required a walker. Pain occurred during attacks of spasms. On motor examination, she had hyperextension of the lumbar spine and severe spasms at the hips and knees, without weakness, atrophy, or fasciculations. The reflexes were normal and a Babinski sign was not present. An extensive work-up was normal except for antibodies to GAD in her CSF (by Dr. DeCaricelli at Yale University). Diazepam was given and helped initially, but a year later she was bedridden and having markedly increased pain. Intrathecal preservative-free methylprednisolone and systemic immunotherapy with azathioprine and plasmapheresis were tried without significant effect. By 1992, she had developed ankylosis at her hip, knees, and feet, secondary atrophy of her leg muscles, and severe pain due to her spasms. Oral narcotics only provided partial relief, and on numerous occasions she was admitted for intravenous narcotics.

Intrathecal baclofen was tried, and 75 μg produced excellent pain relief, stopping the spasms for 4 hours. A drug pump was then implanted, with a constant infusion of 120 μg/d over the last 9 months. She has good control of her spasms and pain. She remains bedridden because of lower-extremity muscle atrophy and ankylosis.

Discussion. Both patients meet the criterion for stiff-man syndrome outlined by Lorish et al.[6] Diazepam was initially effective, but as the disease progressed even high doses (>90 and >140 mg/d) were inadequate. Since diazepam works by potentiation of the effect of endogenously released GABA on the GABA receptor, disease progression may reflect lower GABA availability as GABAergic neurons are lost. Baclofen is a direct agonist of GABA-B receptors and does not require endogenous GABA. This may explain its usefulness in our two patients. Unfortunately, the second patient developed severe muscle and skeletal changes, and these changes have not reversed. Her major problem of painful spasms has been controlled. The first patient was treated earlier in his course and fared better; he continues to do well after 2½ years of intrathecal baclofen treatment.

Intrathecal baclofen is now approved for the treatment of spasticity of spinal origin, and is available at many centers. On the basis of our experience with these two patients, we recommend testing patients with stiff-man's syndrome with a lumbar subarachnoid 75-mcg baclofen bolus injection when oral diazepam is no longer providing adequate symptomatic relief. If successful, a drug pump can be implanted for chronic administration. If our observations on two patients are confirmed in other patients with stiff-man syndrome, it will be the first example of direct replacement of a neurotransmitter by intrathecal infusion.

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From the Department of Neurosurgery (Dr. Penn), Rush-Presbyterian Medical Center, Chicago, IL; and the Northport Hospital (Dr. Mangieri), College of Community Health Sciences, Northport, AL.

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Address correspondence and reprint requests to Dr. Richard D. Penn, Rush-Presbyterian Medical Center, Department of Neurosurgery, 1725 W. Harrison, Suite 755, Chicago, IL 60612.

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The Clinical Dementia Rating (CDR): Current version and scoring rules

John C. Morris, MD

The Washington University Clinical Dementia Rating[1] (CDR) is increasingly used in longitudinal studies and clinical trials for staging the severity of Alzheimer's disease (AD). The CDR is derived from a semistructured interview with the patient and an appropriate informant and rates impairment in each of six cognitive categories (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care) on a five-point scale in which none = 0, question-

Table. Clinical Dementia Rating (CDR)

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconstant forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment and Problem Solving	Solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, and volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Assignment of CDR

(material added to the original rules shown in italic type)

Use all information and make the best judgment. Score each category as independently as possible. Mark in only one box for each category, rating impairment as decline from the person's usual level due to cognitive loss alone, not impairment due to other factors such as physical handicap or depression. *Occasionally, the evidence is ambiguous and the clinician's best judgment is that a category could be rated in either one of two adjacent boxes, such as mild (1) or moderate (2) impairment. In that situation, the standard procedure is to check the box of greater impairment.*

Aphasia is taken into account by assessing both language and nonlanguage function in each cognitive category. If aphasia is present to a greater degree than the general dementia, the subject is rated according to the general dementia. Supply evidence of nonlanguage cognitive function.

The global CDR is derived from the scores in each of the six categories ("box scores") as follows: Memory (M) is considered the primary category and all others are secondary. CDR = M if at least three secondary categories are given the same score as memory. Whenever three or more secondary categories are given a score greater or less than the memory score, CDR = score of majority of secondary categories on whichever side of M has the greater number of secondary categories. However, when three secondary categories are scored on one side of M and two secondary categories are scored on the other side of M, CDR = M.

When M = 0.5, CDR = 1 if at least three of the other categories are scored 1 or greater. If M = 0.5, CDR cannot be 0; it can only be 0.5 or 1. If M = 0, CDR = 0, unless there is impairment (0.5 or greater) in two or more secondary categories, in which case CDR = 0.5.

Although applicable to most AD situations, these rules do not cover all possible scoring combinations. Unusual circumstances that occasionally occur in AD and may be expected in non-Alzheimer's dementia as well are scored as follows:

(1) With ties in the secondary categories on one side of M, choose the tied scores closest to M for CDR (eg, M and another secondary category = 3, two secondary categories = 2, and two secondary categories = 1; CDR = 2).

(2) When only one or two secondary categories are given the same score as M, CDR = M as long as no more than two secondary categories are on either side of M.

(3) When M = 1 or greater, CDR cannot be 0; in this circumstance, CDR = 0.5 when the majority of secondary categories are 0.

able = 0.5, mild = 1, moderate = 2, and severe = 3. (Note: Personal Care has no questionable impairment level.) From the six individual category ratings, or "box scores," the global CDR is established by clinical scoring rules where CDR 0 = no dementia and CDR 0.5, 1, 2, or 3 indicates questionable, mild, moderate, or severe dementia. (Although alternative scoring algorithms exist, use of the clinical rules permits comparability with previously determined CDR scores.) The usefulness of the

CDR may result from several factors: (1) it is clinically based (ie, independent of psychometric test scores); (2) the six categories used for rating dementia severity are directly linked to validated clinical diagnostic criteria[2] for AD; (3) it has high inter-rater reliability for physicians[3] and nonphysicians[4]; and (4) an expanded and more quantitative version of the scale can be achieved by summing the ratings in each of the six categories to provide the Sum of Boxes.[5]

The CDR has been modified slightly over the years, as experience permitted resolution of ambiguities. These refinements primarily have been to sharpen the distinction between specific severity levels within a category. The first revision[6] separated Community Affairs box scores 2 and 3, eliminated the possibility that Home and Hobbies could be "well maintained" for box score 0.5, and removed vague modifiers ("if any" from box score 0.5 in Community Affairs and "occasional" from box score 1 in Personal Care). The next revision[7] distinguished Orientation box scores 0 and 0.5; other changes were slightly reworded descriptions for Orientation box scores 1 and 2 and for Judgment and Problem Solving box score 1, deletion of the modifier "may still" from the box score 1 description of normal appearance in Community Affairs, and substitution of "slight" for "mild" or "only doubtful" to describe 0.5 impairment for Memory, Judgment and Problem Solving, and Community Affairs.

A new version of the CDR more appropriately uses information regarding performance of financial transactions for rating Judgment and Problem Solving rather than Community Affairs. The new version is presented here (table) for interested readers, along with improved clinical scoring rules for the global CDR (material added to the original rules[1] is shown in italic).

From the Departments of Neurology and Pathology (Neuropathology) and the Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO.

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Address correspondence and reprint requests to Dr. John C. Morris, Memory and Aging Project, Washington University School of Medicine, 660 South Euclid Avenue, P.O. Box 8111, St. Louis, MO 63110.

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'Reappearance' of congenital nystagmus after minor head trauma

Deborah I. Friedman, MD, and Louis F. Dell'Osso, PhD

Congenital nystagmus (CN) is typically horizontal, conjugate, and is noticed at birth or in early infancy. Although the appearance of CN does not usually change much throughout life, fluctuations in the amplitude of the nystagmus are common. We report a patient with congenital nystagmus that was first noticed at age 6, "resolved" at age 7, and became clinically apparent again after a minor closed-head injury at age twelve.

Case report. A 12-year-old boy was evaluated for reappearance of nystagmus after a minor head injury. His parents first noticed a head-tilt when he was 2 to 3 years old. Ophthalmic evaluation at age 5 showed no clinical evidence of nystagmus. Pendular nystagmus with excellent visual acuity (20/20 OU) and normal fusional amplitudes were found at age six. CT of the brain was reportedly normal except for sinus disease. The nystagmus was no longer visible at age seven. In the interim, he was an honor student and was active in sports. Two months before his examination, he was struck in the back of the head with a baseball. There was no loss of consciousness. He was brought to the hospital for evaluation. Nystagmus was noted by the ambulance driver, and it subsequently persisted. There were no other neurologic sequelae from the head injury.

Since the injury, the patient needed to position his head to see clearly, and had difficulty catching a baseball. His parents noticed an intermittent head-turn while he was doing close work.

The patient had asthma, but no other medical, ophthalmologic, or neurologic conditions. Several family members had strabismus; there was no known nystagmus in the family.

Neuro-ophthalmic examination revealed normal visual acuity, color vision (Hardy-Rand-Ritter plates), pupils, visual fields, fundi, and intraocular pressures. The extraocular movements were full. The eye movements were videotaped and reviewed. Horizontal pendular-appearing nystagmus was present in primary gaze. The amplitude was variable and, at times, no nystagmus was visible. In lateral horizontal gaze, the nystagmus had a jerk component, beating in the direction of gaze. No definite null position was seen, even with head-tilt. The amplitude of the nystagmus seemed greater at distance than at near, and there was poor generation of horizontal optokinetic nystagmus (OKN). "Inverse" OKN was not observed. There was no observable change in the nystagmus with monocular occlusion, and no head-tilt, head-nodding, or head oscillation was seen. The neurologic examination was normal.

Eye movement recordings. Eye movements were recorded using the infrared reflection technique. Full-system bandwidth was direct current to 100 Hz. The predominant waveform, jerk nystagmus with extended foveation, allowed foveation periods from 150 to 400 msec. In the figure, A and B show the position and velocity records during 4 seconds of fixation on a 0.2° diameter light-emitting diode. Note the periods of extended foveation despite the frequent bias reversals. In the figure, C shows the phase planes of both eyes during this 4-second interval, also indicating well-developed foveation within the foveation window.[1] The ±0.5° window has been extended ±0.1° to allow for the 0.1° radius of the target. The foveating saccades from both directions bring the target within this effective foveation window of ±0.6° and ±4°/sec. Pendular waveforms were not observed during the recording. There was a broad neutral zone with frequent bias reversals within ±20° of primary gaze. Convergence had a minimal damping effect on the nystagmus. Smooth pursuit was normal at low velocities, but of low gain at velocities of 20°/sec and above. The amplitude of the nystagmus was variable throughout the record, and ceased completely with inattention. There was no evidence of a superimposed acquired nystagmus.

Discussion. As is typical of persons with CN, our patient did not experience oscillopsia. His well-developed foveation periods allowed him to enjoy excellent visual acuity most of the time. High-acuity foveation periods require that the eye position and target position coincide with minimal retinal slip. During smooth pursuit, the ability to match eye position to target position during foveation periods declines with increasing target velocity.[2] In our patient, low pursuit gain with pursuit movements of 20°/sec or more accounted for his intermittent blurred vision, especially when trying to fixate on targets moving rapidly across his visual field. Although his nystagmus was not apparent in infancy, the presence of excellent vision and lack of oscillopsia suggested that the nystagmus was not an acquired type; the recorded CN waveforms confirmed this.

Our patient also demonstrated several atypical clinical features of CN: his nystagmus was not noticed until age 6, his waxing and waning course was unusual, and his nystagmus reemerged after minor head trauma. The amplitude of CN can vary with many factors, including head position, eye position, febrile illness, and anxiety. Nystagmus with typical CN waveforms has developed in adolescence or adulthood without any

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ORIGINAL ARTICLES

Neuropathologic, Biochemical, and Molecular Characterization of the Frontotemporal Dementias

Ryan T. Mott, MD, Dennis W. Dickson, MD, John Q. Trojanowski, MD, PhD, Vicki Zhukareva, PhD, Virginia M. Lee, PhD, Mark Forman, MD, PhD, Vivianna Van Deerlin, MD, PhD, John F. Ervin, BA, Deng-Shun Wang, MD, PhD, Donald E. Schmechel, MD, and Christine M. Hulette, MD

Abstract

The frontotemporal dementias (FTDs) are a heterogeneous group of neurodegenerative disorders that are characterized clinically by dementia, personality changes, language impairment, and occasionally extrapyramidal movement disorders. Historically, the diagnosis and classification of FTDs has been fraught with difficulties, especially with regard to establishing a consensus on the neuropathologic diagnosis. Recently, an international group of scientists participated in a consensus conference to develop such neuropathologic criteria. They recommended a diagnostic classification scheme that incorporated a biochemical analysis of the insoluble tau isoform composition, as well as ubiquitin immunohistochemistry. The use and reliability of this classification system has yet to be examined. In this study, we evaluated 21 cases of FTD. Using traditional histochemical stains and tau protein and ubiquitin immunohistochemistry, we separated each case into one of the following categories: classic Pick disease (PiD; n = 7), corticobasal degeneration (CBD; n = 5), dementia lacking distinctive histopathologic features (DLDH; n = 4), progressive supranuclear palsy (PSP; n = 2), frontotemporal lobar degeneration with motor neuron disease or motor neuron disease-type inclusions (FTLD-MND/MNI; n = 2), and neurofibrillary tangle dementia (NFTD; n = 1). Additionally, we independently categorized each case by the insoluble tau isoform pattern, including 3R (n = 5), 4R (n = 7), 3R/4R (n = 3), and no insoluble tau (n = 6). As suggested by the proposed diagnostic scheme, we found that the insoluble tau isoform patterns correlated strongly with the independently derived histopathologic diagnoses ($p < 0.001$). The data show that cases containing predominantly 3R tau were classic PiD (100%). Cases with predominantly 4R tau were either CBD (71%) or PSP (29%). Cases with both 3R and 4R tau were either a combination of PiD and Alzheimer disease (67%) or NFTD (33%). Finally, cases with no insoluble tau were either DLDH (67%) or FTLD-MND/MNI (33%). To further characterize these cases, we also performed quantitative Western blots for soluble tau, APOE genotyping, and, in selected cases, tau gene sequencing. We show that soluble tau is reduced in DLDH and FTLD-MND/MNI and that APOE4 is overrepresented in PiD and DLDH. We also identified a new family with the R406W mutation and pathology consistent with NFTD. This study validates the recently proposed diagnostic criteria and forms a framework for further refinement of this classification scheme.

Key Words: Apolipoprotein E, Frontotemporal dementia, Frontotemporal lobar degeneration, Microtubule-associated protein tau.

From the Departments of Pathology (Neuropathology) (RTM, DES, CMH), and Medicine (Neurology) (JFE, DES, CMH), Duke University Medical Center, Durham, North Carolina; Departments of Neurosciences (DWD, D-SW) and Pathology (DWD), Mayo Clinic, Jacksonville, Florida; and Department of Pathology (Neuropathology) and Laboratory Medicine and the Institute on Aging (JQT, VZ, VML, MF, VVD), University of Pennsylvania, Philadelphia, Pennsylvania.

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Send correspondence and reprint requests to: Christine M. Hulette, MD, Duke University Medical Center, Department of Pathology, Box 3712, Durham, NC 27710; E-mail: hulet001@mc.duke.edu

INTRODUCTION

The frontotemporal dementias (FTDs) are a clinically, genetically, and pathologically heterogeneous group of disorders that occur primarily between the ages of 35 and 75 years with an equal incidence in males and females (1). FTDs are universally fatal with a disease duration that typically ranges from 5 to 10 years. Approximately 20% to 40% of patients have a strong family history of dementia. The clinical presentation is variable, with some patients presenting primarily with frontal lobe signs (personality changes) and others showing mostly temporal lobe dysfunction (language impairment). Indeed, 3 major clinical syndromes are recognized, including frontal variant FTD, semantic dementia, and progressive nonfluent aphasia (2, 3). Additionally, patients may present with features indistinguishable from Alzheimer disease (AD) or may display movement abnormalities similar to those seen in Parkinson disease. FTD is also a recognized feature of motor neuron disease (MND), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD).

Over a century ago, Arnold Pick described several autopsy cases of severe circumscribed atrophy of the frontal and temporal lobes in patients with a clinical history of dementia and language impairment (4–6). Years later, Alzheimer (7) and Altman (8) provided detailed descriptions of the histopathology, including the key features of argyrophilic inclusions within neurons (Pick bodies) and swollen achromatic cells (Pick cells), as well as the absence of senile plaques and tangles. In 1926, Onari and Spatz (9) introduced the eponym Pick disease (PiD) to describe these cases of progressive

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aphasia and personality deterioration with circumscribed frontotemporal atrophy without plaques and tangles. Decades later, Constantinidis (10) popularized the concept that PiD consists of three neuropathologic subtypes. All 3 subtypes show frontotemporal atrophy to some degree and thus were differentiated based on the presence or absence of Pick bodies and Pick cells. According to this classification scheme, type A PiD contains both Pick bodies and Pick cells, type B contains only Pick cells, and type C does not contain Pick bodies or Pick cells. Although this classification system was initially successful at simplifying the neuropathologic diagnosis of FTDs, recent discoveries have rendered this system incomplete. In particular, the realization that tau protein plays a critical role in many of the FTDs, together with the availability of monoclonal antibodies directed against pathologic forms of this protein, have underscored the necessity for an updated classification system.

Recently, an international group of clinical and basic scientists participated in a consensus conference to develop clinical and neuropathologic criteria for the diagnosis of FTD (1). This panel of experts developed a classification scheme that incorporated the classic neuropathologic findings, immunohistochemical analysis of tau protein and ubiquitin, and biochemical studies into the isoform composition of the insoluble tau deposits. To clarify nomenclature differences between the clinical syndrome of FTD and the neuropathologic findings, they recommended the terminology of frontotemporal lobar degeneration (FTLD) when referring to the pathologic changes. Additionally, they recommended a classification system that comprises 5 distinct neuropathologic categories. Three of these diagnostic categories are differentiated based on the isoform composition of insoluble tau as determined through Western blotting. These categories are separated into those with tau protein deposits containing predominantly 3 microtubule-binding repeats (3R tau), those with predominantly 4 microtubule-binding repeats (4R tau), and cases containing both 3R and 4R tau inclusions. The remaining two neuropathologic categories consist of cases without detectable amounts of insoluble tau. These two categories are separated into cases with or without motor neuron disease-type inclusions in the fascia dentata detected with ubiquitin immunohistochemistry. Recognizing that our knowledge of these disorders is incomplete, the 5 neuropathologic categories incorporate several possible diagnoses. These diagnoses include all of the recognized neuropathologic forms of FTD, including classic PiD, CBD, PSP, neurofibrillary tangle dementia (NFTD), dementia lacking distinctive histopathologic features (DLDH), FTLD with motor neuron disease or motor neuron disease-type inclusions (FTLD-MND/MNI), and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).

Given the ever-growing complexity of this group of disorders, the present study was undertaken to evaluate the use and reliability of the newly proposed diagnostic criteria.

MATERIALS AND METHODS

The rapid autopsy program of the Kathleen Price Bryan Brain Bank has been in existence since 1985 (11). The Institutional Review Board at Duke University Medical Center has approved patient recruitment and enrollment procedures. For this study, the brains from 21 patients with a clinicopathologic diagnosis of FTD were selected from the Kathleen Price Bryan Brain Bank. At the time of postmortem examination, the left hemisphere was fixed in 10% buffered formalin, and the right hemisphere was frozen and stored at -70°C for periods of 1 to 14 years. Frozen frontal lobe tissue (approximately 3 g) was removed from each brain for biochemical analysis.

Immunohistochemistry

Paraffin-embedded brain sections (8 μm) were immunostained with antibodies directed against ß-amyloid peptide, AT8 tau, ubiquitin, and α-synuclein. The β-amyloid peptide immunostain required deparaffinized sections, blocked with 2% hydrogen peroxide in methanol for 10 minutes, treated with 95% formic acid (Sigma, St. Louis, MO) for 1 minute, and washed in deionized H_2O. Background staining was blocked with 5% w/v nonfat dry milk in 0.05 M Tris buffer. The monoclonal primary 4G8 antibody (1:1000, 1 μg/mL; Signet, Dedham, MA) was applied and incubated for 45 minutes at 37°C. A biotinylated horse antimouse IgG secondary antibody (1:300 dilution; Vector Labs, Burlingame, CA) was incubated for 20 minutes at 37°C. Horseradish peroxidase-labeled streptavidin (1:800 dilution; Jackson ImmunoResearch Laboratories, West Grove, PA) was incubated for 20 minutes at 37°C. Monoclonal primary antibody AT8 tau (1:40, 5 μg/mL; Innogenetics, Alpharetta, GA) was incubated for 45 minutes at 37°C. Biotinylated horse antimouse IgG secondary antibody (1:300 dilution; Vector Labs) was incubated for 20 minutes at 37°C. Ubiquitin antiserum (1:800; DAKO Corporation, Carpinteria, CA) was applied overnight at room temperature. The reaction was developed using biotinylated swine antirabbit immunoglobulin (1:400; DAKO Corporation) for 30 minutes at 37°C. Fresh horseradish peroxidase-labeled streptavidin (1:500; DAKO Corporation) was incubated for 20 minutes at 37°C. Monoclonal antibody Synuclein-1 (1:100; Transduction Laboratories, Lexington, KY) was applied for 1 hour at 37°C followed by incubations with prediluted biotinylated secondary antibody and prediluted streptavidin–peroxidase antibody (Biomeda, Foster City, CA), each for 20 minutes at 37°C. All sections were developed using diaminobenzidine (Sigma) and counterstained with aqueous hematoxylin (Biomeda).

Western Blot Analysis

Gray matter was carefully dissected from partially thawed frontal lobe samples and homogenized in 200 mg/mL of buffer A (20 mM MES/NaOH at pH 6.8, 80 mM NaCl, 1 mM EGTA, 0.1 mM EDTA, and a cocktail of protease inhibitors). Soluble and sarkosyl-insoluble fractions of tau were prepared as previously described (12, 13). The fractions were boiled in SDS-PAGE sample buffer for 5 minutes and resolved on a 10% SDS-PAGE gel. Proteins were transferred onto nitrocellulose membranes and blotted with WKS44 polyclonal anti-tau antibody (1:1000) at 4°C for overnight. The specific bands were detected using the ECL detection system (Amersham-Pharmacia, Piscataway, NJ). The insoluble tau patterns were noted on each case without prior knowledge of the clinical information or neuropathologic diagnoses. To quantitate soluble tau, the lower portions of the membranes

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were probed with anti-α-synuclein monoclonal antibody (LB509, 1:1000). The ratio of the total amount of soluble tau to α-synuclein was then determined using ImageQuant analysis software. This ratio was then presented as a fraction of control brain tissue as previously described (14, 15).

DNA Sequencing for Microtubule-Associated Protein Tau

DNA was isolated from brain tissue using QIAamp DNA Mini Kit (Qiagen, Valencia, CA). Exons 1–5, 7, and 9–13 of microtubule-associated protein tau (MAPT) were amplified from patient genomic DNA (500 ng) using primer pairs described by Poorkaj et al (16) complementary to the intronic regions of MAPT. Amplification reactions contained 1× polymerase chain reaction buffer, 200 nM of each primer, 2.5 U of Taq DNA polymerase (exon 4), or TaqGold DNA polymerase (all other exons) (Applied Biosystems, Foster City, CA) and 200 μM deoxynucleoside triphosphatase (Applied Biosystems) in a final volume of 50 μL. The amplifications using AmpliTaq Gold included a 10-minute activation step at 95°C, followed by 40 cycles of 95°C for 30 seconds, 58°C for 30 seconds, and 72°C for 30 seconds with a final 5-minute elongation step at 72°C (all exons except 4 and 7) or 95°C for 30 seconds, 58°C for 45 seconds, and 72°C for 1 minute with a final 9-minute elongation step at 72°C (exon 7). The exon 4 amplification was identical to that of exon 7 without the initial activation step. After amplification, polymerase chain reaction (PCR) products were purified using Qiagen PCR purification Kit (Qiagen) according to the manufacturer's directions. An aliquot of the purified PCR products was electrophoresed on a 1% agarose gel in 1× TBE (Tris-borate-ethylenediamine-tetraacetate) buffer containing ethidium bromide. Approximate DNA concentrations were determined by comparison of the intensity of the gel bands to the equivalent band in a 100-bp DNA ladder (New England Biolabs, Beverly, MA) with known DNA mass for each marker band. Using 100 fmol of each purified fragment, both strands of the products were sequenced using the CEQ dye terminator cycle sequencing kit (Beckman Coulter, Fullerton, CA) on a CEQ 8000 (Beckman Coulter) using both the forward and reverse PCR primers. Sequence analysis was performed with Sequencher software (Gene Codes Corporation, Ann Arbor, MI).

Apolipoprotein E Genotype Determination

Genomic DNA was extracted from fresh-frozen brain using the QIAamp DNA minikit (Qiagen). Amplification was carried out using the "single-day apolipoprotein ε" method (17) with the following modifications. The DNA was amplified using a Hybaid Touchdown thermal cycler (Hybaid, Cambridge, UK). Conditions included an initial denaturation at 94°C for 5 minutes, followed by 35 cycles of 94°C for 30 seconds, 50–60°C touchdown annealing for 30 seconds at 0.5°C per cycle, and 72°C for 45 seconds, with a final extension at 72°C for 10 minutes. The primer sequences used for this amplification were: forward 5′-TAAGCTTGGCACGGCTGTCCAAGGA-3′ and reverse 5′-ACAGAATTCGCCCCGGCCTGGTACAC-3′. After amplification, 5 units of Cfo 1 (Promega, Madison, WI) enzyme and its buffer were added directly to 20 μL of PCR product and incubated at 37°C for 5 hours. The digest was run on a 4.5% agarose gel with 1× TBE giving main fragment sizes of 91, 83, 72, and 48 base pairs.

Statistical Analysis

The data were analyzed using STATGRAPHICS Plus version 5.0 (Manugistics Inc., Rockville, MD). The χ^2 test was used to compare the frequency of insoluble tau isoform patterns among the 6 diagnostic categories. Additionally, the χ^2 test was used to compare the frequency of insoluble isoform patterns seen with specific histopathologic features. Linear regression analysis was used to fit a model to describe the relationship between soluble tau levels (dependent variable) and postmortem interval (independent variable). The p value was calculated using an analysis of variance (ANOVA) table. One-way ANOVA was used to compare soluble tau levels among the diagnostic categories. The Student *t*-test was used with 2-group comparisons. Standardized skewness and kurtosis were used to determine the normality of the data distribution. The Cochran C test, Bartlett test, and Levene test were used to determine equality of variance. The cutoff p value for all tests was set at $\leqslant 0.05$ for statistical significance.

RESULTS

Clinical Findings

In this study, we examined the brains from 21 patients with a clinicopathologic diagnosis of FTD (Table 1). Overall, the mean age at death was 70.0 ± 2.2 years (± 1 standard error of mean) with a range of 56 to 89 years. All patients were white and the majority were female (67%). The data show a trend toward increased age among the female patients (female mean age 72.8 ± 2.8 years; male mean age 64.4 ± 2.5 years; p = 0.068; Student *t*-test). Details of the clinical presentation were available in 16 cases and included dementia with personality deterioration (31%), dementia not otherwise specified (25%), dementia with parkinsonism (19%), dementia with language impairment (13%), dementia with motor neuron disease (6%), and dementia with both personality deterioration and parkinsonism (6%). A significant number of patients had a positive family history of dementia (33%; 6 of 18 cases with sufficient clinical history).

Pathologic Findings

Autopsies were performed in each case, with a mean postmortem interval of 10.8 ± 1.7 hours. The mean brain weight was 892 ± 34 g for the female patients and 1172 ± 37 g for the male patients. The location of cerebral atrophy was variable and included frontotemporal (30%), frontal (20%), temporal (15%), frontoparietal (15%), frontotemporoparietal (10%), and minimal to mild global atrophy (10%). Atrophy of the caudate nucleus was also identified in 40% of the cases.

Classic Pick Disease

Seven of the patients were given the histopathologic diagnosis of classic PiD, including 6 females and one male. The mean age was 75.7 ± 3.7 years. Grossly, all of the classic PiD cases were characterized by severe, circumscribed atrophy that was confined to the frontal and anterior temporal lobes. Two of the cases also displayed significant atrophy of the

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TABLE 1. Summary of Clinical, Neuropathologic, and Molecular Findings

Patient	Age (years)	Sex	Clinical Features	Histopathologic Diagnosis	Insoluble tau Pattern	tau Sequence	APOE Genotype
1	68	M	Personality deterioration	PiD	3R	Not done	2,3
2	73	F	Personality deterioration	CBD	4R	Not done	3,3
3	78	F	Dementia not otherwise specified	CBD	4R	Not done	2,3
4	86	F	Not available	PSP	4R	Not done	3,3
5	60	F	Personality deterioration	DLDH	No insoluble tau	Not done	3,4
6	56	M	Mutism	FTLD-MNI	No insoluble tau	Exon 10 polymorphism	2,3
7	79	F	Personality deterioration	PiD	3R	Not done	3,4
8	66	M	Motor neuron disease	FTLD-MND	No insoluble tau	Not done	3,3
9	65	M	Parkinsonism	DLDH	No insoluble tau	Not done	3,3
10	75	F	Not available	PSP	4R	Not done	3,3
11	59	F	Aphasia	PiD	3R	Not done	3,4
12	79	F	Dementia not otherwise specified	PiD and AD	3R/4R	Not done	3,4
13	75	F	Not available	PiD	3R	Not done	3,3
14	65	M	Not available	DLDH	No insoluble tau	Not done	3,4
15	67	F	Dementia not otherwise specified	NFTD	3R/4R	R406W mutation	3,3
16	81	F	Parkinsonism	PiD	3R	Not done	3,3
17	89	F	Not available	PiD and AD	3R/4R	Not done	3,4
18	58	F	Parkinsonism	CBD	4R	Exon 10 5' splice site +16 mutation	3,4
19	75	M	Dementia not otherwise specified	CBD	4R	None	3,3
20	56	M	Personality deterioration	CBD	4R	Not done	2,3
21	60	F	Personality deterioration and parkinsonism	DLDH	No insoluble tau	Exon 11 polymorphism	3,3

PiD, Pick disease; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; DLDH, dementia lacking distinctive histopathological features; FTLD-MND/MNI, frontotemporal lobar degeneration with motor neuron disease or motor neuron disease-type inclusions; AD, Alzheimer disease; NFTD, neurofibrillary tangle dementia.

caudate nucleus. Histologic and immunohistochemical studies revealed tau-immunoreactive Pick bodies and ballooned neurons in all 7 cases, which were localized to the middle frontal gyrus, superior temporal gyrus, inferior parietal lobule, cingulate gyrus, insula, hippocampal formation, amygdala, caudate nucleus, globus pallidus, and substantia nigra. Two of the cases also had neurofibrillary change and neuritic plaques typical of early-stage AD and were given the combined diagnosis of PiD and AD. Astrocytic plaques, thorn-shaped astrocytes, and ubiquitin-immunoreactive motor neuron disease-type inclusions were absent in all cases.

Independent analysis of the tau isoform composition by Western blotting revealed predominantly 3R tau in the five pure PiD cases (Fig. 1). The 2 cases with combined PiD and AD had both 3R and 4R tau deposits. None of these patients were tested for tau gene mutations. The APOE genotypes included 3/4 (n = 4), 3/3 (n = 2), and 2/3 (n = 1).

Corticobasal Degeneration

Five of the patients were given the histopathologic diagnosis of CBD, including 3 females and 2 males. The mean age was 68.0 ± 4.6 years. Grossly, the brains demonstrated moderate to severe cerebral atrophy that was confined to the frontal (n = 2), temporal (n = 2), and frontoparietal regions (n = 1). Significant atrophy of the caudate nucleus was identified in three cases. All 5 cases had tau-immunoreactive astrocytic plaques in the cortex of the superior frontal gyrus, middle frontal gyrus, and superior temporal gyrus (Fig. 2A). Four cases had tau-immunoreactive thorn-shaped astrocytes that were localized to the white matter of the middle frontal gyrus, superior frontal gyrus, superior temporal gyrus, hippocampal formation, entorhinal cortex, amygdala, caudate nucleus,

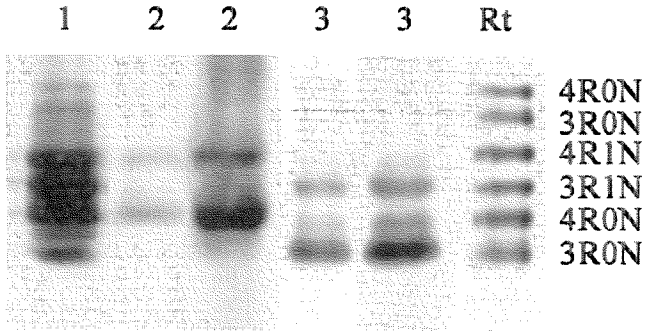

FIGURE 1. Representative Western blot analysis of insoluble tau proteins. Insoluble tau was isolated from frozen tissue samples as described in the "Materials and Methods" section. Each sample was dephosphorylated using alkaline phosphatase from *Escherichia coli*. A mixture of recombinant human tau was used as a standard (Rt). Insoluble tau was isolated from 1) Alzheimer disease, showing a mixture of 3R and 4R tau isoforms; 2) corticobasal degeneration (2 regions from a single case), showing predominantly 4R isoforms; and 3) Pick disease (2 regions from a single case), showing predominantly 3R isoforms.

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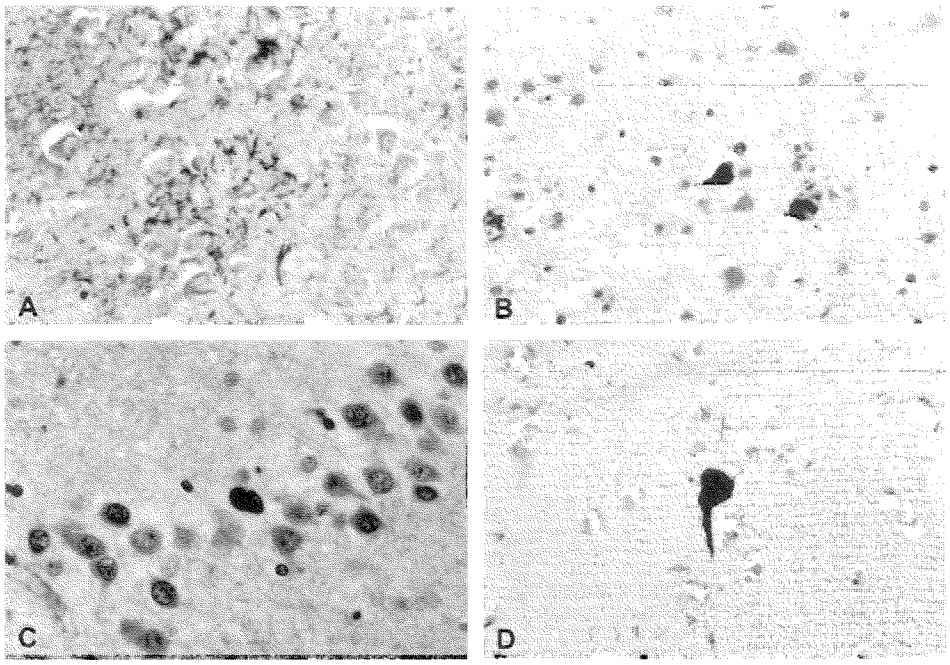

FIGURE 2. (A) Tau-immunoreactive astrocytic plaques were a characteristic feature of corticobasal degeneration (AT8 tau, 400×). (B) Tau-immunoreactive thorn-shaped astrocytes were a common finding in progressive supranuclear palsy (AT8 tau, 400×). (C) Frontotemporal lobar degeneration with motor neuron disease or motor neuron disease-type inclusions cases were characterized by ubiquitin-immunoreactive inclusions in the dentate neurons of the fascia dentata (ubiquitin, 400×). (D) The single case of neurofibrillary tangle dementia was characterized by neurofibrillary change in the absence of glial tau pathology (AT8 tau, 400×). This patient was found to have the R406W mutation.

putamen, globus pallidus, substantia nigra, and thalamus. Neurofibrillary tangles were identified in 4 cases, with a distribution that included the middle frontal gyrus, superior temporal gyrus, hippocampal formation, amygdala, caudate nucleus, putamen, substantia nigra, thalamus, oculomotor nucleus, locus ceruleus, and the pontine nuclei. Ballooned neurons were identified in 2 cases, including in the superior frontal gyrus, middle frontal gyrus, superior temporal gyrus, hippocampal formation, caudate nucleus, putamen, globus pallidus, and thalamus. All cases were negative for Pick bodies, neuritic plaques, and motor neuron disease-type inclusions.

Western blot analysis demonstrated predominantly 4R tau in the insoluble deposits (Fig. 1). Tau gene sequencing was performed in two cases. One of the cases demonstrated the exon 10 5′ splice site +16 mutation. The remaining case was free of mutations or polymorphisms in the tau gene. The APOE genotypes included 2/3 (n = 2), 3/3 (n = 2), and 3/4 (n = 1).

Dementia Lacking Distinctive Histopathologic Features

Four patients, including 2 males and 2 females, were given the histopathologic diagnosis of DLDH. The mean age was 62.5 ± 1.4 years. In each case, there was moderate to severe cerebral atrophy with a frontal (n = 2), frontotemporal (n = 1), and frontoparietal (n = 1) distribution. Two cases had significant atrophy of the caudate nucleus. The histologic features were limited to neuronal loss and gliosis in the grossly affected areas of brain. No tau-immunoreactive inclusions or neurofibrillary changes were identified. Additionally, immunostains for β-amyloid peptide, ubiquitin, and α-synuclein were negative.

Western blot analysis confirmed the absence of insoluble tau. Tau gene sequencing was performed in one case and showed no evidence of mutation. This case did, however, display a polymorphism in exon 11. The APOE genotypes included 3/3 (n = 2) and 3/4 (n = 2).

Progressive Supranuclear Palsy

Two female patients with a mean age of 80.5 ± 5.5 years were given the histopathologic diagnosis of PSP. Both cases were characterized by severe atrophy of the frontal and temporal lobes, moderate atrophy of the parietal lobes, and moderate atrophy of the caudate nuclei and midbrain. Histologically, the frontal, parietal, and temporal lobes displayed significant neuronal loss and gliosis with spongiform changes in the superficial cortex. The hippocampus had mild to moderate neuronal loss throughout the pyramidal cell layer. Both cases demonstrated a dense deposition of tau-immunoreactive thorn-shaped astrocytes in the white matter of the cerebrum and brainstem (Fig. 2B). Although less dense, thorn-shaped astrocytes were also identified in the cortex. Ballooned neurons, Pick bodies, astrocytic plaques, motor neuron disease-type inclusions, and neuritic plaques were absent in both cases. Western blot analysis of the insoluble tau deposits revealed predominantly 4R tau. Tau genetic testing was not performed. Both patients were found to have an APOE genotype of 3/3.

Frontotemporal Lobar Degeneration with Motor Neuron Disease or Motor Neuron Disease-Type Inclusions

Two patients were placed into the category of FTLD with motor neuron disease (FTLD-MND) or with motor neuron disease-type inclusions (FTLD-MNI). One of the patients was a 66-year-old with a clinical history of motor neuron disease and progressive dementia. The other patient was a 56-year-old with a clinical history of mutism and dementia. At autopsy, the patient with motor neuron disease had mild cerebral atrophy. The patient with mutism and

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dementia had severe, circumscribed atrophy of the frontal, temporal, and parietal lobes, and moderate atrophy of the caudate nuclei. The only specific histopathologic feature was the presence of ubiquitin-immunoreactive inclusions in the dentate neurons of the hippocampus in both cases (Fig. 2C) and in the anterior motor neurons of the spinal cord in the patient with motor neuron disease. The anterior motor neuron inclusions consisted of hyaline, Lewy body-like inclusions and irregular basophilic inclusions. No upper motor neuron inclusions or Bunina bodies were identified in the motor neuron disease case. The spinal cord was not available for examination in the second case. There was no evidence of tau, ß-amyloid peptide, or α-synuclein pathology in either case.

Western blot analysis confirmed the absence of insoluble tau in both cases. Genetic testing on the 56-year-old patient with dementia and mutism identified a polymorphism in exon 10, but no evidence of mutation. Genetic testing was not performed on the patient with motor neuron disease. The APOE genotypes were 2/3 and 3/3, respectively.

Neurofibrillary Tangle Dementia

One patient was given the histopathologic diagnosis of NFTD. This patient was a 67-year-old white woman who originally presented 13 years before death with an Alzheimer-type dementia. She had a strong family history of dementia affecting her mother, 2 sisters, and 2 uncles from her mother's side. Gross findings included moderate atrophy of the frontal, temporal, and parietal lobes. The caudate nuclei were unremarkable. Histologic examination revealed moderate to severe neuronal loss involving the entorhinal cortex, hippocampus, amygdala, subiculum, medial temporal lobe, and insula. There was severe neurofibrillary change in the amygdala, entorhinal cortex, layer CA1 of the hippocampus, and subiculum (Fig. 2D). The caudate nucleus, putamen, globus pallidus, and substantia nigra showed only mild neuronal loss and gliosis with scattered neurofibrillary tangles. Pertinent negatives included the absence of amyloid plaques, Pick bodies, ballooned neurons, or Lewy bodies. Western blot analysis showed both 3R and 4R tau in the insoluble deposits. Molecular testing revealed the R406W mutation. The patient's APOE genotype was 3/3.

Insoluble Tau: Summary

The insoluble tau isoform patterns correlated strongly with the independently derived histopathologic diagnoses ($p < 0.001$; χ^2 analysis) (Table 2). The data show that cases containing no insoluble tau were either DLDH (67%) or FTLD-MND/MNI (33%). Cases with predominantly 3R tau were exclusively classic PiD (100%). Cases with predominantly 4R tau were either CBD (71%) or PSP (29%). Finally, cases that contained both 3R and 4R isoforms were either a combination of PiD and AD (67%) or NFTD (33%).

The histologic features that correlated with the tau isoform patterns by χ^2 testing included ballooned neurons and 3R tau ($p = 0.006$); Pick bodies and 3R tau ($p < 0.001$); astrocytic plaques and 4R tau ($p = 0.004$); thorn-shaped astrocytes and 4R tau ($p = 0.001$); neurofibrillary tangles and 4R tau ($p = 0.002$); and neuritic plaques and 3R/4R tau ($p = 0.004$).

TABLE 2. Frequency Table for Insoluble tau Pattern by Histopathologic Diagnosis

	PiD	PiD and AD	CBD	PSP	DLDH	FTLD-MND /MNI	NFTD
No insoluble tau	0	0	0	0	4	2	0
3R tau	5	0	0	0	0	0	0
4R tau	0	0	5	2	0	0	0
3R + 4R tau	0	2	0	0	0	0	1

PiD, Pick disease; AD, Alzheimer disease; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; DLDH, dementia lacking distinctive histopathologic features; FTLD-MND/MNI, frontotemporal lobar degeneration with motor neuron disease or motor neuron disease-type inclusions; NFTD, neurofibrillary tangle dementia.

Soluble Tau: Summary

For each case, the amount of soluble tau was quantitated as a fraction of that found in control brain tissue as previously described (14, 15). The data show that among diagnostic categories, DLDH and FTLD-MND/MNI showed the lowest levels of soluble tau (Fig. 3A), although this did not reach statistical significance ($p = 0.391$; one-way ANOVA). However, if the cases were separated into those with or without insoluble tau, the cases lacking insoluble tau (i.e. DLDH and FTLD-MND/MNI) showed a significantly lower level of soluble tau ($p = 0.045$; Student *t*-test) (Fig. 3B). Although the level of soluble tau was slightly less in cases with a polymorphism in the tau gene (0.34 ± 0.11 vs. 0.52 ± 0.14), this difference failed to reach statistical significance ($p = 0.432$; Student *t*-test). There was not a statistically significant correlation between the soluble tau levels and the postmortem interval ($p = 0.773$; linear regression analysis).

APOE Genotype: Summary

Among all cases, the most common APOE genotype was 3,3 (47.6%), followed by 3,4 (33.3%) and 2,3 (19.1%). The APOE4 allele was identified in patients with PiD (57%), DLDH (50%), and CBD (20%) ($p = 0.394$; χ^2 analysis). Two of the PiD cases with an APOE4 allele also had coexisting AD pathology. The APOE genotypes demonstrated no association with patient age.

DISCUSSION

FTD is the third most common neurodegenerative dementia, behind AD and dementia with Lewy bodies (18, 19). Although this group of neurodegenerative dementias is not uncommon, a simplified classification system has yet to be well-defined. Recent studies into the comparative biochemistry of tau aggregates in neurodegenerative diseases such as FTDs and AD have provided important insight into the pathogenesis of these diseases. Moreover, these studies have provided important tools that may be useful in the diagnostic evaluation of the neurodegenerative tauopathies.

In the human central nervous system, tau protein exists as 6 isoforms that contain either 3 (3R) or 4 (4R) microtubule-binding domains. Excessive phosphorylation of these isoforms leads to pathologic aggregation within neurons and glia. The neurodegenerative diseases that are characterized by tau aggregation such as the FTDs and AD differ in the relative

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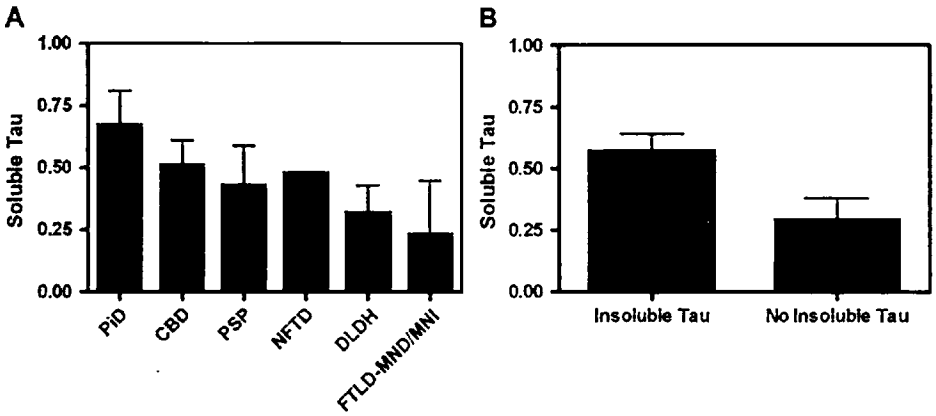

FIGURE 3. Soluble tau was quantitated using Western blot analysis and expressed as a fraction of that seen in control brain tissue. The data represent the mean ± 1 standard error of mean. (A) Among the diagnostic categories, dementia lacking distinctive histopathologic features (DLDH) and frontotemporal lobar degeneration with motor neuron disease or motor neuron disease-type inclusions (FTLD-MND/MNI) showed the lowest levels of soluble tau, although this did not reach statistical significance (p = 0.391; one-way analysis of variance). (B) Separating the cases based on the presence or absence of insoluble tau revealed that cases lacking insoluble tau (i.e. DLDH and FTLD-MND/MNI) had a significantly lower level of soluble tau (p = 0.045; Student *t*-test).

composition of the 6 tau isoforms. For example, in AD, both the 3R and 4R isoforms are abnormally phosphorylated, leading to aggregation into paired helical filaments that can be detected by Western immunoblotting (20–22). In the FTDs, the composition of abnormally phosphorylated tau varies according to the pathologic subtype and may include predominantly 3R isoforms, predominantly 4R isoforms, or both 3R and 4R isoforms. Additionally, many cases lack insoluble tau deposits. Although numerous studies have shown a correlation between various FTD pathologic subtypes and the tau isoform pattern (20, 22–25), biochemical analysis of tau aggregates has yet to be fully incorporated into the FTD classification system. This is in part the result of the complexity of the FTD nomenclature as well as the lack of consensus on the neuropathologic diagnosis of the FTDs.

In response to these issues, McKhann et al (1) recently proposed a neuropathologic classification scheme that incorporates a biochemical analysis of insoluble tau deposits as well as ubiquitin immunohistochemistry. In the present study, we have demonstrated the use of this system by showing a strong correlation between the insoluble tau isoform composition and the independently derived neuropathologic diagnoses obtained using a histopathologic and immunohistochemical approach. The combination of the biochemical, histopathologic, and immunohistochemical approaches should permit the diagnostic accuracy that is necessary in a research setting. We present a simplified algorithm of this combined approach in Figure 4. We reiterate, however, that the cases with tau-immunoreactive inclusions may in fact represent FTDP-17, because no specific histopathologic findings have been linked to this group of disorders. Additionally, our data show that the cases lacking tau-immunoreactive inclusions (DLDH and FTLD-MND/MNI) may demonstrate polymorphisms in the tau gene or reduced levels of soluble tau, thus not completely excluding a pathologic role for tau in these disorders.

FTDP-17 is a group of autosomal-dominant neurodegenerative syndromes that are characterized by deposition of hyperphosphorylated tau protein within neurons and glia (26–31). The clinical and neuropathologic phenotypes among this group of disorders are variable and may simulate a number of sporadic FTDs. Approximately 80 families with FTDP-17 have been identified, with a total of 31 unique tau gene mutations (19). The described mutations involve exons 1, 9, 10, 11, 12, and 13, as well as the exon 10 5′ splice site. The most common mutations, accounting for 60% of cases, involve exon 10 (P301L and N279K) and the exon 10 5′ splice site (+16) (19). The resulting neuropathologic features, particularly with regard to the localization of tau deposits, vary according to the site of the tau gene mutation. Mutations in exons 1 and 10, and in the exon 10 5′ splice site, tend to cause both neuronal and glial filamentous inclusions; conversely, mutations in exons 9, 11, 12, and 13 cause primarily neuronal inclusions. In the present study, we identified 2 patients with tau gene mutations, including a patient with the exon 10 5′ splice site +16 mutation that comes from a previously described family (32) and a patient with the R406W (exon 13) mutation. There are several reports of mutations in the exon 10 5′ splice site (33–39). The neuropathology produced by these mutations includes neuronal loss and gliosis in the cortex, caudate nucleus, putamen, globus pallidus, amygdala, and numerous brainstem nuclei. Tau-immunoreactive inclusions are identified in both neurons and glial cells, with some cases showing significant white matter pathology. Biochemical studies have shown a tendency to form 4R tau isoforms within the filamentous inclusions (29, 35, 37, 40). The mechanism appears to involve disruption of a stem-loop structure that normally forms over the splice site, which leads to increased affinity for U1 snRNP-binding and a subsequent increase in the incorporation of exon 10 into the tau mRNA (35). The patient with the intron +16 mutation in the present study demonstrated neuropathologic findings indistinguishable from CBD with tau-immunoreactive neuronal inclusions, astrocytic plaques, and thorn-shaped astrocytes, all of which were composed of predominantly 4R tau isoforms. The patient with the R406W mutation represents a newly described family with FTDP-17. Consistent with previous reports of this mutation (35, 41, 42), the primary pathologic findings were those of neuronal loss and gliosis with abundant neurofibrillary tangles and neuropil threads in the absence of glial tau pathology or amyloid deposition. The pathology of this case primarily involved the entorhinal cortex, amygdala, hippocampus, subiculum, medial temporal lobe, and insula. The insoluble

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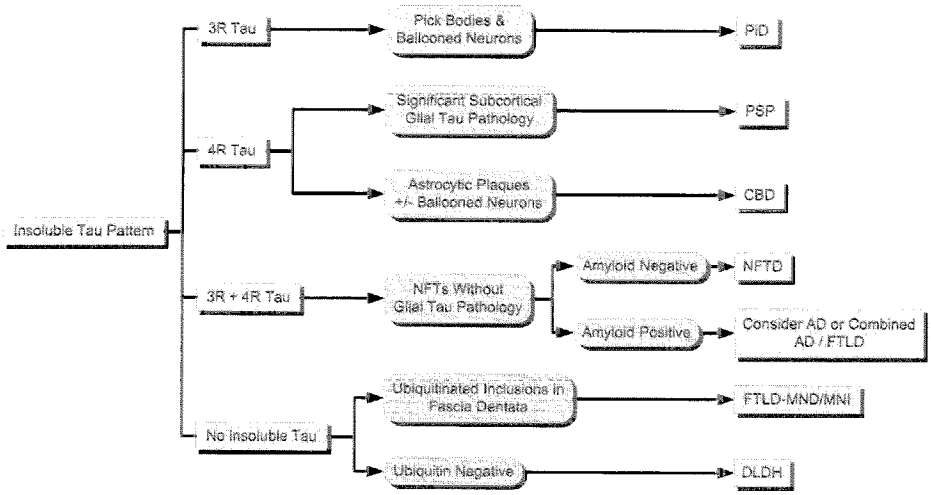

FIGURE 4. Frontotemporal dementia diagnostic algorithm. PiD, Pick disease; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; NFTD, neurofibrillary tangle dementia; AD, Alzheimer disease; FTLD-MND/MNI, frontotemporal lobar degeneration with motor neuron disease or motor neuron disease-type inclusions; DLDH, dementia lacking distinctive histopathologic features.

tau deposits were composed of both 3R and 4R isoforms, which is consistent with previous reports (29). The molecular mechanisms that result in the observed biochemical abnormality have not been fully elucidated.

The strong association between the APOE epsilon 4 allele and AD is well established (43, 44). On the contrary, no consensus has been reached with regard to the association between the FTDs and APOE genotype. Reports in the literature are often conflicting. For example, there are 3 reports showing an increased frequency of APOE4 in patients with FTD (45–47). Only one of these studies, however, had pathologically confirmed diagnoses (47). The importance of the nonpathologically confirmed findings is difficult to interpret given the potential for coexistence of AD and FTD pathology (as seen in the present study) and the overlap in clinical presentation between these disorders. Additionally, there are numerous studies that show no association between FTD and APOE4 (48–54). Again, only a minority of these cases have pathologic confirmation. In our study, we found that 7 of the 21 patients (33%) had a single APOE4 allele, which is significantly higher than published reports of nondemented controls, which usually lies between 14% and 16% (43, 55). However, 2 of the cases in our series had combined PiD and AD pathology, together with a single APOE4 allele. When these cases were excluded, the APOE4 allele frequency remained elevated at 26%. Further analysis of cases with APOE4 demonstrated an apparent overrepresentation of this allele among patients with DLDH and PiD. These findings support previous studies showing an association between PiD and APOE4 (47). Additionally, the results suggest that APOE4 may be associated with DLDH, a potentially novel finding that needs to be confirmed with larger studies.

In conclusion, the three major findings of this study can be summarized as follows. First, the primary neuropathologic subtypes of FTD can be reproducibly categorized by the isoform composition of insoluble tau. Second, the neuropathologic subtypes of FTD that lack insoluble tau may still show evidence of tau aberrations, including polymorphisms in the tau gene and low levels of soluble tau. Third, the APOE4 allele, which is a risk factor for AD, is overrepresented in the 2 most common neuropathologic subtypes of FTD (i.e. PiD and DLDH). Together, these findings suggest that, although the current classification system is useful and reproducible, more revisions will likely be necessary in the future, particularly with regard to the neuropathologic subtypes lacking clearly discernible tau pathology.

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Reduction of β-Amyloid Peptide$_{42}$ in the Cerebrospinal Fluid of Patients with Alzheimer's Disease

R. Motter, MPH,* C. Vigo-Pelfrey, PhD,* D. Kholodenko, MS,* R. Barbour, BS,* K. Johnson-Wood, BA,* D. Galasko, MD,† L. Chang, MD,‡ B. Miller, MD,‡ C. Clark, MD,§ R. Green, MD,‖ D. Olson, MD,‖ P. Southwick, PhD,¶ R. Wolfert, PhD,¶ B. Munroe, PhD,¶ I. Lieberburg, MD, PhD,* P. Seubert, PhD,* and D. Schenk, PhD*

In this clinical study, the cerebrospinal fluid (CSF) level of a novel form of the β-amyloid peptide (Aβ) extending to position 42 (Aβ$_{42}$) was determined in patients with Alzheimer's disease (AD) as well as controls. In addition to measurement of CSF Aβ$_{42}$ levels, total Aβ peptides, microtubule-associated protein τ, and apolipoprotein E (ApoE) genotype were also assessed. It is interesting that CSF Aβ$_{42}$ levels were found to be significantly lower in AD patients relative to controls, whereas total Aβ levels were not. Aβ$_{42}$ has recently been shown to preferentially deposit in the brain tissue of patients with AD, suggesting that diminished clearance may account for its reduction in CSF. As previously reported, τ levels were increased in AD patients; however, neither Aβ$_{42}$ nor τ levels were apparently influenced by the ApoE genotype.

Motter R, Vigo-Pelfrey C, Kholodenko D, Barbour R, Johnson-Wood K, Galasko D, Chang L, Miller B, Clark C, Green R, Olson D, Southwick P, Wolfert R, Munroe B, Lieberburg I, Seubert P, Schenk D. Reduction of β-amyloid peptide$_{42}$ in the cerebrospinal fluid of patients with Alzheimer's disease. Ann Neurol 1995;38:643–648

Alzheimer's disease (AD) is the most common form of dementia in the elderly population [1]. Clinically, it is diagnosed primarily by exclusion of other dementing illnesses. Diagnosis is only definitive at autopsy, or at brain biopsy, and is confirmed by a high density of senile plaques, largely composed of the β-amyloid (Aβ) peptide, and neurofibrillary tangles comprised of the microtubule-associated protein τ [2]. It is established that apolipoprotein E (ApoE) is associated with senile plaques and that the ApoE ε4 allele frequency is increased in the AD population [3]. For these reasons, we and others have focused attention on measurements of τ, Aβ, and ApoE as AD brain pathology–related proteins that might be useful as diagnostic markers during life. In this regard, recent studies have shown that τ is elevated in AD cerebrospinal fluid (CSF) [4, 5]. In contrast, a recent study has shown that total Aβ levels in AD patients did not differ from controls; although early-onset AD patients had slightly higher Aβ levels than elderly controls [6]. However, the generation of specific Aβ antibodies, along with biochemical purification and structural analyses, have revealed that Aβ extending to position 42(Aβ$_{42}$) predominates in both diffuse and senile amyloid plaques in AD brain tissue [7, 8]. Conversely, the predominant form of Aβ found in CSF was shown to contain 40 amino acids [9]. Analysis of CSF Aβ$_{42}$ levels in AD patients, therefore, is of significant interest but has not yet been reported. To address this, and the question of the combined utility of τ and Aβ measurements in the diagnosis of AD, the present study was undertaken on well-characterized groups of AD patients, neurological disease control patients, and normal elderly individuals.

Materials and Methods

All subjects enrolled in this study underwent detailed clinical and neurological evaluation at university medical centers by neurologists expert in the diagnosis of dementia. Informed consent was obtained from subjects, or their guardians, as appropriate. The patient evaluation included medical history,

From the *Athena Neurosciences, Inc, South San Francisco, CA; †Department of Neurosciences (V127), University of California at San Diego, and Veteran's Administration Hospital, San Diego, CA; ‡UCLA Harbor Medical Center, Department of Neurology, Torrance, CA; §University of Pennsylvania, Graduate Hospital, Department of Neurology, Philadelphia, PA; ‖Neurobehavior Program of Neurology, Wesley Woods Center and Emory University School of Medicine, Atlanta, GA, and ¶Hybritech, Inc, San Diego, CA.

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Address correspondence to Dr Schenk, Athena Neurosciences, Inc, 800 Gateway Blvd, South San Francisco, CA 94080.

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physical and neurological examinations, laboratory blood tests to exclude metabolic causes of dementia, a neuroimaging study (head computed tomography or magnetic resonance within the past 3 years for demented patients and neurological controls), and detailed psychometric testing (this varied between institutions). In addition, all subjects received the following assessment instruments: the Mini-Mental State Examination (MMSE) [10], the Hamilton Depression Inventory [11], and the Hachinski Ischemic Index [12]. Patients with more than one dementia diagnosis, recent stroke, head trauma, or significant peripheral nervous system disorders were excluded. Each of the clinical centers involved in this study have either reported a clinical accuracy for probable AD of 85% or more [13] or have established, but have not published, such findings. The following diagnostic criteria were used.

Patients with Alzheimer's Disease

AD patients (n = 37) met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) guidelines for probable AD; those who met criteria for possible AD were excluded [14]. All patients were community dwelling and had mild-to-moderate dementia.

Neurological Disease Controls

Neurological disease controls (ND; n = 32) were patients with non-AD dementia or degenerative disorders affecting the central nervous system. For neurological controls, a summary of clinical records was also reviewed by a second neurologist (D.G.). Patients with frontal lobe dementia were diagnosed according to the criteria set forth by the Lund and Manchester groups [15].

Nondemented Controls

Nondemented controls (NC; n = 20) were subjects who were age 50 or older and lacked significant cognitive complaints, did not have functional impairment, had normal findings on neurological examination, and scored 28 to 30 on the MMSE. A subgroup of these controls had symptoms of depression that did not result in significant cognitive or functional impairment and were judged not to have AD or any organic neurological condition.

Lumbar punctures were performed in the mornings, after an overnight fast. The first 2 to 3 ml of CSF was analyzed for protein, glucose, and cells at the local medical center laboratory, and 4 to 5 ml were removed from original collection tubes and added to 8-ml Sarstedt tubes containing 500 μl of buffer (containing additives such that the final CSF solution composition included 20 mM sodium phosphate, 20 mM triethanolamine, 0.05% Triton X-100, 100 mM NaCl, 0.05% NaN_3, 1 mM diethylenetriaminepentaacetic acid [DTPA], 1 mM EGTA, pH 7.4) and frozen at −20°C until analysis. Assay operators were unaware of the subjects' diagnoses.

Apolipoprotein E Genotyping

ApoE genotyping was performed on available blood samples that had been collected into EDTA vacutainer tubes. Samples were prepared by the method of Kawasaki [16] and polymerase chain reaction analysis performed as described by Wenham and colleagues [17].

Total Aβ Enzyme-linked Immunosorbent Assay

Total Aβ was measured in a sequential double monoclonal antibody sandwich enzyme-linked immunosorbent assay (ELISA) as previously described [18]. In brief, Aβ in CSF was captured by monoclonal antibody 266 (specific for Aβ peptide, residues 13–28), which had been precoated in microtiter plate wells. Detection utilized a second, Aβ-specific, biotinylated monoclonal antibody, 6C6 (recognizing Aβ residues 1–16), followed by reaction with an alkaline phosphatase-avidin conjugate. After incubation with the fluorogenic substrate 4-methylumbelliferyl phosphate (MUP), the fluorescent product was measured using a Millipore Cytofluor 2350 fluorometer.

$A\beta_{42}$ ELISA

$A\beta_{42}$ was measured in a similarly formatted assay using 266 as the capture antibody. The reporter polyclonal antibody 277-2, was raised against a synthetic peptide that included Aβ residues 33 to 42 (GLMVGGVVIA), with cysteine-aminoheptanoic acid at the peptide amino terminus. It was conjugated through the cysteine to cationized bovine serum albumin (Pierce). The antibody 277-2, affinity purified using the synthetic peptide conjugated to Sulfo-link resin (Pierce), reacted strongly with ^{125}I-$A\beta_{1-42}$ as detected by immunoprecipitation of tracer. It showed no detectable cross-reactivity with $A\beta_{1-40}$ by immunoprecipitation. Using the 266/277-2 ELISA directed against $A\beta_{42}$, a variety of peptides including $A\beta_{1-28}$, $A\beta_{1-38}$, $A\beta_{1-40}$, $A\beta_{1-41}$, $A\beta_{1-42}$, and $A\beta_{1-43}$ were assayed in a dose range of 1 to 4,000 pg/ml. The $A\beta_{1-42}$ peptide gave a linear dose–response signal, while peptides $A\beta_{1-28}$, $A\beta_{1-38}$, and $A\beta_{1-40}$ showed no reactivity. $A\beta_{1-41}$ and $A\beta_{1-43}$ showed less than 5% and less than 7.5% cross-reactivity, respectively (data not shown). $A\beta_{1-28}$, $A\beta_{1-40}$, and $A\beta_{1-42}$ were purchased from Bachem. $A\beta_{1-38}$, $A\beta_{1-41}$, and $A\beta_{1-43}$ were synthesized at Athena Neurosciences, Inc. The $A\beta_{1-42}$ used as the standard for quantitation of CSF levels was a gift from Dr Charles Glabe (University of California, Irvine, CA). Detection of the 277-2 reporter antibody was achieved using a donkey anti-rabbit IgG-alkaline phosphatase conjugate and the AMPPD chemiluminescent substrate with Emerald enhancer (Tropix) [5].

To eliminate interassay variability as a factor in the $A\beta_{42}$ analysis, all samples were run in duplicate on the same day with the same lot of standards. The intraassay variability was less than 10%. Prior to measurement, aliquots of CSF samples were heated to 100°C for 3 minutes and then stored at 4°C overnight before assay. The heating step was found to generally increase immunoreactivity in CSF samples, independent of diagnosis, and was therefore included. It should be noted that different lots of synthetic $A\beta_{42}$ generate slightly different standard values, despite being normalized by amino acid analysis (data not shown). Values listed are based upon a single standard used for the entire study. Studies involving addition of synthetic $A\beta_{42}$ to CSF demonstrated that measured recovery was 80 ± 5%.

τ ELISA

The τ ELISA has been described elsewhere [5]. It consists of a two-site sandwich ELISA using two monoclonal antibodies

(16B5 and 16G7). These monoclonal antibodies have been shown to bind to τ independent of its phosphorylation state.

Statistical Analysis

Statistical analysis of data was performed by one-way analysis of variance (ANOVA) using InStat, version 1.21.

Results

Comparison of the three patient groups (Table) showed that they were well matched for age and gender. The AD group had an average MMSE of 17.5 ± 7.1 indicating mild-to-moderate cognitive impairment. The neurological disease control group consisted of a variety of disorders including vascular dementia (4 patients), frontal lobe dementia (7), depression (6), Parkinson's disease (3), corticobasal ganglionic degeneration (2), cerebellar ataxia (2), progressive supranuclear palsy (1), normal pressure hydrocephalus (1), grand mal seizure (1), Bell's palsy (1), age-associated memory impairment (1), dementia with extrapyramidal signs (1), amnestic syndrome (1), and cerebellar degeneration (1).

Analysis of total CSF Aβ levels revealed no significant differences among the different patient groups (see Table). The mean values ranged from 19.0 ng/ml in the AD group to 17.9 ng/ml in the NC group. There was significant overlap with no statistically significant differences among the groups ($p > 0.05$).

Summary of Patient Profiles and Measured Variables

Variable	Alzheimer's Disease (AD)	Neurological Controls (ND)	Normal Controls (NC)
n	37	32	20
Age (mean ± SD; yr)	70 ± 9.1	66 ± 9.1	70 ± 6.2
Sex (M%/F%)	48.6/51.4	59.4/40.6	50/50
MMSE (mean ± SD)	17.5 ± 7.1	23 ± 8.2	29.5 ± 0.6
CSF Aβ (mean ± SD; ng/ml)	19.0 ± 6.9	17.9 ± 6.7	21.8 ± 6.9
APOE ε4 frequency[a]	0.58	0.26	0.21
APOE ε3 frequency	0.38	0.74	0.74
APOE ε2 frequency	0.03	0.00	0.06
$A\beta_{42}$ (mean ± SD; pg/ml)	383 ± 76[b]	543 ± 177	632 ± 156
τ (mean ± SD; pg/ml)	407 ± 241[c]	168 ± 63	212 ± 102

[a]Apolipoprotein E (ApoE) genotypes were determined on 30 of 37 AD, 19 of 32 neurological controls, and 17 of 20 normal controls.
[b]$p < 0.0001$, comparing AD group to either control group.
[c]$p < 0.001$, comparing AD group to either control group.

MMSE = Mini-Mental State Examination; CSF = cerebrospinal fluid; $A\beta_{42}$ = β-amyloid peptide extending to position 42.

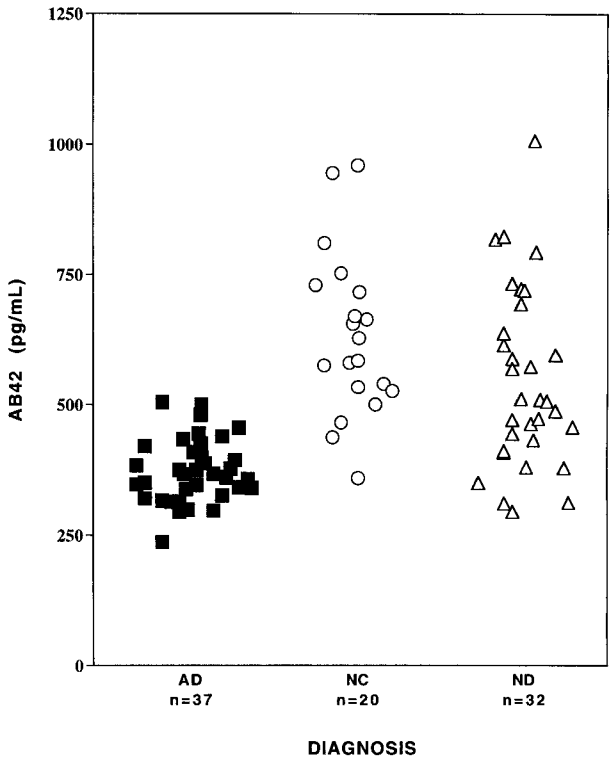

Fig 1. Comparison of individual cerebrospinal fluid levels of β-amyloid peptide$_{42}$ ($A\beta_{42}$). $A\beta_{42}$ was measured as described in the text. All measures are the averages of duplicate determinations; variation was ≤10%. Samples were assigned randomly to plates and the operator was unaware of the subject diagnoses. Reference standards, present on each microtiter plate, were not significantly different between plates. A significant difference exists between the Alzheimer's disease (AD) and either control group (p < 0.0001). NC = nondemented controls; ND = neurological disease controls.

Analysis of the $A\beta_{42}$ form of the peptide, however, demonstrated a reduction in the mean value in the AD group, relative to both the ND and NC subjects (383 versus 543 and 632 pg/ml, respectively), that was significant at the $p < 0.0001$ level (Fig 1). The relatively small standard deviation (76 pg/ml) of the AD group was particularly striking. A cutoff of 505 pg/ml best separated AD patients from ND and NC subjects. All AD patients, 15 of 32 ND, and 4 of 20 NC fell below this level. Therefore, an elevated $A\beta_{42}$ (>505 pg/ml) was an indicator of the likely absence of AD, accounting for 33 of 52 non-AD subjects. These initial data result in a calculated sensitivity of 100% and a specificity of 63%.

τ levels in the same subjects' CSF samples were also examined. Consistent with previous reports [4, 5], AD patients had a mean value of 407 pg/ml, which is significantly higher ($p > 0.001$) than the 168 and 212

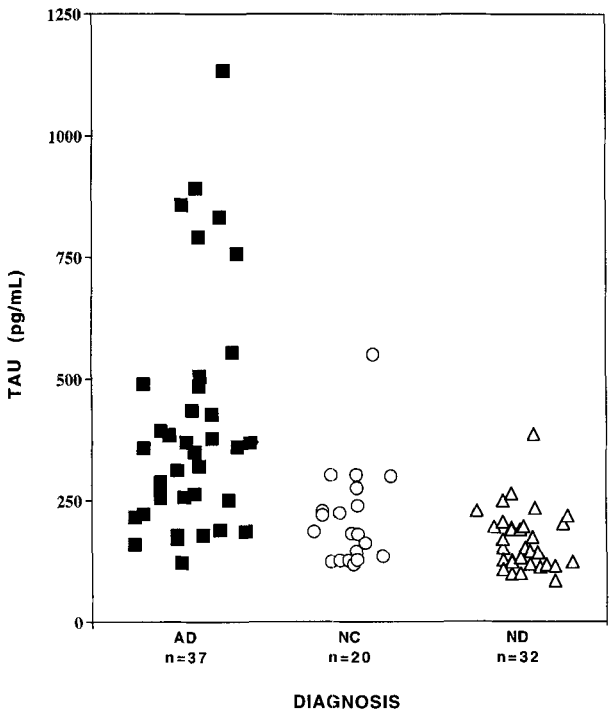

Fig 2. Comparison of individual cerebrospinal fluid levels of τ. τ measurements were performed in duplicate. To ensure consistency, several samples from previous assays were included on subsequent plates and all samples were evaluated in at least replicate measure. Replicate measures were within 15% of original values. A significant difference exists between the Alzheimer's disease (AD) group and either control group ($p < 0.001$). Human brain–derived τ (provided by Innogenetics, Inc) was used as the reference standard. NC = nondemented controls; ND = neurological disease controls.

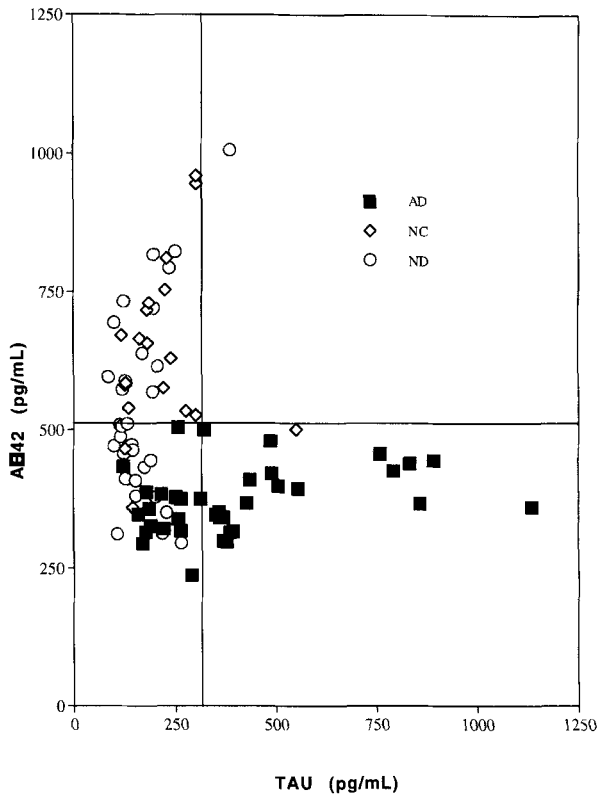

Fig 3. Combined β-amyloid peptide$_{42}$ (Aβ$_{42}$) and τ measures in the diagnosis of Alzheimer's disease (AD). Data from Figures 1 and 2 are combined to illustrate the effect of simultaneous consideration of the two measures in discriminating the AD group. Lines indicate optimized cutoffs. The high τ/low Aβ$_{42}$ quadrant contains AD patients with only a single exception (21 of 22 patients), whereas the low τ/high Aβ$_{42}$ quadrant contains only control individuals.

pg/ml observed in neurological and normal controls, respectively (Fig 2). Although previous studies of CSF τ levels have reported different cutoff values for distinguishing AD from control patients [4, 5], this appears to be due to differences in the τ standards employed in these studies (Van de Voorde A, personal communication). In this study, a cutoff of 312 pg/ml for τ best separated AD subjects from ND or NC. Of the 24 subjects with τ levels above this value, 22 were in the AD group (92% specificity), representing 22 of 37 AD patients (59.4% sensitivity).

CSF levels of Aβ, Aβ$_{42}$, and τ did not differ systematically between participating centers by diagnostic category. Also there were no significant correlations between levels of these markers and age, sex, or MMSE scores in the AD subjects (data not shown).

Of particular interest was the simultaneous analysis of Aβ$_{42}$ and τ measurements in the same CSF samples (Fig 3). Figure 3 is divided into four quadrants using the cutoffs for Aβ$_{42}$ and τ previously described. The presence of elevated τ and reduced Aβ$_{42}$ (lower right quadrant) was highly predictive of AD (22/23 = 96%). Conversely, high Aβ$_{42}$ and low τ (upper left quadrant) was observed only in control patients (see Fig 3). More than half (62%) of all the individuals in this study fell into one of these two quadrants. All but one of the remaining patients exhibited low Aβ$_{42}$ and low τ levels (lower left quadrant).

Analysis of the ApoE allele frequency present in the different patient groups demonstrated a clear overrepresentation of ApoE ε4 in the AD group (see Table). Analysis of the effect of ApoE alleles on τ and total Aβ, however, demonstrated no statistically significant effect on either τ, Aβ peptides, or Aβ$_{42}$ levels in any of the subject categories. Thus, when AD patients were segregated by ApoE genotype, average values of both Aβ$_{42}$ and τ CSF levels did not differ significantly among patients with 0, 1, or 2 ApoE ε4 alleles.

Discussion

τ has previously been demonstrated to be elevated in AD CSF and this study is in agreement with these

findings (see Fig 2 and [4, 5]). The present study augments previous results by demonstrating that levels of τ in AD CSF do not correlate with age, MMSE, total $A\beta$, $A\beta_{42}$, or ApoE $\varepsilon 4$ (data not shown). Although the precise reason for elevation of τ in AD remains unclear, it is likely due to the increased τ levels in AD brain tissue [19] combined with the ongoing degeneration of neurons in the disease.

The finding that $A\beta_{42}$ is consistently low in AD CSF (see Fig 1) is somewhat surprising since total $A\beta$ levels appear to be unchanged (see Table). However, recent observations have shown that while the predominant form of $A\beta$ in CSF and mixed brain-cell cultures is $A\beta_{1-40}$ [9, 18], plaques in AD brain tissue are composed primarily of $A\beta_{42}$ [7, 8]. A possible explanation consistent with these findings is that the $A\beta_{42}$ peptide preferentially deposits in AD brain tissue, leading to reduced levels in CSF. A finding analogous to this exists for another CNS amyloid disease, the Icelandic variant of cystatin C, where the level of the amyloid protein is also reduced in the CSF of affected individuals [20]. Alternative explanations for low $A\beta_{42}$ levels include decreased secretion or other forms of enhanced clearance of $A\beta_{42}$ from AD CSF.

Since plaque deposition most likely precedes cognitive symptoms in AD [21, 22], low CSF $A\beta_{42}$ in some ND subjects could indicate concomitant AD pathology that contributes to the dementia. The significance of low $A\beta_{42}$ in the small number of NC patients needs to be determined by longitudinal studies, ideally with autopsy examination.

The observation that the ApoE $\varepsilon 4$ allele is overrepresented in the AD population in this study is consistent with numerous other reports [e.g., 3]. It has been proposed that ApoE $\varepsilon 4$ might exacerbate AD through either physical interaction with $A\beta$ [23] or τ [24]. It is curious that average values of these markers are equivalent in AD patients with or without the ApoE $\varepsilon 4$ allele, suggesting any differential binding affinity for τ or $A\beta$ by ApoE isoforms is not reflected in steady-state CSF levels of these markers.

Of interest is the combined analysis of CSF $A\beta_{42}$ and τ (see Fig 3). These data show that patients who exhibit high τ and low $A\beta_{42}$ had a strong likelihood of having AD (22/23; 96% specificity). Fifty-nine percent of the AD patients (i.e., sensitivity, 22/37) in this study fall into this category. Conversely, patients who exhibit low τ and elevated $A\beta_{42}$ were free of AD (100% 28/28, see Fig 3). Slightly over half of the non-AD subjects (32/52, 62%) fall into this category. Taken together, the combined analysis of CSF τ and $A\beta_{42}$ was informative of either the presence or the absence of AD in slightly over half of all individuals enrolled in this study. The combined CSF τ and $A\beta_{42}$ measurements, however, were not informative in those patients who fell into the low $A\beta_{42}$/low τ group. Possible reasons for neurological control patients exhibiting low $A\beta_{42}$ include nonspecificity of reduced $A\beta_{42}$ or the presence of plaques and the absence of clinical AD-type symptoms [25]. Autopsy confirmation on the cohort would be required to distinguish these possibilities. Nevertheless, the ability of any test to aid in the inclusion or exclusion of AD with good specificity and even moderate sensitivity is of potential diagnostic importance. This study suggests that the combined measurement of CSF $A\beta_{42}$ and τ might accomplish these goals.

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Frontotemporal lobar degeneration

A consensus on clinical diagnostic criteria

D. Neary, MD; J.S. Snowden, PhD; L. Gustafson, MD; U. Passant, MD; D. Stuss, PhD; S. Black, MD; M. Freedman, MD; A. Kertesz, MD; P.H. Robert, MD, PhD; M. Albert, PhD; K. Boone, PhD; B.L. Miller, MD; J. Cummings, MD; and D.F. Benson, MD

Article abstract—*Objective:* To improve clinical recognition and provide research diagnostic criteria for three clinical syndromes associated with frontotemporal lobar degeneration. *Methods:* Consensus criteria for the three prototypic syndromes—frontotemporal dementia, progressive nonfluent aphasia, and semantic dementia—were developed by members of an international workshop on frontotemporal lobar degeneration. These criteria build on earlier published clinical diagnostic guidelines for frontotemporal dementia produced by some of the workshop members. *Results:* The consensus criteria specify core and supportive features for each of the three prototypic clinical syndromes and provide broad inclusion and exclusion criteria for the generic entity of frontotemporal lobar degeneration. The criteria are presented in lists, and operational definitions for features are provided in the text. *Conclusions:* The criteria ought to provide the foundation for research work into the neuropsychology, neuropathology, genetics, molecular biology, and epidemiology of these important clinical disorders that account for a substantial proportion of cases of primary degenerative dementia occurring before the age of 65 years.

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Frontotemporal lobar degeneration (FTLD) is the third most common cause of cortical dementia, following AD and Lewy body disease. In the past few years FTLD has been studied extensively, and substantial progress has been made in understanding its associated clinical syndromes and underlying pathologic changes. This report provides a consensus statement based on a conference of international investigators familiar with the disorder, and provides an update and extension of previously proposed clinical and pathologic diagnostic criteria for frontotemporal dementia (FTD).[1]

FTLD encompasses two major pathologic substrates which affect primarily the frontal or temporal cortex, in some patients asymmetrically. Three prototypic neurobehavioral syndromes can be produced by FTLD. Results of the consensus conference presented here describe these three behavioral conditions. The most common clinical manifestation of FTLD is a profound alteration in personality and social conduct, characterized by inertia and loss of volition or social disinhibition and distractibility, with relative preservation of memory function (FTD).[2-5] There is emotional blunting and loss of insight. Behavior may be stereotyped and perseverative. Speech output is typically economical, leading ultimately to mutism, commensurate with the patient's amotivational state, although a press of speech may be present in some overactive, disinhibited patients. Cognitive deficits occur in the domains of attention, abstraction, planning, and problem solving, in keeping with a frontal "dysexecutive" syndrome, whereas primary tools of language, perception, and spatial functions are well preserved. Patients are not clinically amnesic. They are typically oriented and negotiate their local environment without becoming lost. Memory test performance, however, is typically inefficient, and impairments arise secondary to patients' frontal regulatory disturbances (inattention, lack of active strategies for learning and retrieval) rather than to a primary amnesia. Executive deficits are typically more evident in inert, avolitional patients than in overactive, disinhibited patients, although even in the latter, abnormalities can be elicited on tests of selective attention.

Two other prototypic clinical syndromes occur in FTLD: progressive nonfluent aphasia (PA)[5-9] and semantic dementia (SD).[5,10,11] PA is a disorder of expressive language, characterized by effortful speech production, phonologic and grammatical errors, and word retrieval difficulties. Difficulties in reading and writing also occur. Understanding of word meaning is relatively well preserved. The disorder of language occurs in the absence of impairment in other cognitive domains, although behavioral changes of FTD may emerge late in the disease course. In SD a severe naming and word comprehension impairment

From the Manchester Royal Infirmary (Drs. Neary and Snowden), Manchester, UK; the Lund University Hospital (Drs. Gustafson and Passant), Sweden; the Rotman Research Institute (Drs. Stuss, Black, and Freedman) Baycrest Centre for Geriatric Care, Toronto and University of Toronto, Canada; the University of Western Ontario (Dr. Kertesz) London, Canada; the Nice University School of Medicine (Dr. Robert), France; the Massachusetts General Hospital (Dr. Albert), Boston, MA; and the University of California at Los Angeles, School of Medicine (Drs. Boone, Miller, Cummings, and Benson), CA.

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Address correspondence and reprint requests to Dr. D. Neary, Department of Neurology, Manchester Royal Infirmary, Manchester M13 9WL, UK.

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occurs in the context of fluent, effortless, and grammatical speech output; relative preservation of repetition; and the ability to read aloud and write orthographically regular words. Also there is an inability to recognize the meaning of visual percepts (associative agnosia). This loss of meaning for both verbal and nonverbal concepts (semantics) contrasts with the preservation of visuospatial skills and day-to-day memory.

The generic term FTLD refers to the circumscribed progressive degeneration of the frontotemporal lobes. The associated clinical syndromes are determined by the distribution of the pathology. In FTD there is prominent bilateral and usually symmetric involvement of the frontal lobes. In PA, atrophy is asymmetric, involving chiefly the left frontotemporal lobes. In SD, atrophy is typically bilateral and is most marked in the anterior temporal neocortex, with inferior and middle temporal gyri being predominantly affected. Asymmetries in the involvement of the left and right temporal lobes in SD mirror the relative severity of impairment for verbal and visual concepts (word meaning versus object recognition). Evidence that the different clinical manifestations may occur within the same family and that there may be an overlap in symptom pattern over the course of disease[5] reinforces the link between the syndromes. Moreover, the distinct clinical syndromes are associated with the same underlying histopathologies. There are two main histologic types: prominent microvacuolar change without specific histologic features (frontal lobe degeneration type) or severe astrocytic gliosis with or without ballooned cells and inclusion bodies (Pick type).[1] The disease etiology is not known but it has a high familial incidence and is likely to be under genetic influence. Molecular studies have shown mutations on chromosome 17[12,13] or linkage to chromosome 3[14] in some families.

The clinical syndromes have a predominantly presenile onset, unlike AD and vascular dementia, which are more common in the elderly. The severe amnesia and visuospatial impairment and myoclonus characteristic of AD are not features of FTD, PA, and SD. Although EEGs show progressive slowing of waveforms in AD, the standard EEG is strikingly normal during the course of FTD, PA, and SD. Functional imaging using SPECT and PET reveal characteristic biparietal posterior abnormalities in the initial stages of AD, whereas in the clinical syndromes of FTLD the salient abnormality lies in the anterior hemispheres.

The course of FTD, PA, and SD is one of gradual evolution without the occurrence of ictal events, which are more characteristic of vascular dementia. The "bradyphrenia" of subcortical vascular disease is not a feature of the clinical syndromes of FTLD. Indeed, in FTLD, although striatal signs may develop late in the disease course, in the early and middle stages neurologic signs are absent or confined to the presence of primitive reflexes. Patients' physical well-being contrasts with the wealth of neurologic symptoms and signs common in vascular dementia. Although MRI frequently discloses extensive lesions in subcortical white matter in vascular dementia, this is not a pronounced feature of FTD, PA, or SD.

There are comprehensive descriptions in the literature of the clinical features and neuroradiologic manifestations of FTD, PA, and SD[1-32] that enable the general and nonspecialist reader to appreciate the nature of historic evolution of the three syndromes. The types of underlying pathologic change have also been described extensively[1,5,33-41] and an empiric nosologic taxonomy proposed prior to ultimate molecular biological definition. The purpose of this article is to present formalized diagnostic criteria for FTD, PA, and SD to enable researchers to perform further work into the neuropsychology, neuropathology, genetics, molecular biology, and epidemiology of these disorders. It is anticipated that usage in different fields of inquiry will lead to modification and improvements in the utility of these clinical criteria.

Criteria. The clinical criteria are set out in lists 1 through 4. The criteria for each of the three major clinical syndromes are divided into sections. The clinical profile statement together with the core clinical inclusion and exclusion features provide the necessary foundation for diagnosis. Additional clinical features, neuropsychological investigation, and brain imaging support the clinical diagnosis. Operational definitions of specific features are outlined later.

Clinical profile. This statement (seen in lists 1 through 3) summarizes the neurobehavioral profile necessary to fulfill criteria for diagnosis.

Core diagnostic features. These are features (see lists 1 through 3) integral to the clinical syndrome. All features must be present to fulfill the criteria for diagnosis.

Supportive diagnostic features. Clinical. These are features (see lists 1 through 3) that are not present in all patients, or they may be noted only during one phase of the disease. They are therefore not necessary conditions for diagnosis. Supportive features are characteristic, often with high diagnostic specificity, and their presence adds substantial weight to the clinical diagnosis. The diagnosis becomes more likely when more supportive features are present.

Physical. In each of the clinical syndromes physical signs are few in contrast to the prominent mental changes. Parkinsonian signs typically emerge only during late disease. The physical features outlined should be regarded as "supportive" rather than as necessary conditions for diagnosis.

Investigations. Formal neuropsychological assessment, EEG, and brain imaging each can provide support for and strengthen the clinical diagnosis. Such investigatory techniques are not available universally, and ought not to be considered a prerequisite for diagnosis. When neuropsychological assessment is per-

List 1 *The clinical diagnostic features of FTD: Clinical profile*

Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well preserved.

I. Core diagnostic features
   A. Insidious onset and gradual progression
   B. Early decline in social interpersonal conduct
   C. Early impairment in regulation of personal conduct
   D. Early emotional blunting
   E. Early loss of insight
II. Supportive diagnostic features
   A. Behavioral disorder
      1. Decline in personal hygiene and grooming
      2. Mental rigidity and inflexibility
      3. Distractibility and impersistence
      4. Hyperorality and dietary changes
      5. Perseverative and stereotyped behavior
      6. Utilization behavior
   B. Speech and language
      1. Altered speech output
         a. Aspontaneity and economy of speech
         b. Press of speech
      2. Stereotypy of speech
      3. Echolalia
      4. Perseveration
      5. Mutism
   C. Physical signs
      1. Primitive reflexes
      2. Incontinence
      3. Akinesia, rigidity, and tremor
      4. Low and labile blood pressure
   D. Investigations
      1. Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
      2. Electroencephalography: normal on conventional EEG despite clinically evident dementia
      3. Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality

List 2 *The clinical diagnostic features of progressive nonfluent aphasia: Clinical profile*

Disorder of expressive language is the dominant feature initially and throughout the disease course. Other aspects of cognition are intact or relatively well preserved.

I. Core diagnostic features
   A. Insidious onset and gradual progression
   B. Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, anomia
II. Supportive diagnostic features
   A. Speech and language
      1. Stuttering or oral apraxia
      2. Impaired repetition
      3. Alexia, agraphia
      4. Early preservation of word meaning
      5. Late mutism
   B. Behavior
      1. Early preservation of social skills
      2. Late behavioral changes similar to FTD
   C. Physical signs: late contralateral primitive reflexes, akinesia, rigidity, and tremor
   D. Investigations
      1. Neuropsychology: nonfluent aphasia in the absence of severe amnesia or perceptuospatial disorder
      2. Electroencephalography: normal or minor asymmetric slowing
      3. Brain imaging (structural and/or functional): asymmetric abnormality predominantly affecting dominant (usually left) hemisphere

formed, the profile of deficits must demonstrate disproportionate executive dysfunction in FTD or disproportionate language/semantic breakdown in PA and SD. With regard to brain imaging, the patterns of abnormality are characteristic, but not seen invariably. For example, prominent atrophy of the temporal lobes is well visualized by high-resolution MRI, but may be undetected by CT. Failure to demonstrate the prototypic appearances on imaging need not result in diagnostic exclusion.

Supportive features common to each of the clinical syndromes. These features (see list 4) support but are not a necessary condition for FTLD. Onset of disease is most commonly before the age of 65 years, although rare examples of onset in the very elderly have been reported. A positive family history of a similar disorder in a first-degree relative has been reported[2,4] in as many as 50% of patients: Some families have shown mutations on chromosome 17 or linkage to chromosome 3. Motor neuron disease is a recognized albeit uncommon accompaniment to the clinical syndromes of lobar degeneration.[42-47] The development of motor neuron disease in patients presenting with a progressive behavioral or language disorder would strongly support a clinical diagnosis of FTD or PA respectively.

Exclusion features common to each clinical syndrome. Clinical. All features (see list 4) must be absent. Early severe amnesia, early spatial disorientation, logoclonic speech with loss of train of thought, and myoclonus are features designed to exclude AD.

Investigations. All features should be absent (when the relevant information is available).

Relative diagnostic exclusion features. These are features (see list 4) that caution against but do not firmly exclude a diagnosis of FTLD. A history of alcohol abuse raises the possibility of an alcohol-related basis for a frontal lobe syndrome. However, excessive alcohol intake may also occur in FTD patients as a secondary manifestation of social disinhibition or hy-

List 3 *The clinical diagnostic features of semantic aphasia and associative agnosia (SD): Clinical profile*

Semantic disorder (impaired understanding of word meaning and/or object identity) is the dominant feature initially and throughout the disease course. Other aspects of cognition, including autobiographic memory, are intact or relatively well preserved.

I. Core diagnostic features
   A. Insidious onset and gradual progression
   B. Language Disorder characterized by
      1. Progressive, fluent, empty spontaneous speech
      2. Loss of word meaning, manifest by impaired naming *and* comprehension
      3. Semantic paraphasias *and/or*
   C. Perceptual disorder characterized by
      1. Prosopagnosia: impaired recognition of identity of familiar faces *and/or*
      2. Associative agnosia: impaired recognition of object identity
   C. Preserved perceptual matching and drawing reproduction
   D. Preserved single-word repetition
   E. Preserved ability to read aloud and write to dictation orthographically regular words

II. Supportive diagnostic features
   A. Speech and language
      1. Press of speech
      2. Idiosyncratic word usage
      3. Absence of phonemic paraphasias
      4. Surface dyslexia and dysgraphia
      5. Preserved calculation
   B. Behavior
      1. Loss of sympathy and empathy
      2. Narrowed preoccupations
      3. Parsimony
   C. Physical signs
      1. Absent or late primitive reflexes
      2. Akinesia, rigidity, and tremor
   D. Investigations
   E. Neuropsychology
      1. Profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition
      2. Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memorizing
   F. Electroencephalography: normal
   G. Brain imaging (structural and/or functional): predominant anterior temporal abnormality (symmetric or asymmetric)

peroral tendencies. The presence of vascular risk factors such as hypertension ought to alert investigators to a possible vascular etiology. Nevertheless, such risk factors are common in the general population and may be present coincidentally in some patients with FTLD, particularly in those of more advanced age.

List 4 *Features common to clinical syndromes of FTLD (extension of lists 1 through 3)*

III. Supportive features
   A. Onset before 65 years: positive family history of similar disorder in first-degree relative
   B. Bulbar palsy, muscular weakness and wasting, fasciculations (associated motor neuron disease present in a minority of patients)

IV. Diagnostic exclusion features
   A. Historical and clinical
      1. Abrupt onset with ictal events
      2. Head trauma related to onset
      3. Early, severe amnesia
      4. Spatial disorientation
      5. Logoclonic, festinant speech with loss of train of thought
      6. Myoclonus
      7. Corticospinal weakness
      8. Cerebellar ataxia
      9. Choreoathetosis
   B. Investigations
      1. Brain imaging: predominant postcentral structural or functional deficit; multifocal lesions on CT or MRI
      2. Laboratory tests indicating brain involvement of metabolic or inflammatory disorder such as MS, syphilis, AIDS, and herpes simplex encephalitis

V. Relative diagnostic exclusion features
   A. Typical history of chronic alcoholism
   B. Sustained hypertension
   C. History of vascular disease (e.g., angina, claudication)

Definitions of clinical features. This information assists in the use of the diagnostic lists.

Frontotemporal dementia. See list 1.

Core features. *Insidious onset and gradual progression.* There should be no evidence of an acute medical or traumatic event precipitating symptoms. Evidence for a gradually progressive course should be based on historic evidence of altered functional capacity (e.g., inability to work) over a period of at least 6 months, and may be supported by a decline in neuropsychological test performance. The degree of anticipated change is not specified because it is highly variable. In some patients change is dramatic over a 12-month period, whereas in others it is manifest only over a period of several years. Dramatic social and domestic events leading to perturbations in the patient's behavior must be distinguished from ictal occurrences of a neurologic or psychological nature. Only the latter are grounds for exclusion.

Early decline in social interpersonal conduct. This refers to qualitative breaches of interpersonal

etiquette that are incongruent with the patient's premorbid behavior. This includes decline in manners, social graces, and decorum (e.g., disinhibited speech and gestures, and violation of interpersonal space) as well as active antisocial and disinhibited verbal, physical, and sexual behavior (e.g., criminal acts, incontinence, sexual exposure, tactlessness, and offensiveness). "Early" for this and other features implies that the abnormality should be present at initial presentation of the patient.

Early impaired regulation of personal conduct. This refers to departures from customary behavior of a quantitative type, ranging from passivity, inertia, and inactivity to overactivity, pacing, and wandering; and increased talking, laughing, singing, sexuality, and aggression.

Early emotional blunting. This refers to an inappropriate emotional shallowness with unconcern and a loss of emotional warmth, empathy, and sympathy, and an indifference to others.

Early loss of insight. This is defined as a lack of awareness of mental symptoms, evidenced by frank denial of symptoms or unconcern about the social, occupational, and financial consequences of mental failure.

Supportive features: behavioral disorder. *Decline in personal hygiene and grooming.* The caregivers' accounts of failure to wash, bathe, groom, apply makeup, and dress appropriately as before are reinforced by clinical observations of unkemptness, body odor, clothing stains, garish makeup, and inappropriate clothing combinations.

Mental rigidity and inflexibility. This refers to egocentricity and loss of mental adaptability, evidenced by reports of any one of the following: the patient has to have his or her own way, is unable to see another person's point of view, adheres to routine, and is unable to adapt to novel circumstances.

Distractibility and impersistence. These are reflected in failure to complete tasks and inappropriate digressions of attention to nonrelevant stimuli.

Hyperorality and dietary changes. This refers to overeating; bingeing; altered food preferences and food fads; excessive consumption of liquids, alcohol, and cigarettes; and the oral exploration of inanimate objects.

Perseverative and stereotyped behavior. This encompasses simple repetitive behaviors such as hand rubbing and clapping, counting aloud, tune humming, giggling, and dancing, as well as complex behavioral routines such as wandering a fixed route, collecting and hoarding objects, and rituals involving toileting and dressing.

Utilization behavior. This is stimulus-bound behavior[48] during which patients grasp and repeatedly use objects in their visual field, despite the objects' irrelevance to the task at hand (e.g., patients repeatedly switch lights on and off, open and close doors, or continue eating if unlimited supplies of food are within reach). During clinical interview they may drink repeatedly from an empty cup or use scissors placed before them.

Speech and language. *Altered speech output.* There are two types of altered speech output: aspontaneity and economy of utterance, and press of speech. In aspontaneity and economy of utterance, the patient either does not initiate conversation or else output is limited to short phrases or stereotyped utterances. Responses to questions involve single-word replies or short, unelaborated phrases such as "don't know." Encouragement to amplify responses are unsuccessful. In press of speech, the patient speaks interruptedly, monopolizing a conversational interchange.

Stereotypy of speech. These are single words, phrases, or entire themes that the patient produces repeatedly and habitually either spontaneously or in response to questions, replacing appropriate conversational discourse.

Echolalia. Echolalia refers to a repetition of the utterances of others, either completely or in part, sometimes with change of syntax (e.g., Interviewer: "Did you go out yesterday?" Patient: "Did I go out yesterday") when this is a substitute for and not a precursor to an appropriate elaborated response.

Perseveration. Perseveration is defined as a repetition of a patient's own responses. It is a word or phrase that, once uttered, intrudes into the patient's subsequent utterances. It differs from a stereotypy in that the repeated word or phrase is not habitual. Perseverations may occur spontaneously in conversation or are elicited in naming tasks (e.g., the patient names scissors as "scissors" and later names a clock as "scissors"). Perseveration includes palilalia, in which there is immediate repetition of a word, phrase, or sentence (e.g., "I went down town, down town, down town").

Mutism. This is an absence of speech or speech sounds. Patients may pass through a transitional phase of "virtual mutism," during which they generate no propositional speech, yet echolalic responses and some automatic speech (e.g., "three" when prompted with "one, two") may still be present.

Physical signs. *Primitive reflexes.* At least one of the following is present: grasp, snout, and sucking reflexes.

Incontinence. This refers to voiding of urine or feces without concern.

Neuropsychology. *Significant impairment on frontal lobe tests, in the absence of severe amnesia, aphasia, or perceptuospatial disorder.* Impairment on frontal lobe tests is defined operationally as failures (scores below the fifth percentile) on conventional tests of frontal lobe function (e.g., Wisconsin/Nelson card sort, Stroop, Trail Making) in which a qualitative pattern of performance typically associated with frontal lobe dysfunction is demonstrated: concreteness, poor set shifting, perseveration, failure to use information from one trial to guide subsequent responses, inability to inhibit overlearned responses, and poor organization and temporal sequencing.

Abnormal scores that arise secondary to memory, language, or perceptuospatial disorder (such as forgetting instructions or the inability to recognize or locate test stimuli) would not be accepted as evidence of impairment on frontal lobe tests as operationally defined.

FTD patients may perform inefficiently on formal memory, language, perceptual, and spatial tests as a secondary consequence of deficits associated with frontal lobe dysfunction, such as inattention, poor self-monitoring and checking, and a lack of concern for accuracy. Poor test scores per se would not therefore exclude a diagnosis of FTD. An absence of severe amnesia, aphasia, or perceptuospatial disorder would be demonstrated by patchiness or inconsistency in performance (e.g., failure on easy items and pass on more difficult items) or demonstration that correct responses can be elicited by cuing or by directing the patient's attention to test stimuli.

Electroencephalography. *Normal despite clinically evident dementia.* Conventional EEG reveals frequencies within the normal range for the patient's age (minimal theta would be considered within normal limits). There are no features of focal epileptiform activity.

Brain imaging (structural or functional). *Predominant frontal or anterior temporal abnormality.* Atrophy, in the case of structural imaging (CT or MRI), and tracer uptake abnormality, in the case of functional brain imaging (PET or SPECT), is more marked in the frontal or anterior temporal lobes. Anterior hemisphere abnormalities may be bilaterally symmetric or asymmetric, affecting the left or right hemisphere disproportionately.

Progressive nonfluent aphasia. Definitions are for features (see list 2) that differ from or are in addition to those of FTD.

Core features. *Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, and anomia.* Nonfluent speech is defined as hesitant, effortful production, with reduced rate of output. Agrammatism refers to the omission or incorrect use of grammatical terms, including articles, prepositions, auxiliary verbs, inflexions, and derivations (e.g., "man went town"; "he comed yesterday").

Phonemic paraphasias are sound-based errors that include incorrect phoneme use (e.g., "gat" for "cat") and phoneme transposition (e.g., "aminal" for "animal"). The frequency of such errors should exceed that reasonably attributed to normal slips of the tongue.

Anomia is defined as a difficulty in naming manifest by an inability to find the correct word, by prolonged word retrieval latencies relative to the norm, or by incorrect word production. The availability of partial knowledge of a word, such as the initial letter, would be consistent with anomia, as would several attempts to produce a word, each yielding a close approximation (e.g., "scinners . . . sivvers . . . scivvers . . . scissors").Supportive diagnostic features: speech and language. *Stuttering or oral apraxia.* Articulation is effortful, and repetition of parts of a word, particularly the first consonant, occurs in the patient's effort to produce a complete utterance. (Developmental stuttering is excluded.)

Impaired repetition. The patient has a reduced repetition span (less than five digits forward; less than four monosyllabic words) or makes phonemic paraphasias when attempting to repeat polysyllabic words, word sequences, or short phrases.

Alexia and agraphia. Reading is nonfluent and effortful. Sound-based errors are produced (phonemic paralexias). Writing is effortful, contains spelling errors, and may show features of agrammatism.

Early preservation of word meaning (understanding preserved at single-word level). Patients should show an understanding of the nominal terms employed during a routine clinical examination. There should be a demonstrable discrepancy between word comprehension and naming: Patients should show understanding of words that they have difficulty retrieving.

Behavior. *Early preservation of social skills.* The language disorder should be the presenting symptom. At the time of onset of language disorder, patients should demonstrate preserved interpersonal and personal conduct.

Late behavioral changes in FTD. The changes outlined for FTD in conduct, if they occur, should not be presenting symptoms. There should be a clear, documented period of circumscribed language disorder before their development.

Neuropsychology. *Nonfluent aphasia in the absence of severe amnesia or perceptuospatial disorder.* There is difficulty in verbal expression. The language impairment may compromise performance on verbal memory tasks, so that poor scores on memory tests per se would not exclude a diagnosis of progressive aphasia. The presence of normal scores on one or more tests of visual memory, or a demonstration of normal rates of forgetting (i.e., no abnormal loss of information from immediate to delayed recall/recognition), would provide evidence for an absence of severe amnesia. An absence of a severe perceptual disorder would be demonstrated by accurate recognition of the line drawings employed during routine naming tasks, as determined by the patient's ability to produce a correct name, an approximation to the name, a functional description of the object's use, or a pertinent gesture or action pantomime. An absence of severe spatial disorder is demonstrated by normal performance on two or more spatial tasks, such as dot counting, line orientation, and drawing copying.

Semantic aphasia and associative agnosia (SD). Core features. *Fluent, empty spontaneous speech.* Speech production is effortless, without hesitancies, and the patient does not search for words. However, little information is conveyed, reflecting reduced use of precise nominal terms, and increased use of broad generic terms such as "thing." In the early stages of

the disorder the "empty" nature of the speech output may become apparent only on successive interviews, which reveal a limited and repetitive conversational repertoire.

Loss of word meaning. There must be evidence of a disorder both of single-word comprehension and naming. A semantic deficit may be alerted by patients' remarks of the type, "What's a **? I don't know what that is." However, impairment may not be immediately apparent in conversation because the patient's effortless speech gives an impression of facility with language. Word comprehension impairment needs to be established by word definition and object-pointing tasks. A range of stimuli needs to be tested, both animate and inanimate, because meaning may be differentially affected for different material types.

Semantic paraphasias. Semantically related words replace correct nominal terms. Although these may include superordinate category substitutions (e.g., "animal" for camel), coordinate category errors (e.g., "dog" for elephant; "sock" for glove) must be present to meet operational criteria.

Prosopagnosia. This is impaired recognition of familiar face identity, not attributable to anomia. It is demonstrated by the patient's inability to provide defining or contextual information about faces of acquaintances or well-known celebrities.

Associative agnosia. This is an impairment of object identity, present both on visual and tactile presentation, that cannot be explained in terms of nominal difficulties. It is indicated historically by reports of misuse of objects or loss of knowledge of their function. It is demonstrated clinically by patients' reports of lack of recognition and by their inability to convey the use of an object either verbally or by action pantomime.

Preserved perceptual matching and drawing reproduction. There should be some demonstration that the patient's inability to recognize faces or objects does not arise at the level of elementary visual processing. Demonstration of an ability to match for identity (to identify identical object pairs, shapes, or letters) or to reproduce simple line drawings (e.g., of a clock face, a flower, or a simple abstract design) would provide the minimum requirement to fulfill criteria for diagnosis.

Preserved single-word repetition. The relative preservation of repetition skills is a central feature of the disorder. This typically includes the ability to repeat short phrases and sequences of words, although for such complex material, errors may emerge ultimately in advanced disease in the context of severe semantic loss. Demonstration of accurate repetition at least at the level of a single polysyllabic word is required to fulfill criteria for diagnosis.

Preserved ability to read aloud and to write to dictation orthographically regular words. The ability to read without comprehension is central to the disorder. However, reading performance is not entirely error free. Orthographically irregular words commonly elicit "surface dyslexic"-type errors (e.g., "pint" read to rhyme with "mint"; "glove" to rhyme with "rove" and "strove"). Patients should demonstrate the ability to read aloud accurately at least one-syllable words with regular spelling-to-sound correspondence. Writing of orthographically irregular words also typically reveals regularization errors (e.g., "caught" written as "cort"). Patients should demonstrate accurate writing to dictation at least of one-syllable orthographically regular words.

Supportive diagnostic features: speech and language. *Press of speech.* The patient speaks without interruption. This occurs in many but not all patients.

Idiosyncratic word usage. Vocabulary is used consistently but idiosyncratically. For example, the word "container" applied to small objects regardless of their facility to contain, and "on the side" applied to spatial locations, both near (e.g., on the table) and distant (e.g., in Australia). The semantic link between the adopted word or phrase and its referent may be tenuous or absent.

Absence of phonemic paraphasias in spontaneous speech. Sound-based errors are absent in conversational speech. The feature, although characteristic, is not included as a core feature because occasional phonemic errors may emerge in advanced disease in the context of a profound disorder of meaning.

Surface dyslexia/dysgraphia. The presence of surface dyslexic errors (described earlier) in reading and writing is a strong supportive feature.

Preserved calculation. The preserved ability of patients to calculate (to carry out accurately two-digit written addition and subtraction) is characteristic. It is not included as a core feature because calculation skills may break down in advanced disease as a consequence of failure to recognize the identity of Arabic numerals.

Behavior. *Loss of sympathy and empathy.* Patients are regarded by relatives as self-centered, lacking in emotional warmth, and lacking awareness of the needs of others.

Narrowed preoccupations. Patients are reported to have a narrowed range of interests that they pursue at the expense of routine daily activities (e.g., doing jigsaw puzzles all day and neglecting the housework).

Parsimony. Patients show an abnormal preoccupation with money or financial economy. This may be demonstrated by hoarding or constant counting of money, by patients' avoidance of spending their own money, by their purchase of the cheapest items regardless of quality, or by their attempts to restrain usage by other family members of household utilities (e.g., electricity and water).

Neuropsychology. *Profound semantic loss, manifest in failure of word comprehension and naming, or face and object recognition; preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memorizing.* Significant impairment should be demonstrated on word compre-

hension and naming or famous face identification or object recognition tasks. It should be shown that poor scores arise at a semantic level and not at a more elementary level of verbal or visual processing by demonstrating that the patient can repeat words that are not understood, can match for identity, and can copy drawings of objects. Patients should demonstrate normal performance on two or more spatial tasks, such as dot counting and line orientation. Performance on formal memory tests (e.g., involving remembering words or faces) is compromised by patients' semantic disorder. Nevertheless, patients retain the ability to remember autobiographically relevant day-to-day events (e.g., that a grandchild visits on Saturdays). Such preservation is striking clinically but may be difficult to capture on formal tests, which by definition are divorced from daily life.

Features common to each clinical syndrome. Diagnostic exclusion features. Early, severe amnesia. Symptoms of poor memory may be present and inefficient performance demonstrated on memory tests; these may occur secondary to executive or language impairments. However, memory failures are patchy and inconsistent, and patients do not present a picture of classic amnesia. Demonstration that a patient is disoriented in both time and place and shows a consistent, pervasive amnesia for salient contemporary autobiographic events would be incompatible with the clinical syndromes of FTLD.

Spatial disorientation. Patients with FTD who wander from a familiar environment may become lost because of failure of self-regulation of behavior (i.e., for reasons that are not primarily spatial). They do not exhibit spatial disorientation in familiar surroundings such as their own home. They negotiate their surroundings with ease, and localize objects in the environment with accurate reaching actions. Preservation of primary spatial skills is demonstrable even in patients with advanced disease by their capacity, for example, to align objects and to fold paper accurately. Evidence of poor spatial localization and disorientation in highly familiar surroundings would exclude clinical diagnoses of FTD, PA, or SD.

Logoclonic, festinant speech with rapid loss of train of thought. Logoclonia is defined as the effortless repetition of the final syllable of a word (e.g., Washington . . . ton . . . ton . . . ton). Festinant speech refers to a rapid, effortless reiteration of individual phonemes. Logoclonic and festinant speech need to be distinguished from stuttering, which has an effortful quality and usually involves repetition of the first consonant or syllable. They need to be distinguished from palilalia, during which there is repetition of complete words and phrases. Loss of train of thought is a common feature of AD: patients begin sentences that they fail to complete, not only because of word-finding difficulty but also because of rapid forgetting of the intended proposition. A demonstration in conversation that patients are rapidly losing track would be contrary to a diagnosis of FTLD.

Conclusion. These criteria provide a mechanism for diagnosis and differentiation of dementias associated with FTLD. The core diagnostic criteria indicate the consensus of the group in identifying the key clinical aspects that differentiate FTD, PA, and SD.

Acknowledgment

This consensus paper is the result of an international collaborative workshop on FTD held in Toronto, Canada, April 1996. It is dedicated to the memory of D. Frank Benson, greatly admired for his contribution to the field of dementia and his inspiration to others.

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ORIGINAL CONTRIBUTION

Evaluating Atypical Dementia Syndromes Using Positron Emission Tomography With Carbon 11–Labeled Pittsburgh Compound B

Steven Y. Ng, MBBS; Victor L. Villemagne, MD; Colin L. Masters, MD; Christopher C. Rowe, MD

Context: A progressive decline in episodic memory affecting activities of daily living is the usual clinical presentation of Alzheimer disease. However, patients presenting with atypical or focal clinical symptoms such as language or visuospatial dysfunction often pose a diagnostic challenge.

Objective: To explore the presence and topography of β amyloid (Aβ) as measured by carbon 11–labeled Pittsburgh Compound B (^{11}C-PiB) in patients with atypical presentations of dementia.

Design, Setting, and Participants: At a tertiary referral center for memory disorders, 15 healthy controls, 10 patients with Alzheimer disease, a patient with primary progressive aphasia (PPA), and a patient with posterior cortical atrophy (PCA) underwent ^{11}C-PiB positron emission tomographic studies. Retention of ^{11}C-PiB was compared between different groups using statistical parametric mapping.

Main Outcome Measure: The topography of cortical ^{11}C-PiB binding in atypical vs typical Alzheimer disease.

Results: Cortical ^{11}C-PiB binding was higher in the group with Alzheimer disease and in the patients with PPA and PCA than the controls ($P<.001$). Both patients with atypical dementia had a similar ^{11}C-PiB binding pattern to Alzheimer disease although ^{11}C-PiB retention was higher on the left cerebral hemisphere in the patient with PPA ($P<.01$) and higher in the occipital cortex in the patient with PCA ($P<.01$).

Conclusions: The presence of distinctive focal ^{11}C-PiB retention patterns was demonstrated in 2 patients with atypical onset of dementia. Pittsburgh Compound B has the potential to facilitate differential diagnosis of dementia and identify patients who could benefit from specific therapeutic strategies aimed at β amyloid reduction.

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Author Affiliations: Department of Nuclear Medicine, Centre for Positron Emission Tomography, Austin Health, Melbourne, Australia (Drs Ng, Villemagne, and Rowe); Department of Pathology, University of Melbourne, Melbourne (Drs Villemagne and Masters); and Mental Health Research Institute of Victoria, Melbourne (Drs Villemagne and Masters).

While the majority of patients with Alzheimer disease (AD) have prominent memory impairment early in the course of the disease, 15% of all patients with AD present with focal syndromes that initially spare memory, attention, executive function, and insight.[1] Patients with atypical AD tend to have a younger age at onset and a more protracted disease course.[1] Five different types of atypical AD presentations have been described: progressive aphasia; posterior cortical atrophy (PCA); and visual-, frontal-, and extra-pyramidal–variant AD.[2] The criteria from the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association[3] for AD are weighted heavily on the memory domain of cognition, which may preclude the early diagnosis of atypical cases.

Primary progressive aphasia (PPA) is currently classified as a subtype of frontotemporal dementia and is diagnosed when a patient suffers from language dysfunction for the first 2 years of the disease course, sparing other aspects of cognition.[4] Primary progressive aphasia includes fluent and nonfluent types with the latter being more common. There is considerable heterogeneity in the pathology of PPA: 60% show nonspecific features such as gliosis and spongiform changes; 20% show β amyloid (Aβ) plaques and neurofibrillary tangles; and 20% show Pick bodies.[5] Neurodegenerative changes have been localized to the frontal and left perisylvian temporal cortex with supporting data from structural and functional neuroimaging studies.[5,6]

Posterior cortical atrophy (PCA) is a neurodegenerative disorder of the posterior cerebral cortex, a highly specialized area responsible for higher-order visual processing and spatial praxis. Posterior

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Table. Demographic Characteristics[a]

Group	Sex	Age, y	MMSE Score[b]	CDR[c]	Disease Duration, y	Education, y
PPA	M	79	26	0.5	8	12
PCA	F	64	9	2	8	11
AD	5 M, 5 F	72.1 ± 13.3	22.4 ± 4.7[d]	1.1 ± 0.5[d]	1.9 ± 0.9	12.7 ± 5.6
HC	10 M, 5 F	71.8 ± 6.7	29.3 ± 1.0	0	NA	12.8 ± 5.7

Abbreviations: AD, Alzheimer disease; CDR, Clinical Dementia Rating; HC, healthy controls; MMSE, Mini-Mental State Examination; NA, not applicable; PCA, posterior cortical atrophy; PPA, primary progressive aphasia.

[a] All subjects are right-hand dominant. Some values are given as mean ± SD.

[b] The maximum score on the MMSE is 30.

[c] The categories of CDR are 0.5, 1, 2, and 3 with 3 being the worst category.

[d] Significant mean difference between AD and HC at $P = .05$.

cortical atrophy is clinically characterized by features of Balint syndrome (ocular apraxia, optic ataxia, and simultanagnosia).[7,8] Other clinical features include visual agnosia, constructional and dressing apraxia, ideomotor apraxia, prosopagnosia, and left hemineglect. Most reported cases of PCA have AD pathology with visual and posterior parietal cortex showing double the concentration of Aβ plaques and neurofibrillary tangles than would be seen in typical AD.[1,7,8] Magnetic resonance imaging (MRI) may show predominantly right-sided parietal and occipital cortical atrophy.[9,10] Predominantly right-sided hypoperfusion on hexamethylpropyleneamine oxime single-photon emission computed tomography and hypometabolism on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) have been reported.[10,11]

The PET imaging ligand carbon 11–labeled Pittsburgh Compound B (^{11}C-PiB) allows in vivo assessment of Aβ plaques. Pittsburgh Compound B (N-methyl-[11C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole) is a derivative of thioflavin T and has been shown to bind specifically to Aβ plaques in human brain homogenates.[12] Human studies have shown significantly higher cortical ^{11}C-PiB retention in AD than controls.[13] The purpose of this study was to explore the presence and topography of ^{11}C-PiB retention in 2 patients, one diagnosed clinically as PPA and the other as PCA, and compare them against age-matched controls and patients with typical AD using voxel-based image analysis.

METHODS

Fifteen elderly individuals with normal cognitive function and 12 patients with well-characterized dementia (10 AD, 1 PPA, 1 PCA) were included in this study. All studies were approved by the Austin Health research ethics committee, and informed consent was obtained from all subjects. Demographic characteristics are summarized in the **Table**.

CASE HISTORY 1: PRIMARY PROGRESSIVE APHASIA

In 2002, a 79-year-old man presented with 6 years of word-finding difficulties. Initial assessment revealed mild dysnomia and confrontation naming sparing other aspects of cognition. Repeat evaluation in 2005 revealed significant word-retrieval difficulties and the occasional phonological paraphasic error. There were significant difficulties with spelling and reading and subtle reduction in semantic processing. His logical grammatical comprehension was intact. Working memory and attention independent of language were only mildly impaired. His visuospatial processing ability was intact, insight was preserved, and there were no behavioral symptoms of frontotemporal dementia. His MRI demonstrated left-sided perisylvian cortical atrophy accompanied by hypometabolism on ^{18}F-FDG PET (**Figure 1**).

CASE HISTORY 2: POSTERIOR CORTICAL ATROPHY

In 2003, a 64-year-old woman presented with progressive visuospatial difficulties and left-arm apraxia over 5 years. Her short-term memory and insight were relatively preserved until 2005. Physical examination confirmed left-sided visual neglect, and motor apraxia (both dressing and constructional). Oculomotor apraxia, optic ataxia, and simultanagnosia were evident. There were no other focal neurological deficits or apparent extrapyramidal features. Magnetic resonance imaging demonstrated severe parietal cortical atrophy (**Figure 2**A), and ^{18}F-FDG PET (Figure 2B) showed profound hypometabolism in the parietal and visual cortices.

NEUROIMAGING

All subjects underwent a T1-weighted spoiled gradient echo sequence MRI for subsequent coregistration with the PET images. T2-weighted and fluid-attenuated inversion recovery sequences were performed to rule out stroke. Each subject received 375 ± 18 MBq ^{11}C-PiB by intravenous injection at the beginning of a 90-minute dynamic PET acquisition. Decay-corrected PET data were standardized for injected dose and individual body weight to generate standardized uptake values. The data acquired between 40 and 70 minutes postinjection were summed and normalized to the cerebellar cortex to generate standardized uptake value ratio (SUVR40-70) images. The cerebellar cortex, being devoid of neuritic amyloid plaques, is used commonly as a reference tissue in ^{11}C-PiB quantification.[14]

STATISTICAL PARAMETRIC MAPPING ANALYSIS

The SUVR40-70 PET images were coregistered to individual MRIs using statistical parametric mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, England) and subsequently spatially normalized to the Montreal Brain template (Montreal Neurological Institute, Montreal, Quebec) to remove intersubject anatomical variability. The voxel-based statistical parametric mapping between-group comparisons using a 2-sample *t* test were performed without any a priori

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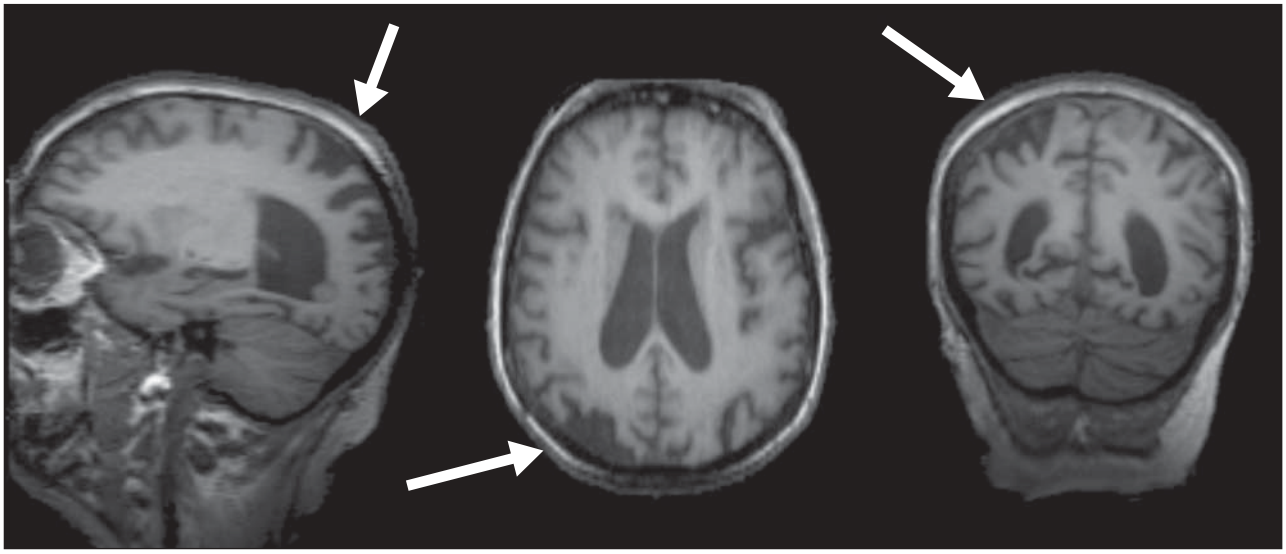

Figure 1. Magnetic resonance image of the patient with posterior cortical atrophy. Arrows indicate areas of cortical atrophy, which are more prominent in posterior parietal cortex.

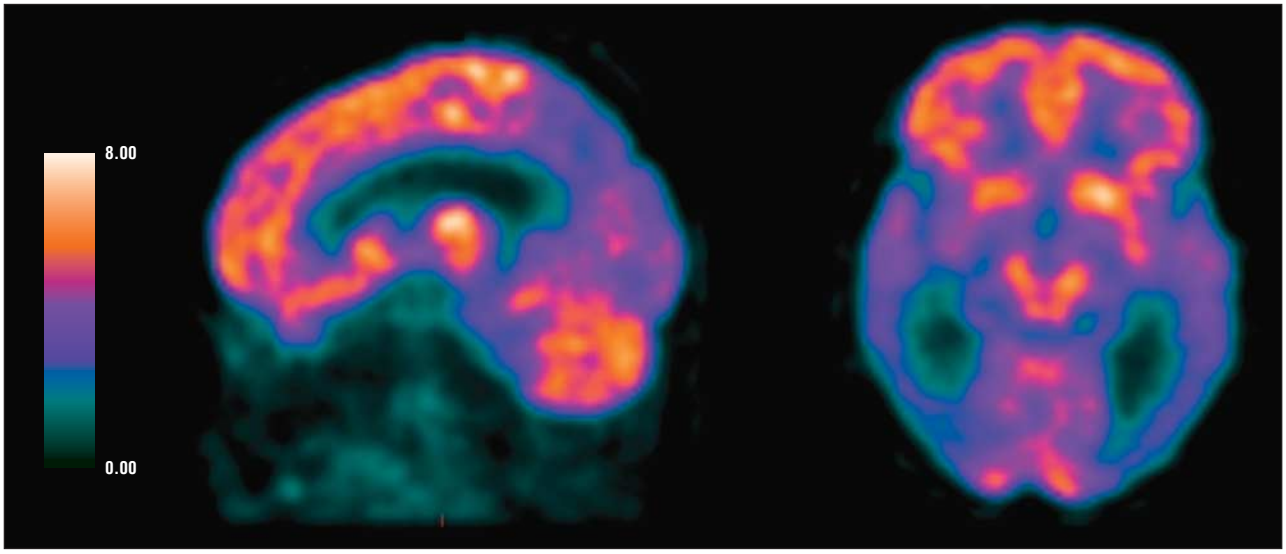

Figure 2. ^{18}F-fluorodeoxyglucose positron emission tomography of the patient with posterior cortical atrophy. The images revealed profound hypometabolism in posterior cingulate, parietotemporal, and visual (lateral and primary) cortex. The frontal, sensorimotor cortex, cerebellum, and caudate nucleus were relatively preserved.

hypothesis or spatial constraints concerning the location of potential group differences in ^{11}C-PiB retention. Statistical analyses were performed at height threshold of $P < .001$ for AD vs controls while a less stringent threshold of $P = .01$ was chosen for atypical cases vs typical AD. Extent threshold was set at 125 voxels to enhance detection of significant clusters.

RESULTS

The between-group statistical parametric mapping analysis showed that ^{11}C-PiB retention in patients with typical AD was higher than control subjects in the orbitofrontal, posterior cingulate, temporal, and parietal cortex with relative sparing of medial temporal, sensorimotor, and occipital cortex (**Figure 3**). The most significant clusters were found in the posterior cingulate, orbitofrontal, and parietal cortex. Both the patient with PPA and the patient with PCA had ^{11}C-PiB retention patterns resembling AD when between-group analysis was performed against the controls. When compared with subjects with typical AD, the patient with PPA showed asymmetric focal ^{11}C-PiB retention of the left frontotemporal cortex (**Figure 4**) and the patient with PCA had visual cortical ^{11}C-PiB retention in contrast to the occipital sparing seen in AD (Figure 4).

COMMENT

The ^{11}C-PiB retention pattern in AD is consistent with the known distribution of AD pathology from postmortem data.[15] Distribution of ^{11}C-PiB in both atypical dementia cases was similar to typical AD although predominantly left-sided in the patient with PPA in a

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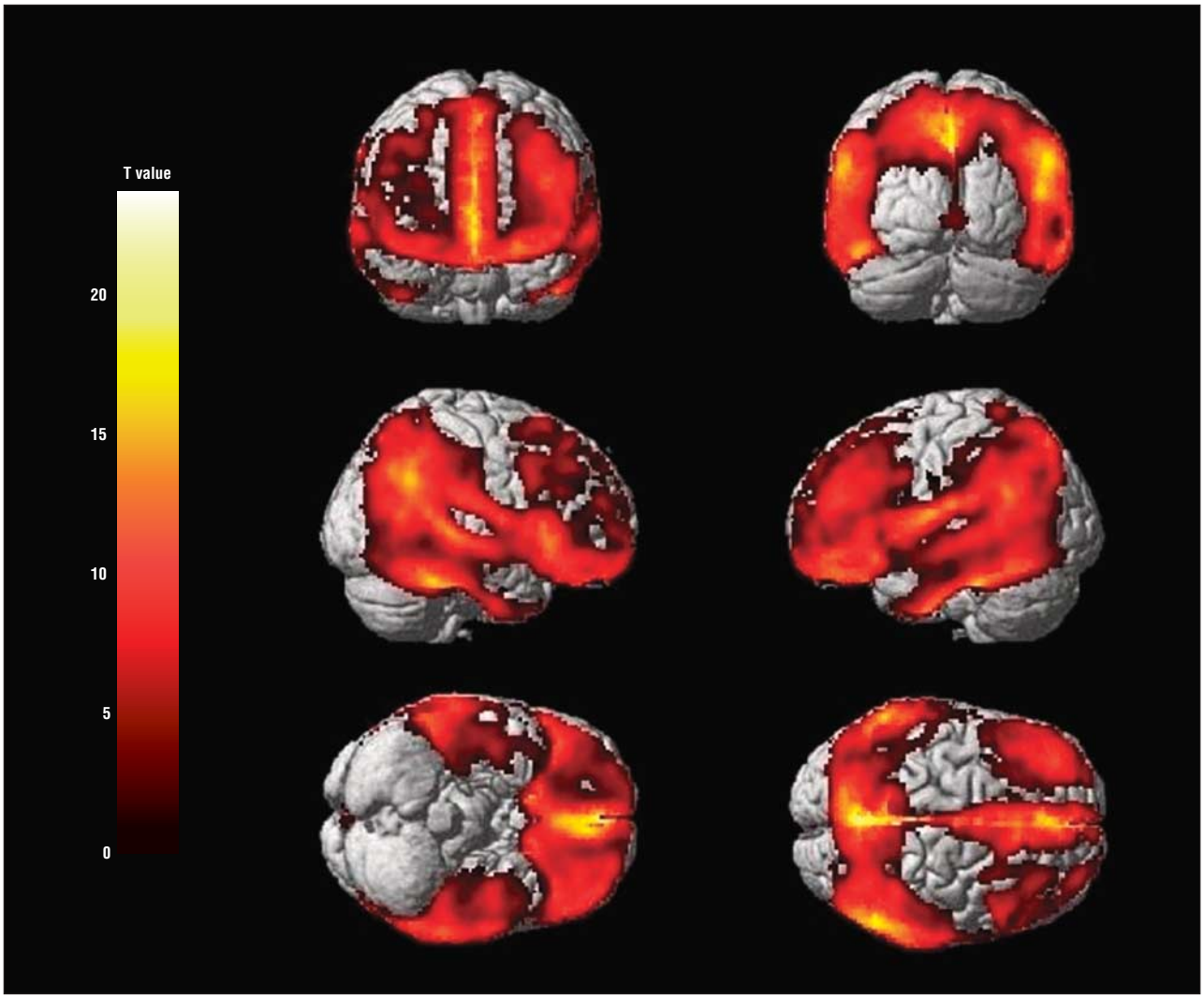

Figure 3. Visualization of the results of statistical parametric mapping analysis. The regions with statistically significant increases ($P<.001$) in retention of carbon 11–labeled Pittsburgh Compound B (^{11}C-PiB) in patients with Alzheimer disease compared with control subjects are highlighted (yellow indicates the most significant difference). Note relative sparing of occipital cortex.

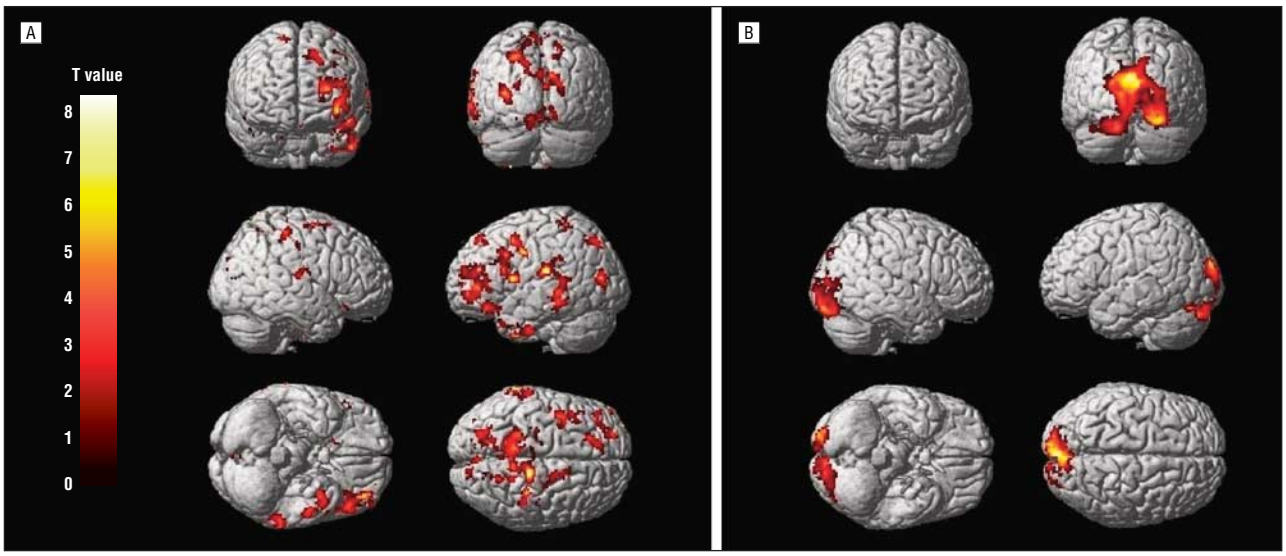

Figure 4. Statistical parametric mapping analysis of typical vs atypical Alzheimer disease (AD). The patient with primary progressive aphasia (A) had retention of carbon 11–labeled Pittsburgh Compound B (^{11}C-PiB) predominantly in the left frontotemporal cortical region when compared with AD ($P<.01$). The patient with posterior cortical atrophy (B) had significantly higher ^{11}C-PiB retention in the visual cortex than the subjects with typical AD ($P<.01$).

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region located in proximity to the motor speech area (Broadmann area 44) and higher in the occipital cortex in the patient with PCA. Whether focal dementia syndromes are variants of AD is still controversial. Some authors believe the long disease course and early preservation of memory and insight make AD as the underlying pathological driving factor unlikely.[6] Our ^{11}C-PiB PET findings do support the concept of atypical AD at least in some cases of focal dementia. Although it is not possible to establish a cause-and-effect relationship with Aβ deposition in our 2 cases because we have no data on the time relationship between Aβ deposition and the onset of symptoms, the distinct ^{11}C-PiB retention pattern and its concordance with clinical features and ^{18}F-FDG hypometabolism suggests that Aβ may play a role in the pathogenesis.

Longitudinal studies with serial amyloid PET imaging and clinical assessment may provide insight into the role of Aβ in atypical dementia syndromes in a manner that postmortem studies cannot. Identification of Aβ may not only contribute to the differential diagnosis of dementia, but as anti-Aβ treatment options become available, it may also allow appropriate therapeutic strategies to be implemented and monitored, potentially preventing a focal deficit from becoming a global dementia.

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Correspondence: Christopher C. Rowe, MD, Department of Nuclear Medicine and Centre for Positron Emission Tomography, Austin Health, PO Box 5555, 145 Studley Rd, Heidelberg, Victoria 3084, Australia (christopher.rowe@austin.org.au).
Author Contributions: *Study concept and design:* Ng, Villemagne, Masters, and Rowe. *Acquisition of data:* Ng. *Analysis and interpretation of data:* Ng, Villemagne, Masters, and Rowe. *Drafting of the manuscript:* Ng, Villemagne, and Rowe. *Critical revision of the manuscript for important intellectual content:* Ng, Villemagne, Masters, and Rowe. *Statistical analysis:* Ng and Villemagne. *Obtained funding:* Masters and Rowe. *Administrative, technical, and material support:* Rowe. *Study supervision:* Villemagne, Masters, and Rowe.
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Consensus Report of the Working Group on: "Molecular and Biochemical Markers of Alzheimer's Disease"

THE RONALD AND NANCY REAGAN RESEARCH INSTITUTE OF THE ALZHEIMER'S ASSOCIATION AND THE NATIONAL INSTITUTE ON AGING WORKING GROUP[1,2,3]

The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association, Chicago, IL and the National Institute on Aging, Bethesda, MD

The ideal biomarker for Alzheimer's disease (AD) should detect a fundamental feature of neuropathology and be validated in neuropathologically-confirmed cases; it should have a sensitivity >80% for detecting AD and a specificity of >80% for distinguishing other dementias; it should be reliable, reproducible, non-invasive, simple to perform, and inexpensive. Recommended steps to establish a biomarker include confirmation by at least two independent studies conducted by qualified investigators with the results published in peer-reviewed journals. Our review of current candidate markers indicates that for suspected early-onset familial AD, it is appropriate to search for mutations in the presenilin 1, presenilin 2, and amyloid precursor protein genes. Individuals with these mutations typically have increased levels of the amyloid $A\beta_{42}$ peptide in plasma and decreased levels of APPs in cerebrospinal fluid. In late-onset and sporadic AD, these measures are not useful, but detecting an apolipoprotein E e4 allele can add confidence to the clinical diagnosis. Among the other proposed molecular and biochemical markers for sporadic AD, cerebrospinal fluid assays showing low levels of $A\beta_{42}$ and high levels of tau come closest to fulfilling criteria for a useful biomarker. © 1998 Elsevier Science Inc.

THE Working Group on Molecular and Biochemical Markers of Alzheimer's Disease was convened to examine the relative merits of biological markers proposed for the early diagnosis of Alzheimer's disease (AD). At present, diagnosing AD and distinguishing it from other dementias depend primarily on clinical evaluation, and ultimately on clinical judgment. Based on this approach, a great deal has been learned about the genetics, age of onset, duration, clinical course, neurological and psychiatric manifestations, response to treatment, and neuropathological lesions of AD. Having molecular and biochemical markers of AD would complement clinical approaches, and further the goals of early and accurate diagnosis. Building on recent information concerning the genetic factors and molecular causes of AD, the Working Group sought to assess the status of various antemortem markers. The Working Group had three goals:

1. define the characteristics of ideal biological markers;
2. outline the process whereby a biological marker gains acceptance in the medical and scientific communities; and
3. review the current status of all proposed biomarkers for AD.

Early in 1997, on the basis of a comprehensive literature search, a general call for papers was sent to all investigators who had published in the field, inviting them to submit a brief position paper on the current state of knowledge concerning antemortem diagnosis of AD. These papers were to address the clinical and scientific issues that need to be resolved in order to improve the accuracy, sensitivity, reliability, and validity of biochemical and molecular diagnostic measures. Fifty-five invitations were sent and thirty position papers were submitted. The titles, authors, and their affiliations are noted in Appendix I. Their contributions reflect the diverse perspectives among the international community of investigators engaged in research on the diagnosis of AD. In September 1997, the Advisory Committee of the Working Group (the Appendix lists the committee members) met to review these papers and develop the accompanying consensus statement on Molecular and Biochemical Markers of Alzheimer's Disease. Some of the position papers, selected by the Advisory Committee, are published along with the consensus statement.

The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging, the sponsors of this Working Group, have begun to convene a series of working groups focused on important topics in dementing disorders such as AD. The mission of each working group is to develop a position paper and, if possible, a consensus statement to help:

1. identify scientific opportunities or new research directions;
2. determine the need for additional research resources;
3. evaluate barriers that impede the progress of research; and
4. guide public policy on research.

[1]The names of the Working Group Members and the names of the Working Group Advisory Committee Members are listed in the Appendix (section VI).

[2]Address correspondence to: John H. Growdon, Chair of the Working Group Advisory Committee, WACC 830, Massachusetts General Hospital, Boston, MA 02114.

[3]The Reagan Institute Working Groups are planned and organized by Z. S. Khachaturian and T.S. Radebaugh; Fax: 301-879-2023; E-mail: zaven@idt.net.

The first Working Group, on Neuropathological Criteria, completed its task in 1997 and published a consensus paper that established new pathological guidelines for the diagnosis of AD (Neurobiol.Aging 4S: 1997). The deliberations and conclusions of the second Working Group, on Molecular and Biochemical Markers, are published here.

CRITERIA FOR DEFINING, DEVELOPING, AND ASSESSING BIOMARKERS

All future publications describing any putative diagnostic marker or its use in a study should include detailed information on target populations, uses, and accuracy of the marker. Target population refers to the distinction between early-onset familial AD (FAD) and sporadic disease and emphasizes the fact that markers that are useful in FAD may not all be useful in sporadic disease. A biomarker has at least five different uses: confirming diagnosis, epidemiological screening, predictive testing, monitoring progression and response to treatment, and studying brain-behavior relationships. The value of a marker will vary across these uses. For example, a biomarker may be well-suited as an aid to clinical diagnosis but have little value in monitoring changes over time in dementia.

Proposed markers for AD should include as many features of an ideal diagnostic test as possible (see Kennard; Klunk). Ideally, the marker should be:

1. able to detect a fundamental feature of Alzheimer's neuropathology;
2. validated in neuropathologically confirmed AD cases;
3. precise (able to detect AD early in its course and distinguish it from other dementias);
4. reliable;
5. non-invasive;
6. simple to perform; and
7. inexpensive.

Among the many proposed molecular and biochemical markers (see below), none has yet achieved universal acceptance, nor fully met the proposed criteria for an ideal biomarker. Nonetheless, there has been sufficient progress toward this goal so that this review and consensus statement are warranted.

Molecular and biochemical markers should be validated in neuropathologically confirmed (definite) AD cases whenever possible. Because most biomarkers will be tested and later used for diagnosing patients who are still living, it will not be possible to have a diagnosis of Definite AD for judging most biomarkers (molecular genetic tests are an exception to this generalization). It is therefore recommended that testing of biomarkers be carried out on patients with the diagnosis of Probable AD, and not in people with Possible AD, to ensure that diagnostic accuracy is as high as possible (see Litvan).

Characteristics of a Useful Biomarker

The setting in which a biomarker will be used should be carefully defined. The utility of various biomarkers will vary depending upon the purpose for which they are used. For example, biomarkers useful for establishing prevalence in epidemiological studies may be less useful in monitoring individual patients over time to evaluate the efficacy of a particular medication. Hence, different criteria for usefulness may be needed for different applications of a biomarker.

Criteria for Evaluating Biomarkers

Molecular and biochemical markers for AD require evaluation based upon their sensitivity, specificity, prior probability, positive predictive value, and negative predictive value (see Mayeux; Robles). Sensitivity refers to the capacity of a biomarker to identify a substantial percentage of patients with the disease. A sensitivity of 100% would indicate a marker that can identify 100% of patients with AD. The mathematical expression of sensitivity is true positive cases of AD divided by true positive cases plus false negative cases. Because the currently used clinical criteria for AD in patients with Probable AD provide a sensitivity of approximately 85% when compared to autopsy-confirmed cases, an excellent biomarker should have a sensitivity approaching or exceeding this value. The biomarker would then be applied to patients with Possible AD, or possibly in testing asymptomatic subjects who may have preclinical disease.

Specificity refers to the capacity of a test to distinguish AD from normal aging, other causes of cognitive disorders, and other dementias. A test with 100% specificity would be capable of differentiating AD from other causes of dementia in every case. Mathematically, specificity represents the true negative instances of AD divided by the true negative cases plus the false positive cases. For a biomarker to have sufficient specificity to be useful in the diagnosis of AD, it should have a specificity of approximately 75–85% or greater.

Prior probability is defined as the frequency of occurrence of a disease in a particular group. If the group under study includes a large number of affected individuals, prior probability is equivalent to prevalence. The mathematical representation of prior probability is the true positives plus the false negatives divided by the total population. A perfect biomarker would detect only true positives and no false negatives and thus would reflect accurately the prevalence of the disease in the population.

Positive predictive value is a measure of the percentage of people who have a positive test who can be shown at subsequent autopsy examination to have the disease. The mathematical representation of positive predictive value is the number of true positives divided by the number of true positives plus the number of false negatives. A positive predictive value of 100% would indicate that all patients with a positive test actually have the disease. For a biomarker to be useful clinically, it should have a positive predictive value of approximately 80% or more.

Negative predictive value represents the percentage of people with a negative test who subsequently at autopsy prove not to have the disease. Mathematically it is represented as the number of true negatives divided by the number of true negatives plus the number of false negatives. A negative predictive value of 100% indicates that the test completely rules out the possibility that the individual has the disease, at least at the time that the individual is tested. A reliable marker with a high negative predictive value would be extremely useful. A test with low negative predictive value might still be useful in some circumstances if it also had a high positive predictive value.

Control Groups

Any diagnostic test must be validated against a control group with a distribution of ages and genders similar to the patient group (see Foster). This requirement presents difficulties because sporadic AD (SAD) principally affects older individuals. Consequently, irrespective of how carefully the control group is screened for cognitive status, some of the group may have preclinical AD. This essentially precludes the possibility that any biomarker would have 100% sensitivity and 100% specificity.

Context

The value of biomarkers will vary depending upon the reason for testing a particular person, group, or population. In a community screening for descriptive epidemiological studies, for exam-

ple, high sensitivity is important in a biomarker because all patients who truly have the disease should be identified. In this instance, specificity may be low, and the test may still be useful. When applied to a single patient, both specificity and sensitivity of a biomarker become very important. Many physicians and their patients will wish to know whether a positive test with a biological marker indicates that the patient has a high probability of having AD (i.e., a high positive predictive value).

Plausibility

Some diagnostic tests have proven to have high positive predictive value, yet the scientific reason for this was unclear initially. The finding of an association between apolipoprotein E4 and sporadic late-onset AD is a good example of this. Nevertheless, it is useful to seek biomarkers with some plausible connection to the known neuropathological changes in AD.

Qualities of an Biomarker

A useful biomarker should be precise, reliable and inexpensive. It should be convenient to use and not threatening to the patient. The biomarker should be noninvasive or only moderately invasive. Noninvasive tests include studies on blood, urine, saliva, or buccal scrapings. Moderately invasive tests are those that utilize skin or rectal biopsies, bone marrow samples, or cerebrospinal fluid (CSF). Highly invasive tests include those that require sampling of brain tissue. A useful biomarker should be sufficiently simple to be adaptable for routine use in screening the elderly. An ideal biomarker would also be useful in monitoring the progression of the disease and evaluating the effects of treatment on disease progression. Use of biomarkers for evaluation of treatment has two aspects. One is to determine whether the treatment induces a measurable biochemical change. For example, a biomarker may consist of an assay to determine whether an enzyme inhibitor is causing a change in enzymatic activity. The second use is to determine whether treatment changes the progression of the illness, using the biomarker as an index of disease status.

Normalization

Some markers may need to be adjusted or normalized for other variables. Examples of adjustments include the age, gender, and possibly the race of an individual patient. Another adjustment might be the anatomic site from which a patient's sample is taken. For example, a CSF sample removed from the cervical region may show different biomarker levels than CSF taken from the lumbosacral region.

Initial Evaluation of Biomarkers

The initial evaluation of a new biomarker should focus on the distinction between patients with Probable AD and normal control subjects with comparable age distributions. Sample size is important and a power analysis should be performed to determine the size of the sample needed. If covariants, such as age, gender, apolipoprotein genotype, will be included in the analysis, a large series of observations with be needed. Geography may also be important, given likely genetic polymorphisms in different countries and races. The biomarker should be examined in more than one group before generalized to all Alzheimer's patients.

Range of the Marker

It is critical to establish a normal range of values for a biomarker (see Galasko). An ideal effective biomarker will show a clear separation between normal control subjects and patients with AD.

Utility of Multiple Markers

A combination of biomarkers may provide greater diagnostic accuracy than any single one individually. Critical evaluation of multiple simultaneous biomarkers should utilize the same principles outlined above, including sensitivity, specificity, prior probability, positive predictive value, and negative predictive value. Of these, high sensitivity and specificity are most important as they indicate the accuracy of the test.

Follow-up Evaluation of Biomarkers

Proposed biomarkers should be tested in patients with Probable AD to ensure as high a diagnostic accuracy as possible. Ultimately, successful biomarkers will be applied to preclinical subjects at risk for the disease and to people with Possible AD. It is vital to follow the patients with Probable AD initially studied with the biomarker through the full course of their disease and obtain autopsy verification of the disease in as many subjects as possible. This process is the optimal means of testing any biomarker against the most credible and accepted diagnostic standard.

RECOMMENDED STEPS IN THE PROCESS OF ESTABLISHING A BIOMARKER

1. There should be at least two independent studies that specify the biomarker's sensitivity, specificity, and positive and negative predictive values.
2. Sensitivity and specificity should be no less than 80%; positive predictive value should approach 90%.
3. The studies should be well powered, conducted by investigators with expertise to conduct such studies, and the results published in peer-reviewed journals.
4. The studies should specify type of control subjects, including normal subjects and those with a dementing illness but not AD.
5. Once a marker is accepted, follow-up data should be collected and disseminated to monitor its accuracy and diagnostic value.

REVIEW OF SOME PUTATIVE MOLECULAR AND BIOCHEMICAL MARKERS

Molecular Genetics

Early-onset autosomal-dominant AD is relatively rare; only 120 families worldwide are currently known that carry deterministic mutations (see St. George-Hyslop). Mutations in the presenilin 1(PS1) gene on chromosome 1 are the most common causes of autosomal-dominant FAD; these account for 30–50% of all early-onset cases and are the primary causes of FAD with onset before the age of 55 years. Mutations in the amyloid precursor protein (APP) gene on chromosome 21 are very rare, affecting fewer than 25 families worldwide. Like PS1 mutations, APP mutations are found in pedigrees with autosomal-dominant transmission of AD with an age of onset before 65 years. Mutations in the presenilin 2 (PS2) gene have been described in only two pedigrees. Compared to the PS1 and APP mutations, families carrying the PS2 mutation exhibit a more variable age of onset, ranging between 40 and 80 years, and a suggestion of incomplete penetrance. Mutational analyses of the PS1, PS2, and APP genes as an adjunct to diagnosing dementia in patients with an early age of onset and strong family history is appropriate. Finding a mutation in the PS1 or APP gene has a high predictive value (presumed to be 100%) for the eventual development of AD. Because the age of onset in PS1 and APP families does not vary much within each family, accurate predictions of risk and approximate age of onset can be made. Pre-test and post-test genetic counseling, education, and support should be offered in all cases of molecular genetic screening. A number of pedigrees with the PS1

or the APP mutations have atypical disease phenotypes, with cases that include cerebral hemorrhage, spongiform encephalopathy, familial spastic paraparesis, and Pick-like inclusions. These observations reinforce the point made in the accompanying paper by St. George-Hyslop that genetic screening for mutations should be limited to early-onset pedigrees where the phenotype, aside from age, is typical for a progressive degenerative dementia.

In contrast to deterministic genetic mutations, there are genetic factors that modify the risk of developing AD. Several of the proposed factors, such as α-antichymotrypsin and HLA A2, are controversial or exert weak effects. Among the proposed genetic modifiers, alleles of apolipoprotein E (APOE) are the most powerful and best documented (2). There is universal agreement that the e4 allele is a strong risk factor for the late-onset and sporadic forms of AD, whereas the e2 allele appears to protect against AD, or at least delay its onset. Having an e4 allele does not confer AD, as many e4 individuals reach old age without developing dementia (see Hyman). Conversely, the absence of an e4 allele does not exclude AD, as many AD patients do not carry an e4 allele. Nevertheless, in autopsy series more than half of the patients with a confirmed diagnosis of AD had an e4 allele. Testing for APOE is appropriate as an adjunct to the suspected clinical diagnosis of AD, where finding an e4 allele has a positive predictive value between 94% and 98% (1,4). The sensitivity and the specificity of the e4 allele alone are low, indicating that this measure cannot be used as the sole diagnostic test for AD. However, when used in sequence with conventional clinical assessments early in the course of disease when diagnostic accuracy is least secure, the presence of an e4 allele can add at least 5–10% confidence to the diagnosis of AD (3). Thus, the clinically relevant use of APOE testing is in patients with early dementia and suspected AD. As with autosomal dominant genetic mutations, APOE genotyping should be linked to adequate pre- and post-test counseling, education, and support. There is unanimous agreement that APOE genotyping should not be conducted in asymptomatic individuals. In line with this view, the commercially available test for APOE genotype is restricted to patients with cognitive impairments.

In summary, searching for PS1, PS2, and APP genetic abnormalities should be limited to probands and families with a pattern of early-onset (<60 years old) FAD. Genetic testing should always be conducted in the framework of genetic counseling. APOE genotyping may be used as an adjunct test in the diagnostic workup of an individual with suspected AD; finding an e4 allele adds a small percentage of confidence to the clinical diagnosis.

Biomarkers Reflecting Neuropathological Changes in Brain

Amyloid Protein Derivatives in Blood and CSF. Numerous studies during the last 5–7 years have examined the possibility that proteolytic derivatives of the β-amyloid precursor protein (APP) are altered in amount in the CSF or plasma of patients with AD compared to age-matched controls. The interest in using APP derivatives as laboratory markers to help confirm a clinical diagnosis of AD arises from evidence that cerebral accumulation of the amyloid β-peptide (Aβ), a fragment of APP, occurs in virtually all cases of AD.

One criterion for a potentially useful diagnostic test is a biologically plausible relationship of the marker to the pathogenesis of the disease. In this regard, all four currently known genetic causes of FAD (missense mutations in the APP, PS1, APP genes, and the e4 polymorphism of the APOE gene) have been linked to increased production and/or deposition of Aβ, as measured directly in the brains and/or biological fluids of patients harboring each of these AD genetic traits. Moreover, deposits of the $A\beta_{42}$ peptide in the form of so-called diffuse plaques have been shown to be among the earliest detectable neuropathological alterations in the brains of patients with both familial and sporadic forms of AD. As a result, numerous research groups have assayed CSF and/or plasma for the APP metabolites APP_s (the large soluble ectodomain fragment of APP normally secreted by cells) and $A\beta_{42}$ and $A\beta_{40}$ (the 42-residue and 40-residue forms of the Aβ fragment of APP normally secreted by cells).

Aβ Peptides. Studies assaying the amounts of total Aβ peptides ($A\beta_{total} = A\beta_{42} + A\beta_{40}$) in human CSF have shown no definite quantitative correlation with the presence of AD; thus, measuring $A\beta_{total}$ has no clear diagnostic utility. In contrast, several studies of $A\beta_{42}$ concentrations in CSF have shown a decrease in the levels of this peptide in subjects with AD compared to age-matched normal or neurologic disease control subjects (see Galasko; Lannfelt). The probable biological explanation for a decrease in $A\beta_{42}$ levels in AD CSF is that the levels of soluble $A\beta_{42}$ in the brain interstitial fluid decrease as the peptide becomes increasingly insoluble and form deposits in the form of large numbers of diffuse and neuritic plaques. According to this formulation, the drop in soluble $A\beta_{42}$ in the brain is reflected by a decline in the soluble peptide in CSF. To date, at least 3 controlled studies by independent research groups in the United States and Japan have reported statistically significant decreases in CSF $A\beta_{42}$ levels in AD patients compared to controls (5,6,7). In each study, the levels of $A\beta_{42}$ in AD patients were significantly lower than those in controls having other neurological diseases. The mean decrease observed in 37 AD subjects was significant at $p < 0.0001$ when compared to mean levels in 32 neurologically diseased controls or 20 healthy controls (6). Simultaneous measurement of CSF $A\beta_{total}$ levels in the same subjects showed no significant differences, underscoring the specific involvement of $A\beta_{42}$ peptide. In this study, a CSF level of 505 pg/mL of $A\beta_{42}$ was used to separate optimally AD from subjects with other neurological diseases and from normal control subjects. Use of this level as a cutoff led to a calculated sensitivity of 100% and a specificity of 63% for low $A\beta_{42}$ as a marker for the presence of clinical AD.

Simultaneous analysis of $A\beta_{42}$ and tau protein measurements in the same CSF sample demonstrated a correlation of low $A\beta_{42}$ plus high tau levels with a clinical diagnosis of AD. With certain specific cutoffs for $A\beta_{42}$ and tau levels, the presence of elevated tau plus reduced $A\beta_{42}$ levels in a CSF sample showed a specificity of 96% for AD. Conversely, high $A\beta_{42}$ and low tau levels were observed only in control patients in this study. The mean $A\beta_{42}$ level in 20 AD patients was less than half the mean level in 34 control subjects with neurological diseases ($p < 0.0005$) (7). Thus, all studies completed to date have shown significant decreases in mean CSF $A\beta_{42}$ levels, usually correlated with significant increases in mean CSF tau levels, in clinically probable AD subjects. Sensitivities for the clinical diagnosis of AD compared to normal non-demented subjects for finding low CSF $A\beta_{42}$/high tau levels have been found to be in the range of 60–94%, and specificities for the clinical diagnosis of AD were in the range of 70–96%. These values are much lower, however, when compared to subjects with non-Alzheimer neurological diseases (5).

Aβ in Plasma. A single published study has reported an increase in plasma $A\beta_{42}$ levels in a small subset (~10–20%) of SAD subjects (8). Elevation of plasma $A\beta_{42}$ levels has also been reported in subjects bearing mutations in the APP or the presenilin genes, including some subjects who were still presymptomatic (see Iwatsubo). Insufficient numbers of well-powered, controlled studies of $A\beta_{42}$ levels in plasma have been completed to allow any firm conclusion about the potential diagnostic utility of plasma Aβ in SAD.

Aβ in Urine. There has been a report of the detection of Aβ peptides in human urine, but no clinical studies of its possible diagnostic utility in AD or control subjects have been completed.

APP_s in CSF. A number of studies quantitating the APP ectodomain derivative, APP_s, in CSF of AD vs. control subjects have been published. Most studies have shown no clear statistically significant difference between these subjects. However, several published studies in which the APP_s levels were assayed by one research group using a particular antibody that recognizes native APP_s provided evidence of deceased levels of APP_s in subjects with clinical AD, including subjects with sporadic or familial forms of the disease (see Lannfelt). Some of the studies utilizing this antibody reported a correlation between low CSF levels of APP_s and poor performance on cognitive tests. One study using the same antibody also found significant decreases in CSF APP_s in four patients with Gerstmann-Straussler-Scheinker disease, leading to the authors' suggestion that low levels of APP_s may not be unique to diseases characterized by β-amyloid deposition, but also occur in other disease processes involving neuritic pathology or neuronal degeneration. Overall, the utility APP_s levels in confirming a clinical diagnosis of AD has not yet been established.

CSF Tau. The known correlation between the abundance of neurofibrillary lesions in the brain and clinical indices of dementia has resulted in a surge of recent studies of CSF levels of tau in AD patients (see Galasko; Hock) (9,11). Using enzyme-linked immunosorbant assays (ELISAs), studies have shown that the levels of CSF tau are significantly elevated in AD patients compared to normal elderly control subjects. However, elevated levels of CSF tau were detected in patients with other acute and chronic neurological diseases, including dementing disorders that resemble AD clinically. Not surprisingly, the sensitivity and specificity of a CSF tau assay will vary depending on the patient population examined. For example, a CSF tau level of 70 pg/mL or greater identified probable AD patients with a sensitivity of 82% and a specificity of 70% when compared to non-demented healthy control subjects (10). However, when patients with a clinical diagnosis of possible AD were compared to control subjects or patients with other non-Alzheimer dementias, it was difficult to determine a CSF tau cutoff level that was diagnostically informative. In addition to their potential as a diagnostic aid, CSF tau assays may become useful as predictors of their progression to AD in individuals with memory impairments but who do not meet clinical criteria for dementia (9). Overall, detecting elevated levels of tau in CSF is a promising antemortem marker for establishing or confirming a diagnosis of AD, and possibly for monitoring progression of disease and response to treatment. Additional research, including development of more specific tau antibodies, might improve measurement of tau (either alone or in combination with other potential protein markers in the CSF such as amyloid fragments, kinases, and proteases) as a reliable, sensitive and specific biomarker of AD.

CSF Neuronal Thread Protein. Neuronal thread proteins (NTP) are a family of molecules that are expressed in the brain, and that are immunologically related to pancreatic thread protein. In a postmortem study, brains from patients with AD contained significantly more NTP-immunoreactivity than brains from patients with other neurological diseases and brains from control subjects without disease (14). Examining CSF, it was reported that levels of NTP were increased in advanced cases of AD, and correlated with progression of dementia and neuronal degeneration (13). The NTP fragment in CSF is a 41-kDa protein; levels above 3 ng/mL identified 62% of patients with clinically diagnosed AD and 84% of neuropathologically verified cases (12). Although measurement of NTP in CSF appears to be a promising biomarker for AD, there is a need to confirm sensitivity and specificity in additional independent studies in living patients.

CSF Neurotransmitters and Neurotransmitter Metabolites. Neurochemical analyses of brain tissue obtained at postmortem examination and with surgical biopsy reveal deficits in multiple neurotransmitter systems. Among neuronal populations affected, those that synthesize and release acetylcholine are most affected, although there are deficits in monoamines and neuropeptides (17). Analyzing CSF for neurotransmitters and their metabolites began shortly after the initial discoveries of these abnormalities in brain. This strategy was based on the fact that CSF bathes the brain and spinal cord and might reflect alterations in the state of activity of adjacent neural tissue. It was therefore anticipated that the neurotransmitter abnormalities in brain would be reflected in the CSF. The initial enthusiasm for this line of investigation quickly faded because all markers had poor sensitivity and specificity (15). Somatostastin is a typical exemple: mean CSF levels were significantly reduced in AD, but the range of individual values overlapped with normal control and neurologic control subjects and precluded diagnostic specificity (16).

In summary, tests directed toward detecting neuropathological features of AD are among the most promising approaches to defining biomarkers. The diagnostic utility of finding increased levels of $A\beta_{42}$ in plasma is mostly limited to FAD, but levels of $A\beta_{42}$ in CSF are significantly decreased in many patients with SAD. A universal finding is that mean CSF levels of tau are increased in AD. CSF measures of Aβ and tau alone have modest sensitivities and specificities, but these indices improve when the two measures are combined. Detecting alterations in other proteins in CSF that are specific to AD, such as NTP, appears promising for early diagnosis and for monitoring change over time or in response to treatment but requires further study prior to clinical use.

Systemic Alterations as Molecular and Biochemical Markers of AD

Skin. The discovery that the Aβ peptide circulated in blood and CSF, coupled with the development of specific antibodies to amyloid fragments, allowed investigators to test the hypothesis that patients with AD would have greater deposits of amyloid in peripheral tissues than those without AD. Although this prediction was true in skin biopsy tissue, there was substantial overlap with non-demented elderly control subjects (24). This lack of specificity precluded testing for amyloid deposits in skin biopsy as a biomarker for AD.

Olfactory Epithelium. AD patients show evidence of olfactory perception deficits early in the course of disease, and the olfactory epithelium is accessible for biopsy during life. Dystrophic neurites in postmortem and in vivo biopsy samples of the olfactory epithelium from patients with AD have been described (29). However, similar lesions have been described in the olfactory epithelium of individuals with other conditions, including those without neurological disease. Thus, examining olfactory epithelium is not a useful biological marker for AD.

Fibroblasts. Electrophysiological and biochemical abnormalities have been identified in fibroblasts that are hypothesized to reflect changes in the central nervous system of patients with AD. (19,23) Dysfunction in potassium channels was described in fibroblasts from AD patients compared to control subjects (19). Changes in protein kinase C activity were identified in AD fibroblasts compared to control subjects (21). These techniques have not gained currency as biological markers for AD, in part because of overlap with non-AD subjects, in part because of the invasive nature of the test (a skin biopsy is required), and in part because of the complexity and sophistication of the assays. Studies

with fibroblasts, however, show promise as a method of studying AD-related mechanisms, including APP processing (20).

Platelets. An abnormality of increased platelet membrane fluidity was first described in 1984 (32). This finding was a surprise, as membrane fluidity generally decreases with advancing age. Nonetheless, subsequent investigations confirmed the decreased fluidity in AD, although there are the substantial overlaps between AD and control subjects that limits its diagnostic value (31). There is even the proposal that increased membrane fluidity is a risk factor that predicts development of AD (33), but this observation requires independent confirmation. There is increasing evidence of mitochondrial abnormalities in AD that lead to reductions in ATP and increases in oxygen-reactive species that damage neurons (26). Decreased mitochondrial cytochrome C oxidase activity in platelets of AD patients has been described (27). Subsequently, the decrease in cytochrome oxidase activity in AD patients compared to control subjects was confirmed, and it was shown that this deficit corresponded to an increase in reactive oxygen species (18). This finding is controversial however and may reflect a technical artifact (30). Additional studies will be needed to substantiate the role of oxidative stress in the neuronal damage of AD, and the sensitivity and specificity of complex IV abnormalities in AD, before this test can be accepted as a biological marker.

Blood. It has been reported that the soluble form of the iron-binding protein p97 was elevated in AD patients compared to control subjects (25). All AD patients had elevated levels of p97 in their serum compared with controls, and there were no overlaps between these two groups. To date, this report has not been extended by the authors; no reports confirming or repudiating these data have appeared from other groups.

Tropicamide Eye Test. Pupil dilation in response to installation of a dilute solution of tropicamide has been proposed as a non-invasive biological diagnostic test for AD (28). In the original report, the test had a sensitivity of 95% and a specificity of 94%. In subsequent studies, the specificity was lower with much more overlap between AD and control groups; in some reports (22), there was no difference in dilation response between AD and non-demented control subjects.

In summary, none of the systemic alterations proposed as characteristic biological markers of AD can be accepted for widespread use at present. Some of the markers such as amyloid deposits in the skin, detecting dystrophic neurites in olfactory epithelium, and measuring pupil dilation in response to a dilute solution of tropicamide, lack sufficient specificity to qualify as useful biological markers. Although serum levels of the p97 protein showed complete separation between AD and control groups in the sole report to date, additional confirmatory studies will be necessary before accepting this test as a biological marker. Studies with fibroblasts provide a method of examining electrophysiological and biochemical changes believed to take place in brains of patients with AD. This potential use outweighs their current clinical value as diagnostic markers.

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APPENDIX

Members of the Working Group submitted position papers. The ideas and the perspectives represented in these papers helped shape the consensus statement and were useful in the preparation of the final report. The Advisory Committee of the Working Group gratefully acknowledges the contribution of these authors. Some of these papers, listed below, are being published in this supplement.

The Working Group Advisory Committee

Peter Davies, Ph.D., Judith and Burton Resnick Professor of Alzheimer's Disease Research, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York.

Sid Gilman, M.D., Chair, Department of Neurology, Michigan Alzheimer's Disease Research Center, University of Michigan, Ann Arbor, Michigan.

John H. Growdon, M.D., Chair, Professor, Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts.

Zaven S. Khachaturian, Ph.D., Director, Ronald and Nancy Reagan Research Institute, Alzheimer's Association, Chicago, Illinois.

Teresa S. Radebaugh, Sc.D., Deputy Director, Ronald and Nancy Reagan Research Institute, Alzheimer's Association, Chicago, Illinois.

Allen D. Roses, M.D., Vice-President and World-Wide Director, Genetics, Glaxo Wellcome Research and Development, Research Triangle Park, North Carolina.

Dennis J. Selkoe, M.D., Director, Center for Neurologic Diseases, Brigham & Women's Hospital, Boston, Massachusetts.

John Q. Trojanowski, M.D., Ph.D., Professor, Pathology & Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania.

The Members of Working Group

John P. Blass (Gary E. Gibson, K.-F. R. Sheu), Burke Medical Research Institute/Cornell University Medical College, White Plains, New York.

Kaj Blennow, Department of Clinical Neuroscience, Unit of Psychiatry and Neurochemistry, University of Goteberg, Sweden, and the Swedish Medical Research Council, Stockholm, Sweden.

Andre Delacourte, Director of Research INSERM, Place de Verdun, Lille, France.

Giovanni B. Frisoni, Geriatric Research Group, Istituto, Sacro Cuore di Gesu, Brescia, Italy.

Wilfred A. Jefferies, The Biotechnology Laboratory and the Departments of Medical Genetics, Microbiology and Immunology, and Zoology, the University of British Columbia, Vancouver, British Columbia, Canada.

Amanda McRae, Department of Anatomy and Cell Biology, University of Goteborg, Goteborg, Sweden.

H. M. Wisniewski (P.D. Mehta, T. Pirttla), New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York.

Ram Parshad, Department of Pathology, College of Medicine, Howard University, Washington, D.C.

Leonard F. M. Scinto, Laboratory of Higher Cortical Functions, Brigham and Women's Hospital, Boston, Massachusetts.

Philip Scheltens, Department of Neurology, Academisch Ziekenhuis Vrije Universiteit, Amsterdam, The Netherlands.

Paavo J. Riekkinen (Hilkka S. Soininen), Department of Neuroscience and Neurology, Kuopio University, Kuopio, Finland.

Gregory R. J. Swanwick, Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin, Ireland.

Lars-Olof Wahlund, Department of Clinical Neuroscience and Family Medicine, Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden.

John Q. Trojanowski (S. E. Arnold, Virginia M.-Y. Lee), Department of Pathology and Laboratory Medicine, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania.

Bengt Winblad (Lars-Olof Wahlund), Department of Clinical Neuroscience and Family Medicine, Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden.

Yasuo Ihara (Tsuneo Yamazaki), Department of Neuropathology, Faculty of Medicine, University of Tokyo, Tokyo, Japan.

Position Papers Published in this Volume

Hiroyuki Arai, Christopher M. Clark, Douglas C. Ewbank, Sadao Takase, Susumu Higuchi, Masakazu Mirua, Hisatomo Seki, Makoto Higuchi, Toshifumi Matsui, Virginia M.-Y. Lee, John Q. Trojanowski, Hidetata Sasaki, Department of Geriatric Medicine, Tohoku University School of Medicine, Sendal 980, Japan. "Cerebrospinal Fluid Tau Protein as a Potential Diagnostic Marker in Alzheimer's Disease."

Norman L. Foster, Michigan Alzheimer's Disease Research Center, University of Michigan, Ann Arbor, Michigan. "The Development of Biological Markers for the Diagnosis of Alzheimer's Disease."

Douglas Galasko, Department of Neurosciences, University of California, San Diego, San Diego, California. "CSF Tau and AB42: Logical Biomarkers for Alzheimer's Disease?"

Christoph Hock, Department of Psychiatry, University of Basel, Basel, Switzerland. "Biological Markers of Alzheimer's Disease."

Bradley T. Hyman, Harvard Medical School, Boston, Massachusetts. "Biomarkers in Alzheimer's Disease."

P. H. St. George-Hyslop, Center for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada. "Role of Genetics in Tests of Genotype, Status and Disease Progression in Early Onset Alzheimer's Disease."

Takeshi Iwatsubo, Department of Neuropathology and Neuroscience, University of Toyko, Toyko, Japan. "Amyloid B Protein in Plasma as a Diagnostic Marker for Alzheimer's Disease."

Malcolm Kennard, The Biotechnology Laboratory, The University of British Columbia, Vancouver, British Columbia, Canada. "Position Paper Regarding: Diagnostic Markers for Alzheimer's Disease."

William E. Klunk, University of Pittsburgh Medical Center, Laboratory of Neurophysics, Pittsburgh, Pennsylvania. "Biological Markers of Alzheimer's Disease."

Lars Lannfelt, Karolinska Institute, Department of Clinical Neuroscience (Geriatric Medicine), Huddinge Hospital, Huddinge, Sweden. "Biochemical Diagnostic Markers to Detect Early Alzheimer's Disease."

Irene Litvan, Neuroepidemiology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland. "Methodological and Research Issues in the Evaluation of Biological Diagnostic Markers for Alzheimer's Disease."

Richard Mayeux, Gertrude H. Sergievsky Center, Columbia University, College of Physicians and Surgeons, New York, New York. "Evaluation and Use of Diagnostic Tests in Alzheimer's Disease."

Alfredo Robles, Division of Neurology, Complejo Hospitalario, University of Santiago, Santiago de Compostela, Spain. "Some Remarks on Biological Markers of Alzheimer's Disease."

Note: The following three additional, previously published, papers were submitted, and are noted for information of the reader.

Fabian, V. A.; Jones, T. M.; Wilton, S. D.; Dench, J. E.; Davis, M. R.; Lim, L.; Kakulas, B. A. Alzheimer's Disease and Apolipoprotein E Genotype in Western Australia: an Autopsy-verified Series, MJA 165:77–80; 1996.

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Senile dementia of Lewy body type

A clinically and neuropathologically distinct form of Lewy body dementia in the elderly

Robert H. Perry[1,3], Dorothy Irving[1], Garry Blessed[2], Andrew Fairbairn[2] and Elaine K. Perry[3]

[1]*Department of Neuropathology,* [2]*Brighton Clinic, and* [3]*MRC Neurochemical Pathology Unit, Newcastle General Hospital, Newcastle upon Tyne (U.K.)*

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SUMMARY

A dementing syndrome has been identified in a group of psychiatric cases aged 71–90 years, presenting initially with a subacute/acute confusional state, often fluctuating and associated with visual hallucinations and behavioural disturbances. Clinically, these cases did not meet criteria for a diagnosis of Alzheimer's disease, and many were assigned to the multiinfarct dementia group, although no significant ischaemic lesions were evident at autopsy. Mild extrapyramidal features were apparent in a number of cases but the characteristic clinical triad of Parkinson's disease, i.e., tremor, rigidity, and akinesia, was absent. Detailed neuropathological examination revealed Lewy body formation and selective neuronal loss in brain stem and other subcortical nuclei, accompanied by Lewy body formation in neo- and limbic cortex, at densities well below those previously reported in diffuse Lewy body disease. A variable degree of senile degenerative change was present; numerous senile plaques and minimal neurofibrillary tangles in most cases. Neither the clinical nor the neuropathological features of this group are typical of Parkinson's or Alzheimer's disease, but suggest a distinct neurodegenerative disorder, part of the Lewy body disease spectrum, in which mental symptoms predominate over motor disabilities and lead to eventual psychogeriatric hospital admission. In a sequential series of autopsies conducted on clinically assessed demented patients, neuropathological analysis has indicated that such cases may comprise up to 20% of a hospitalized population of demented old

Correspondence to: Dr. R.H. Perry, Department of Neuropathology, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, NE4 6BE, U.K.

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people over the age of 70 years, an observation clearly relevant to the diagnosis and management of dementia in the elderly.

Key words: Senile dementia; Lewy bodies; Parkinson's disease; Alzheimer's disease; Diffuse Lewy body disease; Lewy body dementia

INTRODUCTION

In a previous analysis of correlates of cognitive impairment in Parkinson's disease [PD] and dementia (Perry et al. 1985) it was noted that two elderly cases with increased neocortical plaque density, had presented primarily with psychiatric symptoms rather than a movement disorder. Ongoing neuropathological examination of clinically assessed dementia cases coming to autopsy at the Newcastle General Hospital between 1982 and 1987, has revealed a further 18 out of 93 cases (19%) over the age of 70 years to have the histological features (particularly Lewy body formation) traditionally associated with PD, although the patients had not presented with an obvious movement disorder but had a psychiatric history of acute confusion, cognitive impairment and behavioural disturbances not typical of Alzheimer's disease (AD), and often initially diagnosed as multiinfarct dementia (MID). In view of the number involved and the unusual presentation these cases were examined more fully in conjunction with a detailed review of clinical assessments. In the present report the findings in this atypical group are compared with those seen in idiopathic PD (with and without dementia), classical senile dementia of Alzheimer-type (SDAT), diffuse Lewy body disease (DLBD) and with age-matched controls. A brief report of preliminary findings has been published (Irving et al. 1988, 1989; Perry et al. 1989a,b).

MATERIALS AND METHODS

Case selection

Ninety-three cases of dementia over the age of 70 years from the psychogeriatric units of Newcastle General Hospital and St Nicholas Hospital coming to autopsy between 1982 and 1987, were assigned to categories according to previously described (Tomlinson et al. 1968, 1970) or recently modified clinical and neuropathological criteria (Table 1). For comparative purposes age-matched control and nondemented PD patients coming to autopsy from the general medical and neurology wards of Newcastle General and other local hospitals were included. The largest dementia category consisted of 45 cases with classical Alzheimer pathology (Tomlinson et al. 1970). The atypical group comprised 18 cases – the second largest category of dementia – and the 30 remaining cases were assigned to other diagnostic groups such as MID (6), mixed

TABLE 1

DEMENTIA IN THE ELDERLY >70 years: SUMMARY OF CASE CLASSIFICATION INCLUDING CONTROLS

Non-demented [19]			Demented [93]	
Controls [14]	Parkinson's disease [12]		Senile dementia Lewy body type [18] (Atypical)	Senile dementia Alzheimer type [46]
	Non-demented [5]	Demented [7]		
Clinical				
Previously capable of living an independent existence with no known neurological or psychiatric illness.	All cases presented with the classical movement disorder of Parkinson's disease (tremor, rigidity and akinesia) 7 cases developed dementia during the course of their illness.		Presented with acute/subacute confusion with behavioural disturbance, and mild dementia; developed mild extrapyramidal features during the course of their illness.	All cases presented with a slowly progressive dementia and one case developed the classical features of Parkinson's disease.
Pathological				
No histological evidence of Alzheimer's disease, Parkinson's disease or significant ischaemia.	Severe neuron loss (70%) with Lewy bodies in SN and other subcortical nuclei; occasional Lewy bodies in neocortex and limbic[a] cortex.		Moderate neuron loss (42%) with Lewy bodies in SN and other subcortical nuclei; Lewy bodies in limbic[a] cortex, variable in neocortex.	Normal or minimal SN neuron loss, Lewy bodies absent in 45 cases; Severe neuron loss with Lewy bodies in SN and other subcortical nuclei in one case (Parkinson's disease).
Moderate plaques in 2, and sparse neocortical NFT in 4 cases.	Non-demented Moderate plaques and sparse NFT in neocortex in 2 cases.	Demented Moderate/high plaques in 3 and sparse NFT in neocortex in 5 cases.	Moderate/extensive plaques in 13 cases, sparse neocortical NFT in 15 cases; 1 case with moderate neocortical NFT; one with extensive neocortical NFT (mixed SDLT/SDAT)	Extensive neocortical and archicortical plaques and NFT in all cases; minor ischaemic lesions (<20 ml) in 16 cases.

[a] Limbic cortex = cingulum, amygdaloid and hippocampal gyrus.
NFT = neurofibrillary tangles. SN = substantia nigra.
Other causes of dementia [22].
Diffuse Lewy body disease [2].
Multiinfarct dementia [6].
Multiinfarct dementia/SDAT [5].
Rarer causes (see text) [9].

MID/SDAT (5), PD developing dementia (7), diffuse Lewy body disease (DLBD) (2), SDAT combined with PD (1), and isolated examples of less common neuropsychiatric diseases such as Korsakoff's psychosis (1), progressive supranuclear palsy (1), multi-system atrophy (1), dementia in motor neuron disease (1), and dementia of unknown aetiology (5).

Fourteen atypical and 14 age-matched SDAT cases were selected (on the basis of tissue availability) for detailed comparative clinical and neuropathological assessment. This comparative study also included 12 PD cases: 5 non-demented cases in addition to the 7 cognitively impaired PD patients (see above); all presented with classic parkinsonian movement disorder (tremor, rigidity, akinesia) and had been prescribed and responded to anti-parkinsonian drug therapy. The normal or control group consisted of 14 age-matched patients capable of living an independent existence, with no recorded neurological or psychiatric abnormalities, or neuropathological evidence of AD or PD (Perry et al. 1978; Tomlinson et al. 1968).

Neuropathological methods

At autopsy the right hemisphere and hemi-midbrain, brain stem and cerebellum were fixed in neutral formalin, and the left hemisphere coronally sectioned and snap-frozen for neurochemical assay (Perry et al. 1982). Any ischaemic lesions in the fresh or fixed brain sections were charted, quantified, and analysed as described previously (Tomlinson et al. 1968). The right hemisphere was sliced coronally and tissue for paraffin processing taken from standard areas in the four major cortical lobes (Tomlinson et al. 1968), and from anterior and posterior cingulum, hippocampus, amygdaloid, basal ganglia (including substantia innominata and thalamus), midbrain (at least 2 levels), upper and upper-mid pons, medulla, and cerebellum. From these hand-processed tissue blocks, 5-μm sections were cut and stained with haematoxylin and eosin (H&E) and 20-μm sections with cresyl fast violet (CFV) for RNA (Nissl substance), Loyez haematoxylin (myelin), and a modification of Palmgren's silver technique (Cross 1982) for neurofibrillary tangle demonstration (Fig. 1a,b). The Von Braunmühl silver impregnation technique was used to demonstrate senile plaques (Fig. 1c,d) in 25-μm frozen sections cut from tissue blocks adjacent to those taken for paraffin processing.

All sections were screened for pathological changes including foci of ischaemia. Quantitation of Alzheimer-type pathology (plaques and tangles), in the 4 neocortical lobes (Brodmann areas 8/9, 17/18/19, 20/21/22, and 39/40), was carried out using previously described methods (Tomlinson et al. 1968) or methods modified as follows. The mean tangle density was obtained by counting tangles in consecutive fields (0.61 mm^2 in area) through the cortical layers at right angles to the grey/white matter surface in each of 5 randomly marked areas positioned at intervals around gyri (2 crest, 2 mid-sulcal zone, and 1 base of sulcus); mean plaque density was calculated from counts in fields (3.1 mm^2 in area), at 5 similarly marked points. Both plaque and tangle densities were expressed as mean values per mm^2 and in cases where tangles were sparse total numbers were counted in each section and the density derived by measuring the grey matter area of the section using a Kontron MOP-videoplan analyser.

Lewy bodies (LB) in the substantia nigra (SN) and other subcortical nuclei were identified in H&E sections, and LB or Lewy-like inclusions (cortical LB (Fig. 1e,f) generally lacking a peripheral halo in contrast to the classical LB of subcortical nuclei; see Gibb et al. (1987)) identified in neo- and limbic cortex (defined as cortex associated with the limbic lobe including cingulum, hippocampal gyrus and amygdaloid; – see Brodal (1969)) and their density per cm^2 estimated by counting the total number per section using the grey matter area measurements described above. The counterstain in the H&E method (used routinely in the Neuropathology Department) is a composite of eosin, phloxine and erythrosin in 20% alcohol which gives a wider spectrum of pinks to reds than standard eosin counterstains, and aids recognition of cortical LB. Identification of LB was further assisted by the use of a standard green photographic filter (Kodak Wratten No. 11) placed between the light source and the microscope stage to enhance contrast.

Dopaminergic neuromelanin pigmented neurons in SN were assessed in CFV stained sections from a mid level of midbrain (Fig. 2), and all those with visible nucleoli counted. Similarly, noradrenergic neurons in the locus coeruleus (LC) were counted bilaterally at the upper midpons level.

Clinical evaluation of cases

In addition to the original clinical diagnosis, case notes of the atypical and the age-matched SDAT groups were retrospectively assessed by one of us (GB) for comparative purposes, and the resulting clinical diagnosis based upon the International Classification of Diseases (ICD) (WHO, 9th revision, 1977). All cases had been subject to initial and repeated multidisciplinary psychogeriatric clinical evaluations which included: a semi-structured psychiatric history and examination (Bergmann and Eastham 1974) and a medical history and examination augmented by laboratory and/or radiological screening for organic dysfunction. Severity of dementia was assessed in three ways: by calculation of the best (usually initial) recorded Mental Test Score (MTS, the modified Roth Hopkins test; Blessed et al. 1968) and by the MTS recorded closest to death; by calculation of the Crighton Geriatric Behavioural Rating Scale (CGBRS) (Robinson 1965), again utilising best (usually initial) recorded score and that nearest to death; and by assessment of temporal and parietal (higher mental) function (TPF) using an unpublished test devised by M. R. Wilde in 1971, calculated and scored as follows: left/right orientation (3), calculation (5), nominal aphasia (7), tactile agnosia (5) and constructional apraxia (copy match arrangements 8, copy pencil diagrams twice 10 + 10), giving a highest possible score of 48.

Further psychiatric and neurological assessments included: Hachinski score (Hachinski 1975); presence and number of extrapyramidal features such as tremor, rigidity, akinesia, flat facies and gait disturbances (Barbeau 1986) recorded individually on a scale of 1–10; presence or absence of hallucinations, sleep disturbance, aggressive behaviour, falling, restlessness, incontinence; and duration of the dementing process from identification of initial symptoms by relatives to the patient's eventual death.

RESULTS

Neuropathological features

Neuropathological findings are presented before the clinical evaluation since the atypical group was originally identified on the basis of its unusual neuropathological profile. Findings in the atypical compared with SDAT, PD, and control categories are summarized in Table 2 and illustrated in Figs. 1–3. The control group showed minimal Alzheimer-type pathology and no evidence of Parkinson-type pathology (significant neuron loss and Lewy body formation in SN) in any case.

TABLE 2

QUANTITATIVE NEUROPATHOLOGICAL DATA[a] IN CORTICAL AND SUBCORTICAL REGIONS

	Controls	SDLT (atypical)	PD	SDAT	DLBD
Case Nos.	14	14	12	14	2
Age (years)	78 ± 6	81 ± 6	76 ± 5	81 ± 5	73,74
Senile plaques/mm^2					
Neocortex[b]	3.0 ± 3.8	16.4 ± 10.4	7.2 ± 7.1	16.2 ± 6.6	30.7,20.0
Tangles/mm^2					
Neocortex[b]	0.01 ± 0.02	1.5 ± 4.3	0.06 ± 0.14	29.9 ± 19.6	0.1, 2.0
Lewy bodies/cm^2					
Temporal lobe	ND	9.3 ± 12.4	1.9 ± 3.5	ND	28,155
Frontal lobe	ND	1.9 ± 3.1	0.8 ± 1.2	ND	87,143
Parietal lobe	ND	1.0 ± 1.2	0.9 ± 2.2	ND	33, 30
Occipital lobe	ND	ND	ND	ND	ND
Hippocampal gyrus	ND	50.8 ± 35.7	17.0 ± 17.0	ND	69,172
Cingulum (anterior)	ND	43.9 ± 44.9	35.5 ± 26.6	ND	223,175
Cingulum (posterior)	ND	17.3 ± 24.9	10.9 ± 12.4	ND	92,194
Neurons/20-μm section					
Substantia nigra [SN]	561 ± 141	328 ± 152	173 ± 108	540 ± 108	162, 158
Locus coeruleus [LC]	101 ± 27	29 ± 22	17 ± 12	32 ± 22	38, 24

ND = not detected.

[a] Data are expressed as mean ± SD, statistical differences between the atypical and other groups (Student's *t* test) were as follows:

Senile plaques	: controls	(P = <0.001), PD (P = <0.02).
Tangles	: all groups	(P = <0.02 or less).
SN neuron density	: controls	(P = <0.0001), PD (P = <0.01), SDAT (P = <0.01).
LC neuron density	: controls	(P = <0.01).
Lewy body density	: PD	(P = <0.05) for neocortex.
	: PD	(P = <0.01) for hippocampal gyrus.

[b] Neocortex, mean densities derived from frontal, temporal, parietal and occipital lobes.

For individual Brodmann areas see text. SDLT = senile dementia of Lewy body type; SDAT = senile dementia of Alzheimer type; DLBD = diffuse Lewy body disease.

Lewy bodies

Brain stem and subcortical regions. In the atypical group, PD, and the 2 cases of DLBD, LB were present in brain stem nuclei including SN, LC, raphe nuclei and periventricular grey matter, and in the substantia innominata. Neuroaxonal spheroids were also identified in dorsal vagal nuclei in all these categories.

Limbic cortex. In 13 out of 14 atypical cases LB and Lewy-like inclusions (cortical LB, Fig. 1e,f) were present throughout the depth of the cortex in parahippocampal gyrus, uncus of amygdaloid, and cingulum; they were limited to the amygdaloid complex in the remaining case. In PD cortical LB were present throughout the limbic cortex in the 7 cases with dementia, but were absent from either parahippocampal gyrus or cingulum in two of the non-demented cases. The mean parahippocampal cortical LB density was significantly higher ($P < 0.01$) in the atypical category when compared with the PD group (see Table 2). In the two cases of DLBD cortical LB were present in dense concentrations in all limbic cortical areas at several times the density found in atypical or PD groups. LB were not detected in hippocampal pyramidal layer or dentate hilus in any case.

Neocortex (frontal, temporal, parietal and occipital lobes). When present cortical LB were generally found in the deeper (IV, V and VI) layers of the neocortex, temporal lobe being more affected than frontal or parietal lobes, and occipital (striate cortex) being spared (with the possible exception of the 2 DLBD cases). In 7 out of 14 atypical cases cortical LB were present in low densities in temporal, frontal, and parietal lobes. In the remaining atypical cases they were confined to the temporal and frontal lobes (2 cases), temporal and parietal lobes (2 cases), and temporal lobe (1 case); and were undetected in neocortex in the 2 remaining atypical cases, although present in the amygdaloid or cingulum. In PD low densities of cortical LB were found in temporal, frontal and parietal lobes in 2 cases (both demented), and confined to the temporal and frontal lobes (2 cases non-demented); temporal lobe (2 cases, non-demented), or frontal lobe (2 cases, one demented). Four PD cases (2 demented and 2 non-demented) showed no neocortical LB. In contrast to the sparse, focally distributed or absent neocortical LB in the atypical and PD groups, the two cases of DLBD showed dense, diffuse concentrations of cortical LB (frequently 2–3 per HP microscopic field in deeper cortical layers) with an anatomically widespread distribution, the neocortical density being 10 or more times higher than in the temporal, frontal, or parietal lobes of both the atypical and PD groups. LB formation was not identified in subcortical, cortical, or any other region in the control or SDAT groups.

Neuron loss in subcortical nuclei

In SN there was a moderate but highly significant neuronal loss of 42% (compared with age-matched controls) in the atypical group, 69% in PD and no significant loss in SDAT. There was no significant difference in mean density in PD with or without dementia, and neuron density in the two cases of DLBD fell into the range of that seen in PD (Fig. 3). In LC the pattern was different, with a significant 72% loss in the atypical group, similar to that in SDAT (71%) and in the non-demented PD cases (72%) but less than that seen in the PD group as a whole (83%). In the PD cases

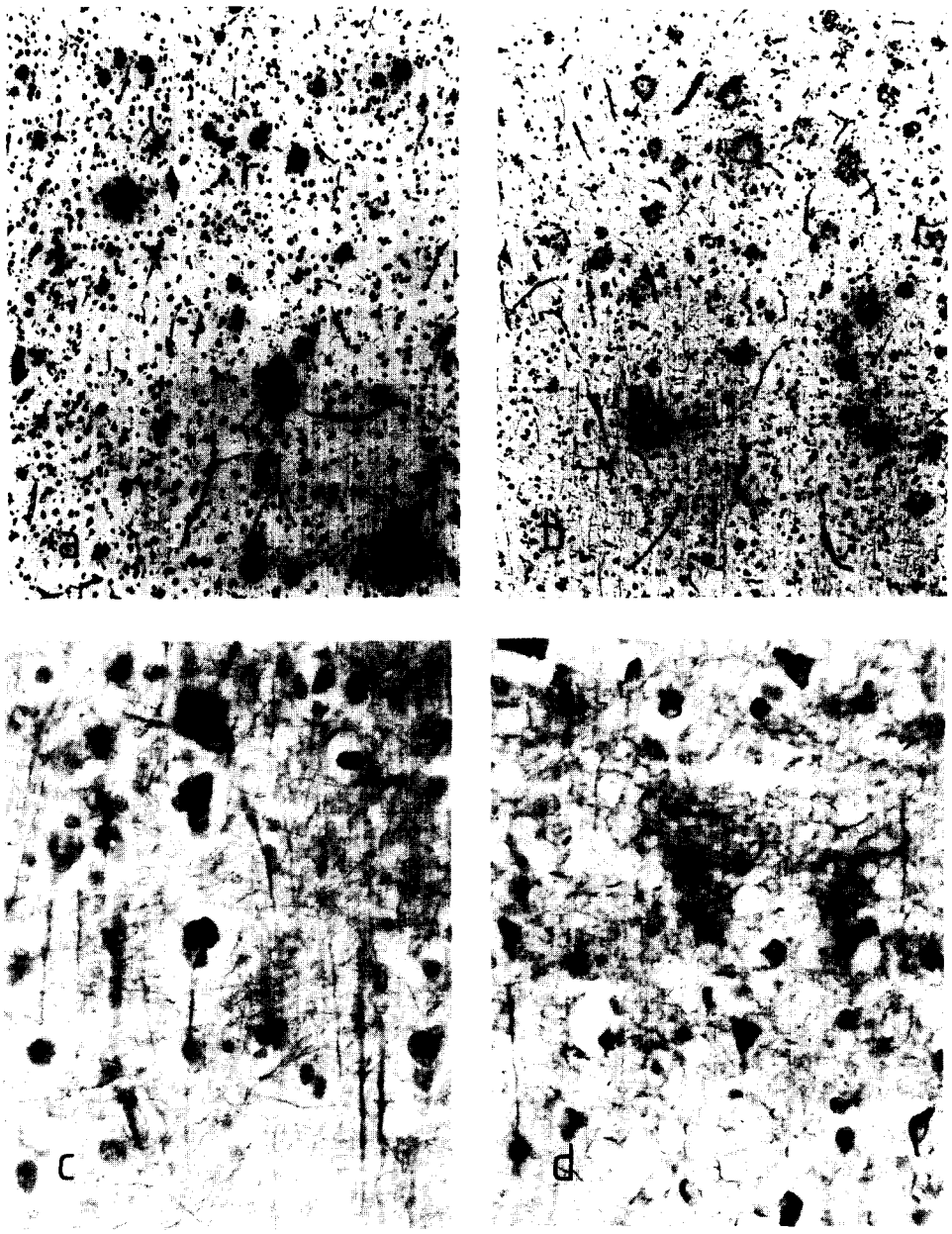

Fig. 1. Histopathological features in senile dementia of Lewy body type (SDLT) and senile dementia of Alzheimer type (SDAT). Senile plaques in temporal cortex (a) in SDLT and (b) in SDAT; 25-μm frozen sections, Von Braunmühl, $\times$ 100. Neurofibrillary tangles in temporal cortex (c) in SDLT and (d) in SDAT; 20-μm paraffin sections, Cross modification of Palmgren, $\times$ 500. Lewy bodies or Lewy-like inclusions in cingulum (e) in SDLT and (f) in diffuse Lewy body disease (DLBD); 5-μm paraffin sections, H&E, $\times$ 800; arrows indicate neurons with Lewy bodies and one Lewy body with a faint peripheral halo (f) is marked by a double-headed arrow. Lewy body density in the section illustrated at (f) was 166/cm^2 compared with 157/cm^2 in an adjacent section reacted with ubiquitin antiserum (standard PAP technique, 1 : 200 dilution, kindly donated by Professor B. Anderton).

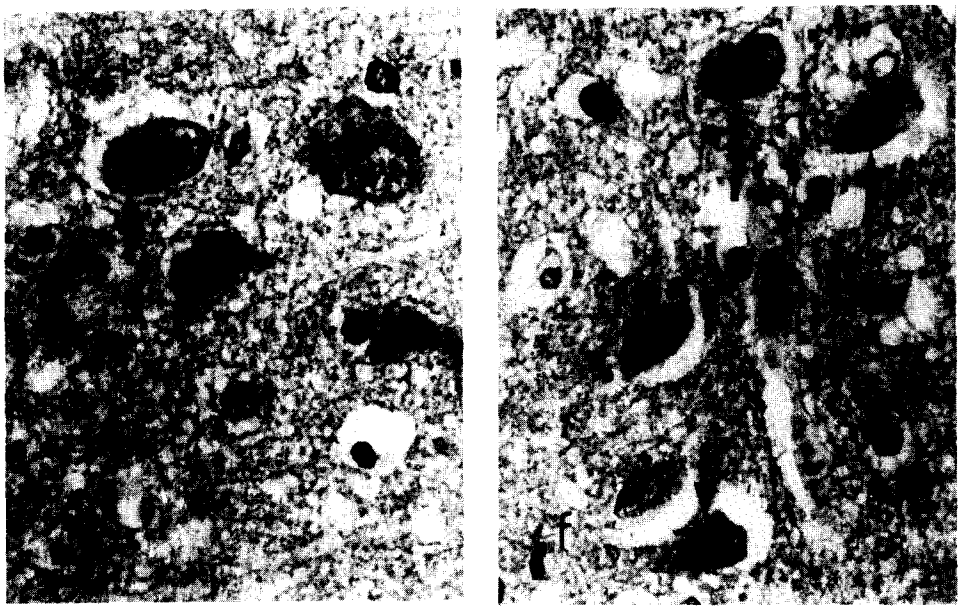

Fig. 1e–f.

with dementia mean LC neuron loss was 91% and in DLBD neuron density was in the range of that seen in SDAT and non-demented PD (Fig. 3). A preliminary survey of other subcortical nuclei indicated a moderate loss of cholinergic neurons in the nucleus of Meynert and serotonergic neurons in the dorsal raphe nuclei in most atypical cases. In one case neuron loss (>70%) in nucleus of Meynert matched the severity of that seen in PD with dementia (Irving et al. 1987; Perry et al. 1985).

Alzheimer-type pathology

Neocortical tangles were present in all but one case in the atypical group (that with the lowest plaque density 1.7/mm^2), being focally but by no means invariably present in all four major cortical lobes (and in one case in high focal concentrations in occipital cortex) but at much lower mean densities (<10%) than in the aged-matched SDAT group (Table 2). The average senile plaque density, in contrast, was similar to or above that seen in SDAT in 11 out of 14 atypical cases. In the two cases of DLBD, mean plaque density was also high (20.0, 30.7/mm^2) and neocortical tangles were present but sparse. Alzheimer-type pathology (plaques, tangles, granulovacuolar degeneration and Hirano bodies) in the hippocampus exceeded that found in the control group but was less than that present in SDAT (data not shown). Tangle formation was present in the brain stem raphe nucleus in all but one atypical case, exceeding the density found in the control group but below that in SDAT.

In the PD cases, neocortical tangles were either totally absent or present to a minimal degree, as in the control group, while plaque densities were moderately raised in some cases and slightly but not significantly increased in the subgroup with dementia when compared with the age-matched controls. Plaque formation in all groups including

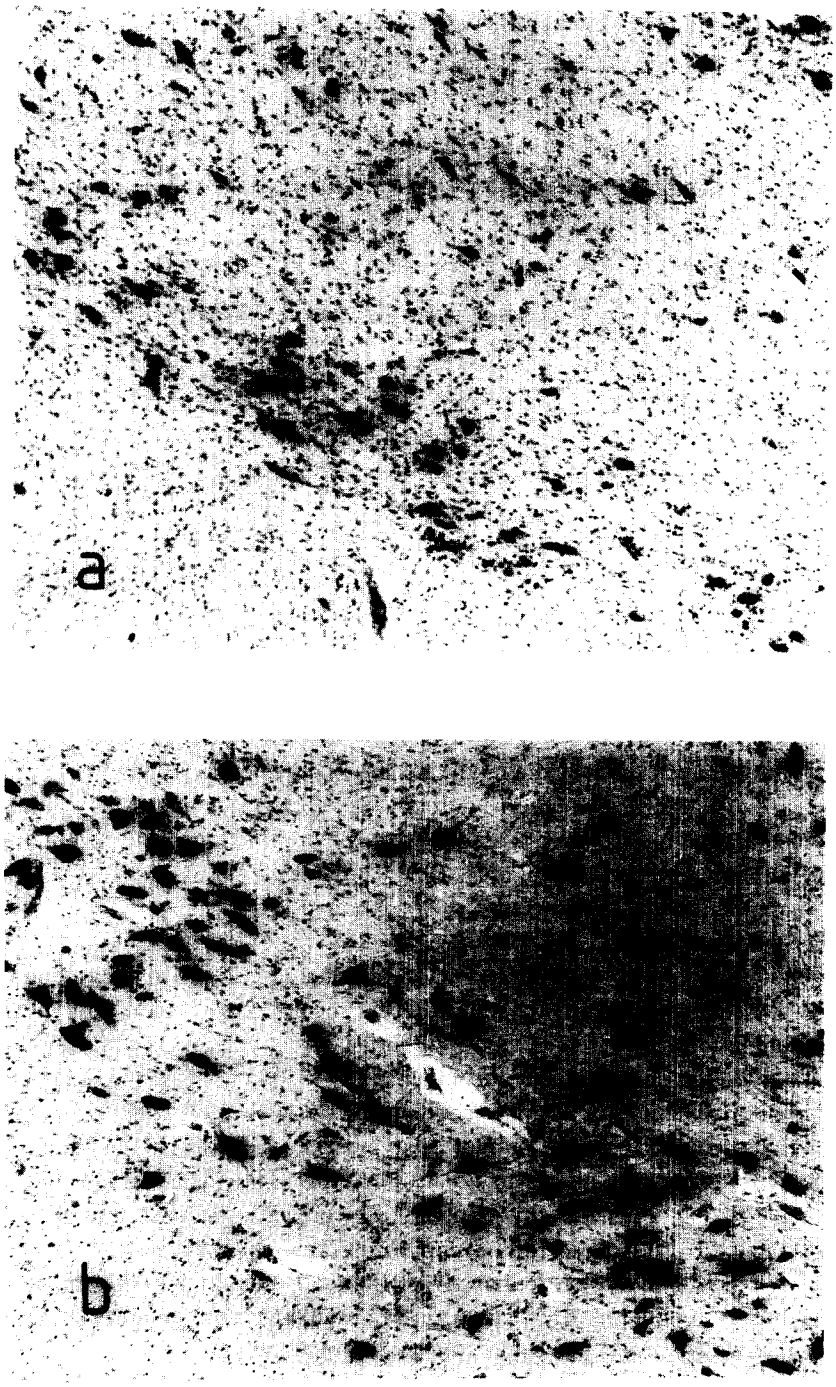

Fig. 2. Photomicrographs illustrating neuron density in the mid zone of substantia nigra in (a) Parkinson's disease (PD) with dementia, (b) in SDLT, and (c) in SDAT; 20-μm paraffin sections, cresyl fast violet, $\times$ 64. The severe neuron loss in PD contrasts with less extensive loss in SDLT and in SDAT, a density within the normal range.

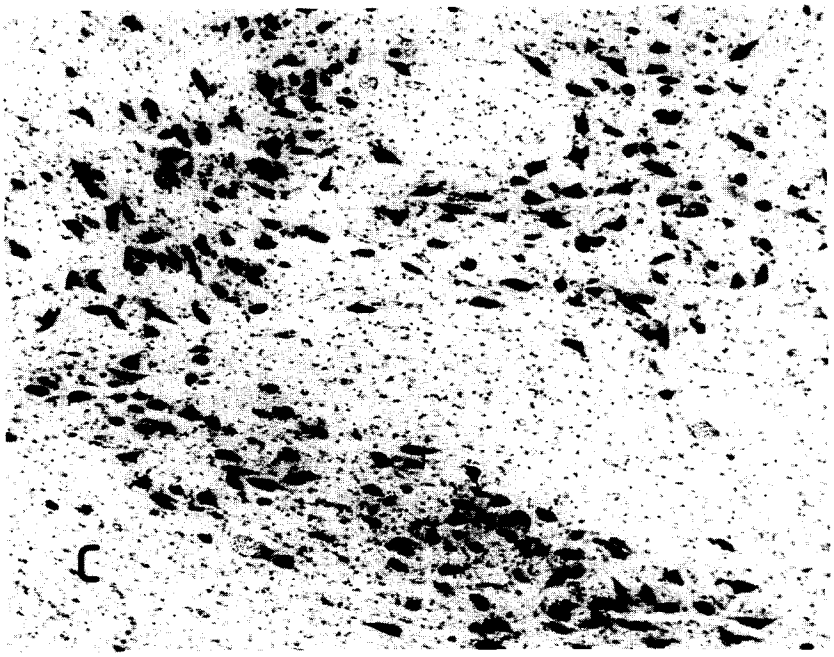

Fig. 2c.

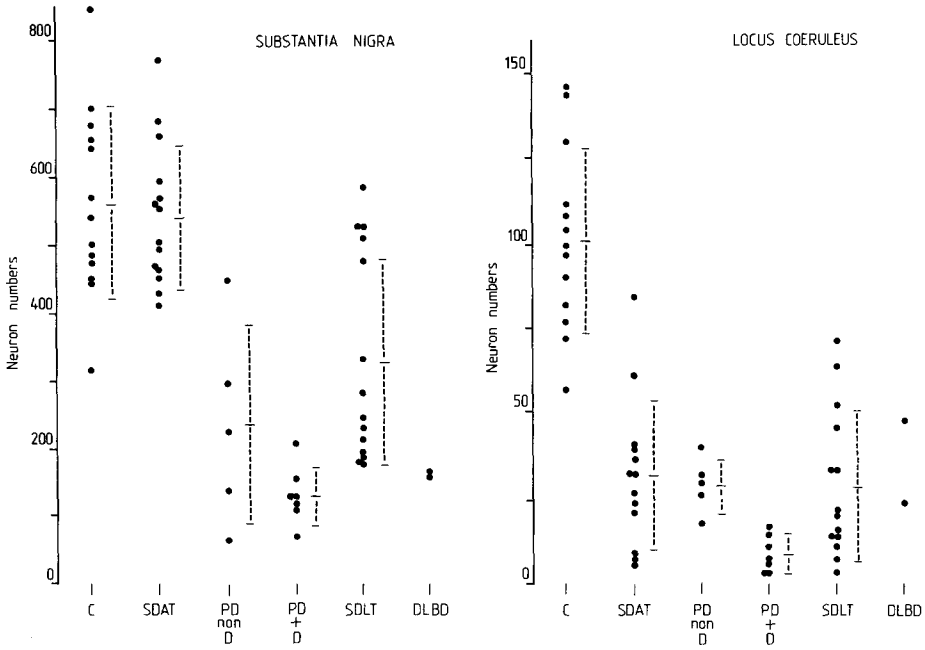

Fig. 3. Substantia nigra and locus coeruleus neuron numbers in control (C), SDAT, PD, (non D = non-demented; + D = demented), SDLT, and DLBD. Total neuron numbers in 20-μm sections stained with cresyl fast violet from the mid level of each nucleus. Points represent counts from individual cases with bar lines indicating means and SD. For statistical comparisons see Table 2.

controls reacted with antisera directed to the A4 component of amyloid protein (demonstrated using standard PAP immunohistochemistry, antisera to A4 protein 1 : 200 dilution).

None of the atypical cases showed evidence of ischaemic lesions sufficient to warrant a diagnosis of MID (more than 50 ml of infarcted brain; Tomlinson et al. 1968), though 3 small ischaemic lesions (max. 5 mm^2) in basal ganglia, body of pons, and dentate nucleus in one case may have contributed to the symptoms.

Psychiatric and neuropsychiatric features (atypical and SDAT cases)

After case note review, psychiatric classification (ICD, Table 3) in the atypical group revealed that acute confusion complicating dementia was much the commonest diagnosis (9 cases) followed by acute or subacute confusional state (3 cases). In no case was the confusional state due to metabolic disturbances or a toxic delirium associated with intercurrent physical illness or drug treatment. In contrast, in the SDAT group, an Alzheimer-type aetiology or simple senile dementia was judged to be the probable cause in 10 cases (Table 3). Of the observed differences in classification, only the high prevalence of acute confusion/dementia in the atypical group, 9/14 vs. 1/14 reached significance ($\chi^2 = 7.62$; $P < 0.01$ using Yates correction for small numbers).

Severity of dementia (Table 4)

MTS was significantly higher in the atypical cases at referral or soon afterwards in comparison with SDAT (best recorded score; $P < 0.01$) and while it deteriorated significantly in both groups as death approached, the atypical group retained better

TABLE 3

PSYCHIATRIC DIAGNOSIS ACCORDING TO DSM-III CRITERIA[a]

Case note review of atypical and senile dementia of Alzheimer type groups.

	Category No.	SDLT (atypical)	SDAT
SD (Alzheimer type)[b]	Nil	0	5
SD simple type	290.0	0	5
SD with acute confusional state	290.3	9	1
SD, depressed or paranoid type	290.2	1	1
Dementia unspecified	290.9	0	2
Arteriosclerotic dementia	290.4	1	0
Acute confusional state	293.0	1	0
Subacute confusional state	293.1	2	0
Totals		14	14

[a] International Classification of Diseases (WHO, 9th rev., 1977).
[b] Cases thought to be of Alzheimer aetiology, but arising after the age of 65 yrs.

TABLE 4

CLINICAL RATINGS

Comparison of severity of dementia in senile dementia of Lewy body (SDLT) and Alzheimer types (SDAT).

	SDLT (atypical)	SDAT
	Mean ± SD	Mean ± SD
(1) Initial/best recorded MTS	25.1 ± 7.0	14.6 ± 9.0
(2) MTS nearest to death	12.6 ± 9.1	5.4 ± 8.0
(3) Initial/best recorded CGBRS	9.1 ± 5.0[a]	14.0 ± 6.4
(4) CGBRS nearest to death	19.0 ± 6.8[a]	20.3 ± 5.9
(5) Best recorded TPF test	29.4[b]	33.9[c]
(6) Hachinski score	5.6 ± 2.2	2.3 ± 2.0

[a] 12 cases tested,
[b] 10 cases tested,
[c] 9 cases tested.
MTS : 37 item Mental Test Score; modified Roth Hopkins Test (Blessed et al. 1968)
CGBRS : 45 item Crighton Geriatric Behavioural Rating Scale (Robinson 1965)
TPF : 48 item Temporal and Parietal (Higher Mental) Function Test (see text).
Statistics: Comparison of means between the groups (Student's *t* test):
(1) & (6) $P = <0.01$;
(2) & (3) $P = <0.05$;
(4) & (5) no significant difference.

cognitive function ($P < 0.05$). CGBRS was significantly lower in the atypical group at referral, i.e., patients less handicapped ($P < 0.05$) and again deteriorated significantly in both groups although near to death there was only a slight difference in the scores. The TPF, which theoretically should have been sensitive to parietotemporal deficits of Alzheimer's disease, was less reduced in the SDAT than in the atypical cases, but not to a significant extent.

Extrapyramidal features

The appearance of often isolated mild extrapyramidal features (see Methods) was recorded in many of the case notes. In the SDAT group, these were recorded in 8 cases (number of features 1–3, mean 0.86 ± 0.95), while in the atypical group, 12 cases (80%) had between 1 and 5 mild extrapyramidal features (mean 2.36 ± 1.50), as recorded in the cases notes following presentation. The occurrence of these symptoms was significantly greater in the atypical group compared with SDAT ($P < 0.01$). One atypical case presenting with mental impairment and hallucinations was subsequently found to have been treated for extrapyramidal symptoms prior to hospital psychiatric assessment, with deterioration in mental function and increasing prevalence of hallucinations on L-DOPA therapy. Five of the atypical and 2 SDAT cases were prescribed anti-parkinsonian medication following psychiatric referral. In no case was the classical triad of tremor, akinesia and rigidity typical of Parkinson's disease present.

Features suggestive of MID aetiology

In the atypical group an arteriosclerotic aetiology for the dementia was often initially considered by the clinician, largely because the cases presented acutely and showed some fluctuation in the clinical course. Only three had a history of apparent minor strokes (not pathologically confirmed); these atypical cases and 1 SDAT case satisfied Hachinski (1975) criteria for MID (retrospectively assessed from case notes), and 2 further atypical cases with focal neurological signs had borderline scores of 7 (means 5.57 ± 2.20 and 2.29 ± 2.05 for atypical and SDAT, respectively), significantly higher scores being assigned to the atypical group ($P < 0.01$).

Duration of illness

Despite difficulties in dating the precise onset of dementia which is typically insidious in AD, when the duration of symptoms prior to referral (on the basis of information provided by relatives) were added to subsequent survival times, the atypical group had a significantly shorter duration of illness, a mean of 3.3 ± 2.3 years compared with 5.6 ± 2.6 years in SDAT ($P < 0.05$) and 7.9 ± 3.6 years in PD.

Other features

As preliminary scrutiny of the atypical group revealed that visual hallucinations were present in 8 cases, a search was made for the presence of these and other symptoms. Three cases of SDAT had visual hallucinations recorded but the apparent difference in prevalence did not reach statistical significance ($\chi^2 = 2.39$ (NS) using Yates' correction for small numbers). Transient episodes of apparent loss of conciousness were recorded in some of the atypical cases and 2 showed mild pyramidal signs: bilateral extensor plantar responses. The occurrence of the other features such as falls, aggressive behaviour, restlessness, sleep disturbance and incontinence was approximately equal in both groups, with between one-half and two-thirds of all cases being affected.

Neuropathological correlates of the dementing syndrome

Potential neuropathological correlates of the dementing syndrome in the atypical cases were investigated. Whilst there was an overall trend for increasing plaque densities to correlate with the degree of mental impairment, this did not reach significance ($r = -0.46$), and exceptions were noted. Thus in one case with a low MTS (6/37), senile plaque formation was minimal (mean $1.7/mm^2$) with neocortical tangles absent; conversely the highest plaque density (mean $37.5/mm^2$) was found in a case with a relatively less established clinical dementia (MTS 24.5/29). The MTS in the atypical group did not correlate with neuron loss in the substantia nigra ($r = -0.19$) or locus coeruleus ($r = 0.45$) and neither neocortical tangles nor Lewy body density appeared to relate directly to the severity of cognitive impairment as assessed by the MTS in the majority of the cases.

DISCUSSION

The present clinicopathological survey suggests that a substantial subgroup (up to 20%) of elderly demented patients who presented to the clinician with confusion, cognitive impairment, and behavioural disturbances have an atypical neurodegenerative syndrome characterized by the presence of both cortical and subcortical Lewy body formation, a variable degree of senile plaque formation, and neuronal loss in some subcortical nuclei. This observation has important implications for the classification and management of dementia in old age, both widening the spectrum of neurodegenerative diseases in the senium, and changing concepts of Lewy body disease in the elderly from a predominantly movement disorder (idiopathic Parkinson's disease) to one associated with wider neuropsychiatric disturbances involving impaired cognition, episodic confusion, and the development of dementia.

A major and complex issue raised by the present findings is the question of the co-existence of Alzheimer's and Parkinson's diseases. The data presented in Tables 1 and 2 suggest that whilst the classic neuropathological features of AD (combined numerous neocortical plaques and neurofibrillary tangles) are rare in PD, the neocortex does appear to be more susceptible to plaque formation in Lewy body disease than the normal elderly population. In contrast, neuropathology typical of idiopathic PD (severe (70–80%) neuron loss and Lewy body formation in SN) in elderly cases with Alzheimer-type dementia is not obviously increased on the basis of this and other reports (Molsa et al. 1984; Leverenz and Sumi 1986; Ditter and Mirra 1987). Despite distinct clinical and neuropathological differences between classical cases of Parkinson's and Alzheimer's disease, it has long been recognised that a minority of patients with either condition may in turn develop certain features of the other. Thus a proportion (20–50%) of patients with PD develop dementia (Lieberman et al. 1978; Boller 1980; Huber et al. 1986; Oyebode et al. 1986), either with (Hakim and Mathieson 1979; Boller et al. 1980) or without significant cortical Alzheimer-type pathology (Perry et al. 1985). Similarly, Alzheimer's disease is variously reported to be associated with parkinsonian movement disorder and at least some of the neuropathological features of Parkinson's disease (Pearce 1974; Forno et al. 1978; Rosenblum and Ghatak 1979; Gaspar and Gray 1984; Molsa et al. 1984; Leverenz and Sumi 1986) with estimates varying from a few to 50% of patients. In these reports many such cases were classified as either Alzheimer's or Parkinson's disease, or a subgroup or combination of the two. Whilst the relative lack of detailed clinical neuropsychiatric assessments and quantitative neuropathological data on cortical and subcortical regions restricts precise comparison with the cases classified in the present study, it is probable that these various reports include examples of the atypical cases identified in the present survey, which have been designated (on the basis of distinctive neuropathological and clinical features) as senile dementia of Lewy body type (SDLT, Perry et al. 1989a), part of the spectrum of Lewy body dementia. Within the spectrum of Lewy body diseases (Table 5, and Perry et al. 1989b) SDLT cases in this survey occupy an intermediate position (Tables 2 and 5) between DLBD and PD: DLBD being characterised by dense, anatomically widespread concentrations of cortical LB and SN pathology similar to classical PD

TABLE 5

SENILE DEMENTIA OF LEWY BODY TYPE[a]

Classified within the spectrum of Lewy body disease

Category	Distinctive clinical features	Lewy body prevalence
Parkinson's disease	Classical movement disorder (tremor, rigidity, akinesia) in a broad age range. Dementia developing in a minority (mainly elderly)	Primarily subcortical and brainstem; age or dementia related increase in limbic[b] cortex; absent/low densities in neocortical lobes
Senile dementia of Lewy body type	Fluctuating confusion/dementia in the elderly (over 65y), often with visual hallucinations and/or mild extra pyramidal features	Present in brainstem and subcortical areas; moderate numbers in limbic cortex; low densities with variable distribution in neocortical lobes
Diffuse Lewy body disease	Dementia, mainly in younger cases, usually associated with extrapyramidal features of Parkinson's disease	Anatomically widespread; high densities throughout cortex, including limbic & neocortex; also present in brainstem and subcortical regions
Intermediate or combined syndromes	Symptomatology not yet fully defined	Variable: PD or SDLT combined with Alzheimer's or vascular disease

[a] In the present series of 93 cases of dementia (over 70y), 18 fell into the SDLT category, 2 were diffuse Lewy body disease, 7 Parkinson's disease developing dementia, and 2 were classified as combined or intermediate syndromes. Substantia nigra neuron loss was less extensive in SDLT compared with Parkinson's disease and diffuse Lewy body disease; see text and Fig. 3. Lewy body distribution associated with the parkinsonian dementia complex of Guam, Hallervorden-Spatz disease, and psychotic states are not included in this series.

[b] Cortex associated with the limbic lobe, including amygdaloid, hippocampal and cingulate gyri.

(Okasaki et al. 1961; Yagishita et al. 1980; Yoshimura 1983; Kosaka et al. 1984), and PD representing as a movement disorder with a longer natural history and extensive (> 70%) SN neuron loss, but less intense cortical LB pathology compared with SDLT. Technically, the use of H&E stained sections with the composite counterstain (see Methods) proved a satisfactory, if somewhat laborious, method for identifying and quantifying cortical LB with comparable densities to those shown using anti-ubiquitin immunocytochemistry (see Fig. 1, legend). Identification of cortical LB using ubiquitin antisera should enable SDLT cases to be assessed more rapidly, but not necessarily more accurately, since small tangle-bearing neurons or corpora amylacea (both ubiquitin positive) may be misinterpreted as cortical LB. Nevertheless the report of a constant ratio between cortical LB densities demonstrated by H&E and ubiquitin reacted sections (Lennox et al. 1989a) further supports the data shown in Table 2, although correlations between tinctorial and immunocytochemical methods are dependent on

individual antisera/histological staining techniques used, factors which are currently being assessed in a larger series of cases (Lennox and Perry, unpublished).

The precise neurobiological correlates of the psychiatric syndrome in SDLT are not yet clearly defined although some are more likely than others. Thus whilst plaques, tangles, or Lewy bodies do not obviously relate to the severity of dementia as assessed by the MTS in the present series, a trend in which increasing plaque density related to decreasing MTS was noted. Previous studies of idiopathic PD have also established that neocortical Alzheimer-type pathology is not invariably correlated with the presence and severity of dementia in PD (Alvord et al. 1974; Hakim and Mathieson 1979; Boller et al. 1980; Gaspar and Gray 1984; Chui et al. 1986; Gibb and Lees 1987; Perry et al. 1987; Xuereb et al. 1987) and although a Parkinson dementia syndrome associated with anatomically widespread high densities of cortical Lewy bodies – DLBD (see above) shows similar symptoms to those reported in this study, the cortical Lewy body density is many times higher than in SDLT cases (Table 2; see also Perry et al. (1989b) and Lennox et al. (1989b). Low densities or occasional Lewy bodies in the cortex are unlikely to correlate directly with dementia in SDLT, since cortical Lewy bodies are found in many elderly, non-demented PD cases (Table 2; and Perry, R. H., unpublished). It is also of interest to note that decreased LC noradrenergic neuron density (Fig. 3) is a more consistent finding in SDLT than SN dopaminergic neuron loss, a finding dissimilar to both PD and DLBD. Other potential correlates of parkinsonian dementia reported include: degeneration of cholinergic neurons in the nucleus of Meynert (Candy et al. 1983; Whitehouse et al. 1983; Perry et al. 1985), and degeneration of cortically projecting dopaminergic or noradrenergic neurons (Jellinger and Riederer 1984; Dubois et al. 1987). Although no clear correlation between mental impairment and the neuropathological features of SDLT has been found in the present series, future investigations should include a more detailed analysis of subcortical and cortical brain areas and tests of mental function more applicable to this atypical group.

Neurochemically, a relationship exists between dementia in PD and involvement of the basal forebrain cholinergic system (Whitehouse et al. 1983; Perry et al. 1985); other sub-cortical cholinergic nuclei, such as brain stem pedunculopontine neurons (Sugimura and Hattori 1984), may also contribute to mental symptoms in SDLT. Analysis of neocortical (parietal) choline acetyltransferase (ChAT) in controls and demented cases in this series revealed a 74, 70, and 60% reduction in SDLT, PD and SDAT cases, respectively. In 7 SDLT cases there was a significant correlation with MTS ($r = 0.90$, $P < 0.01$), supporting the concept of a major cholinergic derangement in this group (Irving et al. 1989). Interestingly, neurochemical analysis of 6 cases with hallucinations in the SDLT group revealed significantly greater ChAT loss (85%) compared with 5 non-hallucinating cases (53%, $P < 0.05$). The occurrence of hallucinations may be, therefore, a clinical index of severe cholinergic degeneration and the relative absence of neocortical tangles in the SDLT cases raises the question of whether "responders" in clinical trials of cholinergic drugs (e.g., Summers et al. 1986), may belong to the atypical/SDLT category.

In psychiatric practice it is often difficult to be certain of the precise aetiological diagnosis in elderly demented patients, since cerebral pathology varies from the

"classical" description of AD, MID, PD, Pick's and other diseases to an admix of pathological change which may influence the clinical presentation in individual cases. An important question arises as to whether the atypical group identified here neuropathologically is a recognisable clinical entity. As a group there are certainly differences in the clinical presentation compared with SDAT cases, but it remains to be established whether these are sufficiently precise to allow a definite diagnosis in individual cases. Compared with SDAT, at initial presentation the atypical group demonstrated symptoms which are more likely to arise acutely, and the patients are more cognitively preserved on referral as judged by both Mental Test ability and measures of dependency (CGBRS); they are also more likely to have a shorter history and survival time. Clinicians using Hachinski's scheme for identifying MID may assign such a diagnosis in perhaps a quarter to a third of the cases described here. A clinical diagnosis of Alzheimer's disease based on the typical presentation of slowly progressive memory impairment and dementia will rarely be considered in the SDLT group. Mild extrapyramidal features will commonly be found as the disease progresses, but the patient will not usually be diagnosed as suffering from Parkinson's disease nor warrant appropriate anti-parkinsonian drug treatment. Although the assessment of distinctive symptoms and signs in individual cases will be dependent on the stage of the illness, retrospective analysis of clinical features in the present series suggests that atypical presentation reflects atypical pathology, and that this may be more common than has been hitherto suspected.

Given the prevalence of dementia in the elderly (13% above 75 years; Kay et al. 1978) and the number of patients with SDLT in the current Newcastle dementia survey (19%), it is likely that patients with this syndrome represent the largest single category of the population with Lewy body disease (approx. 2–3% of the total population aged 75 years), exceeding the reported clinical prevalence of 1% for idiopathic Parkinson's disease in the senium (range 0.5–1.9% in 7 surveys; reviewed by Marttila and Rinne 1976). Further, if the total number of patients with Lewy body disorders associated with dementia in this Newcastle survey (including DLBD, Parkinson's disease, combined Alzheimer's and Parkinson's disease; Table 1), are included as examples of Lewy body dementing disorders occurring in the senium, the prevalence of Lewy body-associated dementing diseases increases to 25% of the elderly demented population. Since Lewy body formation is not, in contrast to plaques and tangles, a common feature in the brains of the normal elderly population (2.3% in a series of 131 controls over 50 years without any established history of neurological or psychiatric illness; Perry, R. H. and Irving, D., unpublished results), intriguing questions are raised regarding the aetiopathological significance of LB and their relationship with neurodegenerative dementing syndromes.

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Tangles and Plaques in Nondemented Aging and "Preclinical" Alzheimer's Disease

Joseph L. Price, DPhil,*† and John C. Morris, MD†‡§

The distribution and density of neurofibrillary tangles and amyloid plaques was studied in a unique series of cases whose premortem cognitive status had been assessed with the Clinical Dementia Rating (CDR), including 39 nondemented cases (CDR = 0; age, 51–88 years), 15 very mildly demented cases (CDR = 0.5), and 8 severely demented (CDR = 3) cases. The initial formation of tangles and plaques in healthy aging appeared to be independent of each other. Tangles were found in all the nondemented cases, especially in hippocampal and parahippocampal areas; the average tangle concentration increased exponentially with age. In contrast, plaques were absent in some brains up to age 88, and the earliest plaque formation in other cases occurred in the neocortex, in patches of diffuse plaques. Widely distributed neuritic as well as diffuse plaques throughout neocortex and limbic structures characterized a further group of nondemented cases. In these cases there was also a substantial increase over other nondemented cases, both in the number of tangles and in the rate of increase in tangles with age, suggesting an interaction between amyloid and neurofibrillary change at this stage. Such cases closely resemble CDR = 0.5 cases, and it is proposed they represent "preclinical" Alzheimer's disease.

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It is generally recognized that the incidence of Alzheimer's disease (AD) is age related, increasing exponentially after the sixth decade of life.[1] Neurofibrillary tangles and β-amyloid plaques are commonly reported to occur in the brains of aged individuals, even without clinical criteria for AD.[2–4] Despite this, recent studies have suggested that when AD or other disorders are carefully excluded, aging itself may not result in substantial cognitive or neuronal loss.[5–7]

In contrast, even the mildest stage of dementing change may indicate the presence of AD, as supported by sufficient plaques and tangles for pathological diagnosis of the disease,[8,9] and substantial neuronal loss in vulnerable areas such the entorhinal cortex[6]. To define the pattern of tangle and plaque formation during healthy aging, it is necessary to identify and study individuals without even very slight cognitive or memory impairment. We have an opportunity to study these issues, because of availability of a unique series of nondemented and very mildly demented cases who were assessed with the Clinical Dementia Rating (CDR).[10] This instrument is sensitive enough to identify nondemented cases accurately, as well as to recognize the earliest clinically detectable stage of AD (CDR = 0.5).[8,11–13]

In addition, it is very likely that there is a "preclinical" stage of AD, where the disease is present neuropathologically but has not produced any clinically detectable cognitive change. Because cases at the threshold for clinical detection of dementing change (CDR = 0.5) already have large numbers of tangles and plaques, as shown by several previous studies,[8,9,14,15] the initial development of AD and the earliest formation of tangles and plaques must occur before any detectable cognitive change. Well-characterized nondemented cases (CDR = 0) may therefore be expected to divide into two groups, "healthy" aging cases without changes that are characteristic of AD, and preclinical cases with substantial AD-related lesions. Recognition and characterization of a preclinical stage has important implications for treatment. If AD is well-established pathologically before it can be detected clinically, therapeutic interventions will need to focus on prophylaxis to be fully effective, as diagnosis may come too late to allow AD lesions to be reversed.

Materials and Methods

Selection and Collection of Material

The observations here were made on 39 nondemented cases without any indication of cognitive change (CDR = 0; 21

From the Departments of *Anatomy and Neurobiology, ‡Neurology, and §Pathology, and †Alzheimer's Disease Research Center, Washington University School of Medicine, St Louis, MO.

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Address correspondence to Dr Price, Department of Anatomy and Neurobiology, Washington University School of Medicine, 660 S. Euclid Avenue, St Louis, MO 63110.

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male and 18 female), 15 cases with very mild dementia (CDR = 0.5; 8 male and 7 female), and 8 severely demented cases (CDR = 3; 4 male and 4 female). The age at death of the nondemented cases ranged from 51 to 93 years, including 26 cases age 75 and older and 13 cases younger than 75 (Table 1). The age at death of the very mildly demented cases ranged from 75 to 95, closely corresponding to the ages of the older nondemented group. The severely demented cases were age 62 to 95 years. None of the cases were members of AD kindreds with known genetic mutations. Those with dementia met clinical research inclusionary and exclusionary diagnostic criteria for dementia of the Alzheimer type that have a diagnostic accuracy rate for neuropathological confirmation of AD of 93%.[13] The brains were also evaluated with a standard neuropathological battery; none of the demented cases had indications of Parkinson's disease or other neurological or psychiatric disorders that might have contributed to the cognitive change. The apolipoprotein E genotype was available for 28 of the 62 cases studied. The occurrence of the ε4 allele was relatively high in the CDR = 3 cases (8 of 12 alleles determined), but no other effect of the apolipoprotein E genotype was apparent.

The CDR of each of the cases was determined by clinicians in the Memory and Aging Project of the Washington University Alzheimer's Disease Research Center.[10] A CDR score of 0 indicates no dementia, and CDR scores of 0.5, 1, 2, and 3 indicate very mild, mild, moderate, and severe dementia, respectively. The CDR score is derived from semistructured clinical interviews, and is assigned without reference to psychometric test results or to any postmortem neuropathological findings. Although CDR = 0.5 has previously been characterized as "questionable" dementia, in the carefully characterized subjects enrolled for our studies the designation of CDR = 0.5 is a dependable predictor of progression to more severe stages of dementia[8,12] and correlates with histopathological AD.[8,11,13] In these circumstances and with our highly selected sample, CDR = 0.5 appears equivalent to very mild dementia.

Two closely related assessment methods were used. The subjects of 40 cases were enrolled in a longitudinal study and were assessed before death using interviews with the subject and an informant. All subjects were assessed annually, and the last assessment was within a year of their death. At entry and every 2 years thereafter, the assessment was videotaped for independent review by a second clinician. In a few cases, there was disagreement about whether the CDR was 0 or 0.5 because of differences either between the two clinicians who assessed the interview or between the final and penultimate assessments.[11] Such cases were designated CDR = 0/0.5. The 40 cases assessed premortem included 22 CDR = 0 cases, 5 CDR = 0/0.5 cases, 6 CDR = 0.5 cases, and 7 CDR = 3 cases.

Table 1. Subjects Grouped by CDR and Age

CDR and Age Group	Median Age (Range), yr	n
CDR = 0, age < 75 yr	62 (51–73)	13
CDR = 0, age ≥ 75 yr	82 (75–93)	26
CDR = 0/0.5	88 (75–95)	8
CDR = 0.5	89 (75–95)	7
CDR = 3	79 (62–95)	8

CDR = Clinical Dementia Rating.

Cognitive status was also assessed with a validated retrospective postmortem interview with an informant.[16] For the 40 cases assessed premortem, this provided a CDR for the subject's cognitive ability just before the terminal events leading to death. The same validated postmortem interview[16] was used in an additional 23 cases (17 cases CDR = 0; 2 cases CDR = 0/0.5; 1 case CDR = 0.5; and 3 cases CDR = 3) from whom brain tissue was obtained from either the autopsy service of Barnes Hospital or the body donation program of the Department of Anatomy and Neurobiology of Washington University. In these cases, a CDR was assigned from the information provided by the interview. These cases were used to supplement the cases assessed premortem, especially for younger CDR = 0 cases. Retrospectively assessed cases constituted 78% of younger CDR = 0 cases (age <75 years), 25% of older CDR = 0 cases (age ≥75 years), 20% of CDR = 0.5 cases, and 43% of CDR = 3 cases. Within each group, the age of the retrospectively assessed cases did not differ substantially from the age of the premortem assessed cases.

In all cases designated CDR = 0/0.5, plaques and tangles were present in sufficient densities for a neuropathological diagnosis of AD. The CDR = 0/0.5 cases comprise 8 of the 15 very mildly demented cases in this series. Data from the CDR = 0/0.5 and CDR = 0.5 cases are presented separately in Figures 5 and 7. Because the histological findings on the two groups were so similar, however, the data were grouped together (as CDR = 0.5) in other analyses.

Histological Procedures

The brains were fixed by immersion in buffered 10% formalin, cut into coronal slices about 1 cm thick, and then cut into smaller blocks for sectioning. In most cases blocks were taken from the ventral part of the cerebral hemisphere, from the posterior orbital cortex through the basal forebrain, the insula, and the entire temporal lobe. Sections were cut at 50 mm on a freezing microtome, and divided into series of 1 in 22 for staining.

In all cases, series of sections were stained with a modified Bielschowsky reduced silver method optimized for fixed frozen sections.[9] These sections were used for all of the quantitative analyses described below. Adjacent sections were stained by the Nissl method for correlation with brain cytoarchitecture.

In addition, all observations were confirmed qualitatively with immunohistochemistry. Sections adjacent to the silver-stained sections that had been selected for mapping and quantitative analysis (see below) were stained with antibodies against β-amyloid (anti-A4 antiserum, gift of Dr Colin Masters; monoclonal antibody "Angela," gift of Dr Dennis Selkoe; or monoclonal antibody "10D5," gift of Athena Neurosciences), and with antibodies against paired helical filaments (monoclonal antibody "Pam," gift of Dr Dennis Selkoe, or monoclonal antibody "PHF-1," gift of Drs Sharon Greenberg and Peter Davies). In many cases, an additional series of sections was stained immunohistochemically with

the Alz-50 antibody (gift of Dr Peter Davies). Although the Bielschowsky silver stain was the most consistent across all the cases studied, and was therefore used for the quantitative analyses, in many cases the immunohistochemical stains (especially with antibody 10D5 for amyloid and antibody PHF-1 for paired helical filaments) were more sensitive. In a few cases, apparent plaques could not be confirmed with the immunohistochemical stains; on careful examination, these were found to be artifacts of the silver stain.

Methods of Analysis

Amyloid plaques, as demonstrated by the Bielschowsky silver method, were divided into two types, diffuse and neuritic. Diffuse plaques were flocculent depositions of amyloid, without any inclusion of thickened, dark-staining neurites, or a dense central core. They ranged from small, rounded structures to large, irregular complexes. Any stained neurites running through these plaques were normal in diameter and appearance. Neuritic plaques were defined as those with thickened, darkly stained, and often contorted neurites within or extending from the region of amyloid deposition, and/or with a dense β-amyloid core. Double immunohistochemical staining with two antibodies (one against β-amyloid and one against paired helical filaments) was used in some brains to confirm that the dystrophic neurites within neuritic plaques contain the same paired helical filaments found in tangles. For purposes of analysis, no distinction was made between intracellular and extracellular tangles.

The distribution of tangles, plaques, and immunoreactive cells was mapped from silver-stained sections with the aid of a computerized microscope digitizer (Minnesota Datametrics, St Paul, MN), as described previously.[9] An accessory computer program allowed the number and density of markers to be measured within defined areas. The structures sampled included the anterior olfactory nucleus and other olfactory cortical areas, the nucleus basalis of Meynert, the amygdaloid nuclei, the entorhinal cortex and other parts of the hippocampal formation, the posterior orbital cortex, and most of the insular and temporal cortex. Depending on differences in tissue availability and structure size, each structure was sampled from one to four times in each brain.

To compare the patterns of tangle distribution between cases with different numbers of tangles due to age or level of dementia, areas were ranked in order of tangle density within each brain. The area with the highest tangle density was rated first, and so on. Areas with the same tangle density (eg, areas that had no tangles) were given the same, averaged rank.

Results

As observed previously from a smaller set of cases,[9] the pattern of tangle formation in aging nondemented brains is very different from that of plaques. At least a few tangles were found in vulnerable areas of all aging brains, beginning in at least the sixth decade of life. Plaques, in contrast, were found in only a fraction of nondemented cases and were absent from some brains even in the late 80s. Furthermore, tangles occurred preferentially in specific parts of the hippocampus and related structures (especially the entorhinal and perirhinal cortical areas and field CA1), but plaques were found in neocortical areas. Because of these differences in both incidence and distribution, tangles and plaques are described in separate sections. In a third section, possible interactions between plaques and tangles are considered.

Tangles

NONDEMENTED CASES (CDR = 0)

Variation in tangle density with age. In the nondemented cases younger than 75 years, there were relatively small numbers of tangles, although at least a few tangles were found in all cases, especially in the perirhinal and entorhinal cortex (Fig 1) and in the anterior olfactory nucleus. Other limbic areas, including field CA1 of the hippocampus, consistently had many fewer, if any, tangles in these younger cases. There were almost no tangles in the neocortex or in the nucleus basalis of Meynert.

In the nondemented cases aged 75 years or older, there were greater numbers of tangles but the distribution was very similar to that in the younger cases (see Fig 1). Many tangles were again found in the entorhinal and perirhinal cortex and, in contrast to the younger cases, there were also many tangles in hippocampal field CA1. A few tangles were found in the neocortex, especially in the inferior temporal cortex.

The age-related increase in tangles in nondemented cases is exponential (Fig 2A), indicating that the rate of tangle formation increases with age, especially after age 70. There is also an increase in variability with age. Some of the older cases had large numbers of tangles, but others had low tangle densities that were comparable with those in younger cases. Although some of the nondemented cases also had amyloid plaques that might have influenced tangle formation, the same pattern of tangle density with age was also seen in 21 nondemented cases without plaques (although there is an increase in the average number of tangles in cases with plaques; see below) (see Fig 2B). Thus, a highly significant, exponential increase in tangle density occurs in nondemented aging, with or without plaques.

Pattern of distribution of tangles. As described in Materials and Methods, a rank order analysis was used to compare the patterns of distribution of tangles in brains with different ages. As expected, this analysis showed that the distribution of tangles was very similar in younger and older groups of cases, despite the marked differences in the number of tangles at different ages (Fig 3). The entorhinal cortex, perirhinal cortical area 35, and the anterior olfactory nucleus had the highest concentrations of tangles and there was a much lower density of tangles in hippocampal field CA3, the subiculum, the piriform cortex, the nucleus basalis of

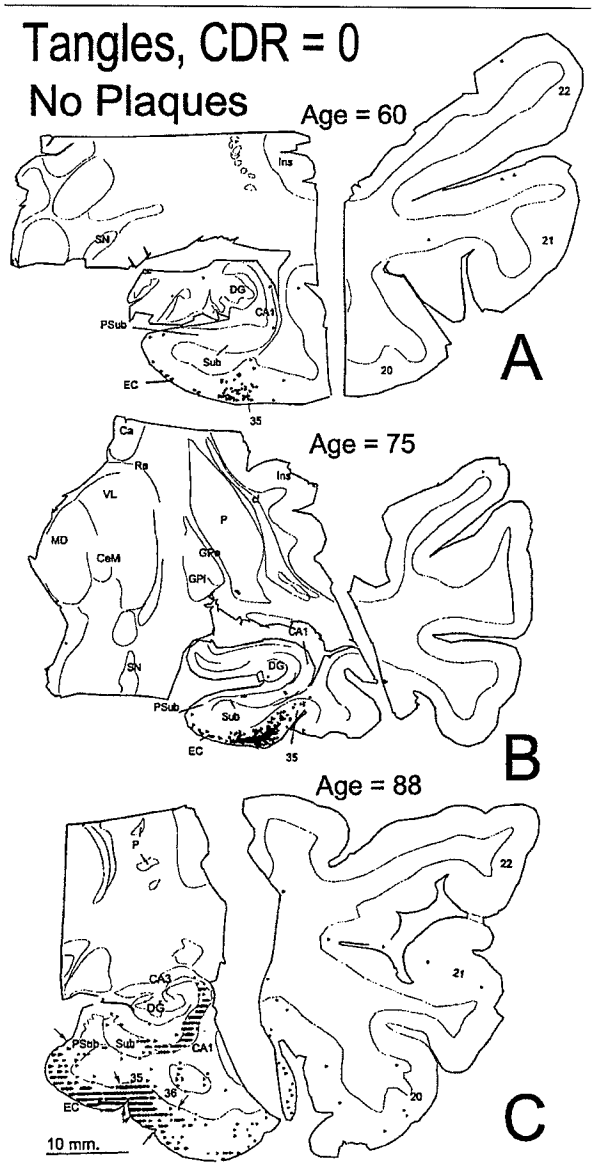

Fig 1. Maps of neurofibrillary tangles from sections through the temporal lobe of 3 CDR = 0 cases of different ages. Each dot represents one tangle. None of these cases had any plaques. The number of tangles increases with age, although the pattern of distribution is about the same. CA numbers = hippocampal fields; other numbers = Brodmann areas (20 = inferior temporal cortex; 21 = middle temporal cortex; 22 = superior temporal cortex; 35 = perirhinal cortex; 36 = perirhinal cortex); Ins = insula; SN = substantia nigra; DG = dentate gyrus; PSub = presubiculum and parasubiculum; Sub = subiculum; EC = entorhinal cortex; Ca = caudate nucleus; Re = reticular nucleus of thalamus; VL = ventrolateral nucleus of thalamus; P = putamen; MD = mediodorsal nucleus of thalamus; CeM = centromedian nucleus of thalamus; GPe = globus pallidus, external division; GPi = globus pallidus, internal division. CDR = Clinical Dementia Rating.

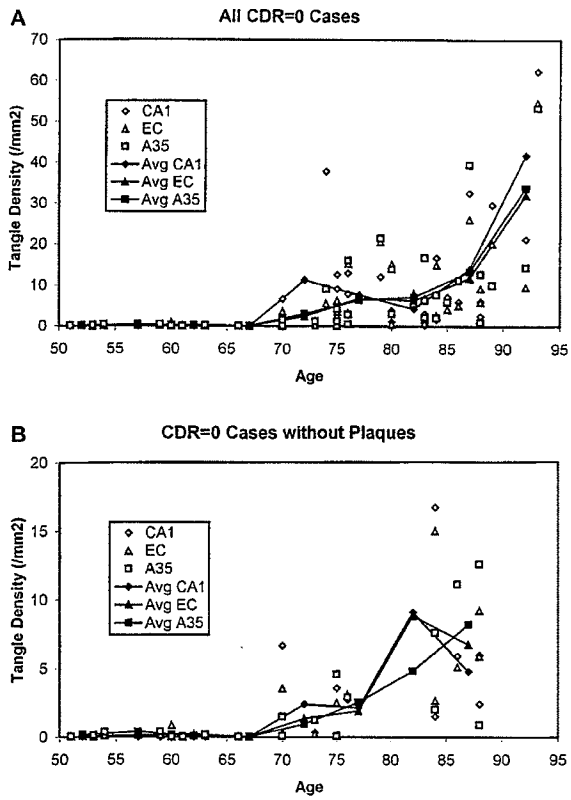

Fig 2. Graphs of the density of tangles in three limbic areas, as a function of age in nondemented (CDR = 0) cases. The open symbols *represent values for each area from individual brains. The* lines connecting the filled symbols *represent the average value for all cases within each 5 years of age. (A) Data from all cases rated CDR = 0. Spearman rank correlation:* r = *0.78, 0.77, and 0.70, for the entorhinal cortex (EC), perirhinal cortex (A35), and CA1, respectively;* p < *0.001, for all three areas. (B) Data from only those cases in which no amyloid plaques were detected with silver or immunohistochemical stains. Spearman rank correlation:* r = *0.79, 0.70, 0.77 for the entorhinal cortex, perirhinal cortex, and CA1, respectively;* p < *0.001, for all three areas. Note that although the younger cases all had tangles, they were too few to register on this scale. CDR = Clinical Dementia Rating.*

Meynert, and the neocortical areas. The only significant difference between younger and older cases was that hippocampal field CA1 and the periamygdaloid cortex developed tangles at relatively older ages. Thus, field CA1 and the periamygdaloid cortex had few tangles in the younger cases but ranked among the most affected areas in the brains of those cases aged 75 years or older (see Fig 3). The apparent difference in neocortical areas (temporal cortical areas 20, 21, and 22, and the orbital and insular cortex) was due to the virtual absence of tangles in the neocortex in younger brains, such that no distinctions were apparent between them. As tangles developed in these areas in the older

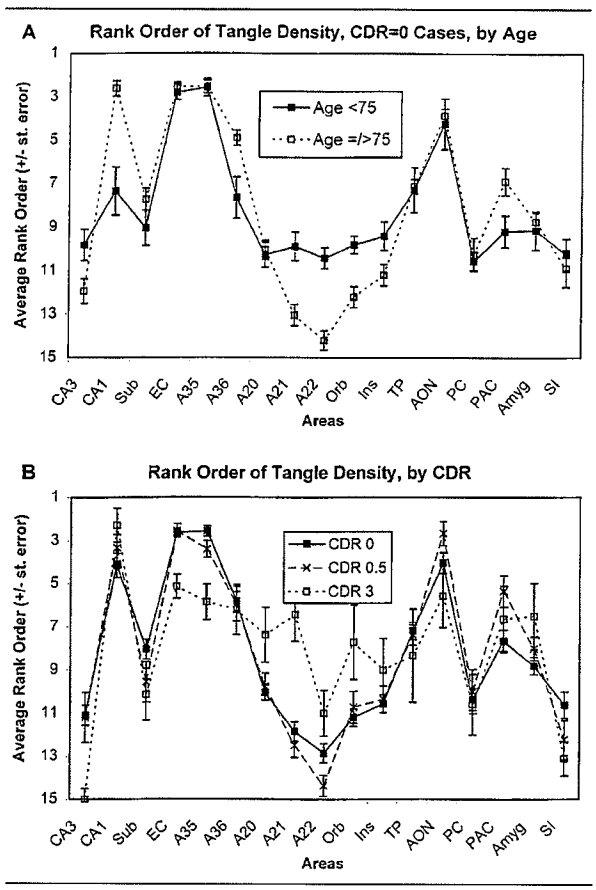

Fig 3. Graphs illustrating the distribution of tangles across 17 brain areas, expressed as the rank order of each area (see Materials and Methods). Those areas with the highest tangle density within each brain are ranked near 1, areas with progressively fewer tangles had numerically larger ranks. The rank orders are averaged across two age groups (age < 75 years and age ≥ 75 years) in A, or across CDR groups (CDR = 0, CDR = 0.5, and CDR = 3) in B. The error bars represent SEM values. The patterns are similar, despite that the number of tangles increases markedly across the age and CDR groups (see text). CA numbers = hippocampal fields; A numbers = Brodmann areas (A20 = inferior temporal cortex; A21 = middle temporal cortex; A22 = superior temporal cortex; A35 = perirhinal cortex; A36 = perirhinal cortex); Sub = subiculum; EC = entorhinal cortex; Orb = orbital cortex; Ins = insular cortex; TP = temporal polar cortex; AON = anterior olfactory nucleus; PC = piriform cortex; PAC = periamygdaloid cortex; Amyg = amygdala; SI = substantia innominata (nucleus basalis of Meynert).

brains, it became apparent that the inferior temporal area 20 and the orbital and insular cortex had more tangles than the middle and superior temporal areas 21 and 22. Even with these differences, the correlation between the rank order values for the two age groups was highly significant (linear correlation coefficient $r = 0.85$, $p < 0.001$).

VERY MILDLY DEMENTED CASES (CDR = 0/0.5 OR 0.5). No difference was found in the number or distribution of tangles in CDR = 0/0.5 and CDR = 0.5 cases. Both groups of very mildly demented cases had more tangles, distributed over a wider region than found in most of the older nondemented cases (Fig 4), although there was overlap in individual cases (see below; see Fig 7). The very mildly demented cases consistently had high tangle densities in vulnerable areas such as the entorhinal or perirhinal cortex, with lower numbers of tangles in the neocortex. The increase in tangle density with age seen in nondemented cases was not found in the very mildly demented cases, presumably because the age effect has been overwhelmed by a disease effect in these cases. As shown by the rank order comparison, the qualitative pattern of distribution of tangles in CDR = 0.5 cases was the same as in the nondemented cases (see Fig 3B).

SEVERELY DEMENTED CASES (CDR = 3). In the severely demented cases, the density of tangles increased further over that seen in very mildly demented cases, although there was still some overlap between individual cases (see Fig 8). The patterns of distribution of tangles in the CDR = 3 cases, as shown by the rank order analysis, were very similar to that in the CDR = 0 and CDR = 0.5 cases (see Fig 3B). The only noteworthy difference was that the much greater number of tangles throughout many parts of the brain decreased the variation between areas.

Plaques

NONDEMENTED CASES (CDR = 0). Substantial differences in the number and distribution of plaques were found in the nondemented cases. Because these differences were very distinct, the nondemented cases were most readily analyzed in three groups (A, B, and C), based on the qualitative differences in the type, and distribution of plaques (Table 2). Although the three groups also differ in the number of plaques, quantitation of plaques is uncertain because of their large variation in size and shape. The use of clear, qualitative criteria allows stages in the development of plaques to be distinguished that are independent of precise numbers.

Group A had no plaques in any part of the forebrain, in sections stained either with the modified Bielschowsky silver method or with antibodies against β-amyloid. This group consisted of the 13 younger cases (age, 51–73 years) and 8 of the 26 older nondemented cases (age, 75–88 years) (see Table 2). Group B consisted of 11 of the 26 cases aged 75 years or older (see Table 2). These cases had relatively few amyloid plaques, all of which were diffuse in type and were distributed in restricted patches in the neocortex (Figs 5 and 6A–C). Across the different brains, the patches

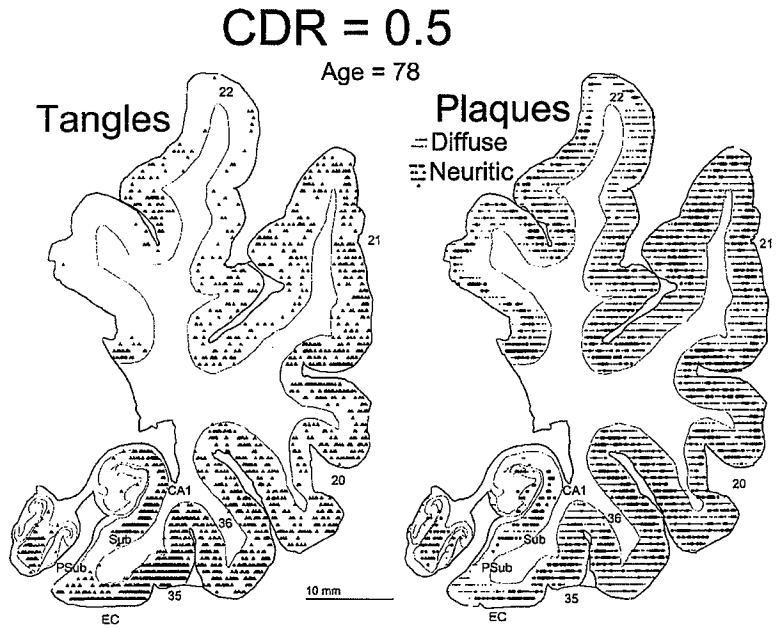

Fig 4. Maps of neurofibrillary tangles and amyloid plaques in a section through the temporal lobe from a typical CDR = 0.5 case. Each small triangle *(on the left side) represents one tangle, and each* dot *(on the right) represents one plaque. Diffuse plaques are shown by small dots, while neuritic plaques are designated by larger dots. Tangles are concentrated in the entorhinal cortex, perirhinal cortex (area 35), and hippocampal field CA1, and plaques are most concentrated in neocortical areas 36, 20, and 21. Numbers = Brodmann areas (20 = inferior temporal cortex; 21 = middle temporal cortex; 22 = superior temporal cortex; 35 = perirhinal cortex; 36 = perirhinal cortex); CA1 = hippocampal field CA1; Sub = subiculum; PSub = presubiculum and parasubiculum; EC = entorhinal cortex.*

Table 2. Nondemented (CDR = 0) Subjects Grouped by Plaque Type

	Median Age (Range), yr	n	Plaque Type	Number	Distribution
Group A, age < 75 yr	63 (51–73)	13		None	
Group A, age ≥ 75 yr	84 (75–88)	8		None	
Group B	83 (75–92)	11	Diffuse only	Few	In patches
Group C	78 (75–93)	7	Neuritic/diffuse	Many	Extensive

CDR = Clinical Dementia Rating.

varied from a few small areas with relatively few plaques to more extensive areas with a higher plaque density. The patches tended to be located within sulci, but they were not consistently concentrated in any given cortical region.

In the third group (Group C), made up of 7 of the 26 cases older than 75 (see Table 2), there were neuritic plaques as well as diffuse plaques, distributed extensively in large numbers across the neocortex (see Figs 5 and 6D). In addition, there were also many plaques in limbic structures, especially the entorhinal and perirhinal cortex. In the neocortex, most plaques were diffuse in type, but in limbic structures, a much higher percentage of plaques were neuritic (see Fig 5). In these respects, cases in Group C resembled the very mildly demented cases (CDR = 0.5, see below). Although the mean density of neocortical plaques in Group C was lower than in CDR = 0.5 cases, there was overlap between individual cases. As discussed below, the cases in Group C are presumed to be preclinical cases of AD.

VERY MILDLY DEMENTED CASES (CDR = 0/0.5 AND 0.5). The very mildly demented cases had substantial numbers of both diffuse and neuritic plaques distributed widely throughout the cerebral cortex (see Fig 4). There was little or no difference between the CDR = 0/0.5 and CDR = 0.5 groups (see Fig 5). Most plaques in the neocortex were diffuse in type, although there was a sizable number of neuritic plaques.

The limbic areas, especially the hippocampus, had relatively fewer plaques than the neocortical areas (see Figs 4 and 5). The plaque density in the amygdaloid nuclei and the entorhinal and perirhinal cortex was moderate, but the average plaque density in hippocampal field CA1 and the subiculum was less than one-third of that in the temporal, insular, or orbital cortex. As in the nondemented Group C, the proportion of plaques that were neuritic was substantially higher in the limbic areas than in the neocortex (see Fig 5).

SEVERELY DEMENTED CASES (CDR = 3). In severely demented cases, there was little if any change in the total

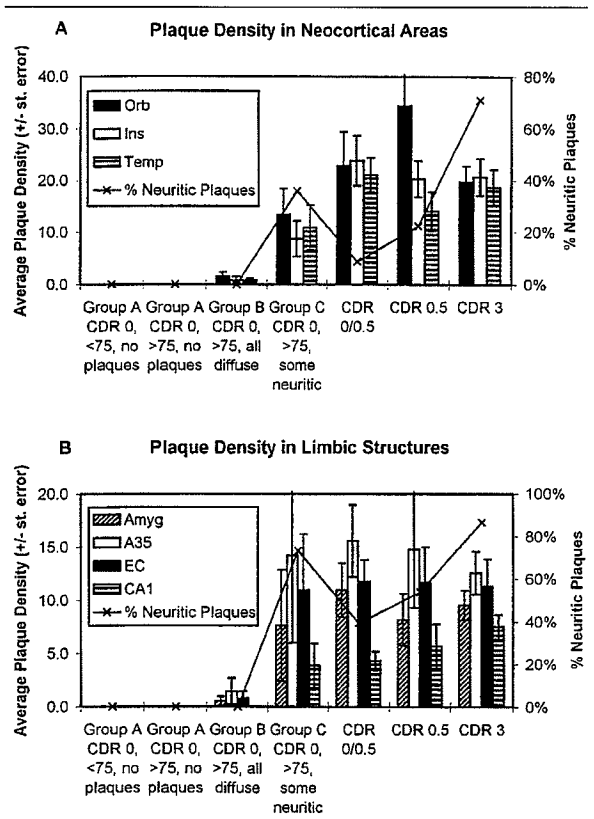

Fig 5. Graphs of plaque density in the orbital (Orb), insular (Ins), and temporal neocortex (Temp) (A) and in the amygdala (Amyg), perirhinal cortex (area 35, A35), entorhinal cortex (EC), and hippocampal field CA1 (B). The CDR = 0 cases are divided into the following three groups: Group A, with no plaques (subdivided between cases age <75 years and cases age ≥75 years); Group B, with only diffuse plaques; and Group C, with neuritic and diffuse plaques. The line depicts the percentage of plaques that are neuritic in each group.

density of plaques over those seen in very mildly demented cases, with almost complete overlap between individual cases (see Fig 5). There was a shift in the type of plaques, however, to an increased proportion of neuritic plaques and a commensurate decrease in the proportion of diffuse plaques, especially in the neocortex.

Tangle Formation as a Function of Plaque Density

The description above indicates that the earliest formation of tangles is separate from that of plaques. Observations in Down syndrome and familial forms of AD in which changes in β-amyloid and amyloid precursor protein result in neurofibrillary as well as amyloid changes,[17] however, strongly suggest that there is interaction between amyloid deposition and neurofibrillary changes at a subsequent stage. The density of tangles in the entorhinal cortex, perirhinal cortical area 35, hippocampal field CA1, and the temporal neocortex of nondemented cases was therefore analyzed as a function of Groups A, B, and C (Fig 7). This analysis showed that there is an increase in the age-related accumulation of tangles in cases with substantial numbers of plaques.

As expected from the description above, the younger cases in Group A (age, <75 years) had relatively few tangles in the entorhinal cortex, perirhinal cortical area 35, and the hippocampal field CA1, and virtually none in the temporal cortex (see Fig 7). In keeping with the increase in tangles with age (described above), there were significantly more tangles in the older cases (≥75 years), either those with no plaques (Group A) or those with patches of diffuse plaques (Group B). The presence of diffuse plaques in Group B was associated with a slight but not significant increase in average tangle density over the older cases in Group A. On the other hand, in Group C, the substantial number of neuritic and diffuse plaques was associated with a substantial and significant increase in tangle density in both limbic areas and the temporal neocortex. Approximately the same density of tangles was found in the very mildly demented cases (CDR = 0/0.5 and CDR = 0.5), with no significant difference between Group C and the CDR = 0/0.5 or CDR = 0.5 groups (see Fig 7). In the severely demented cases (CDR = 3), there was a further, significant increase in tangle density.

By plotting tangle density versus age for Groups A, B, and C, it was also possible to analyze the interaction between plaque deposition and the age-related rate of formation of tangles (Fig 8). The slope of a linear regression line fitted to these plots provided an estimate of the increase in tangles per year of age (see Fig 8A). As expected from the results described above, among the cases with no plaques (Group A), there was a higher rate of increase in tangle density with age in the older cases (≥75 years) than in the younger cases, both in limbic structures (the entorhinal cortex, perirhinal cortical area 35, and the hippocampal field CA1) and in the temporal neocortex (see Fig 8B). The rate of increase in tangle density was slightly greater in the cases with patches of diffuse plaques (Group B). In Group C, with many more plaques, there was a marked increase in the rate of tangle accumulation. This suggests that the deposition of amyloid plaques accelerates the age-related formation of tangles.

Discussion

These observations on carefully assessed nondemented cases indicate that the initial formation of tangles is separate from that of plaques, both spatially and temporally. Tangles form preferentially in the limbic structures, and plaques form first in the neocortex. At least a few tangles were found in all brains examined, and the average tangle density increases with age, even in the absence of plaques. In contrast, plaques were not

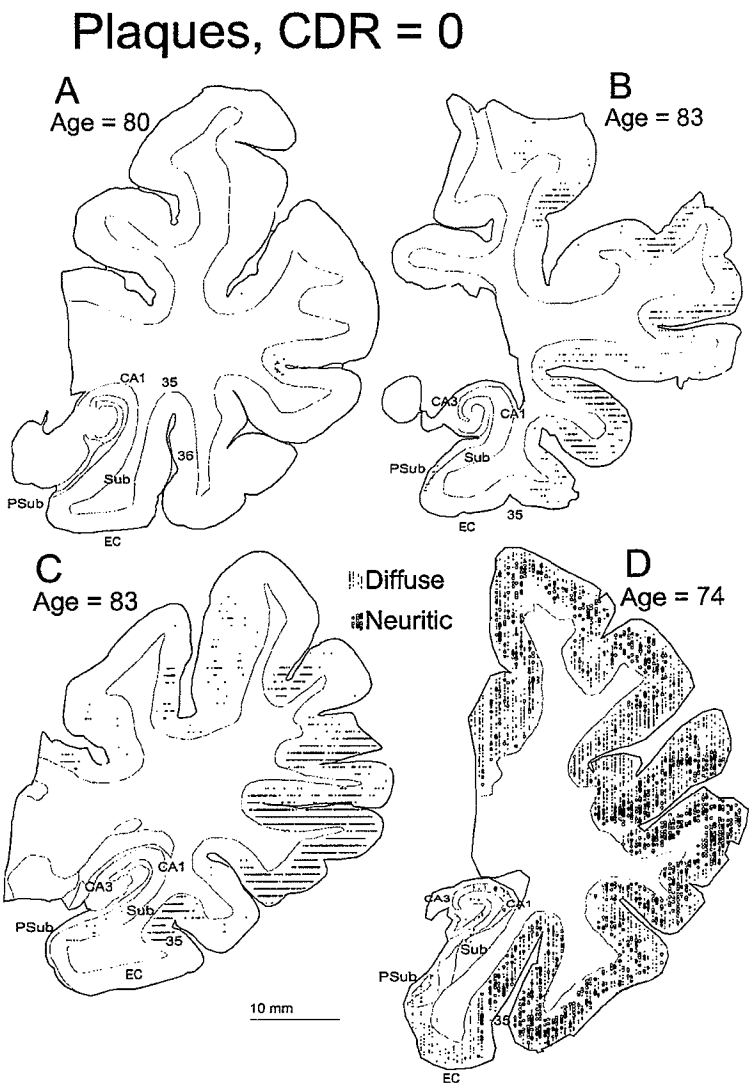

Fig 6. Maps of the distribution of amyloid plaques in sections through the temporal lobe of 4 CDR = 0 cases. (A, B, and C) Representative cases from Group B, with patches of diffuse plaques in parts of the temporal cortex. The case in A has only a very small patch of plaques, whereas B and C have larger, multiple patches. (D) Representative case from Group C, with widespread neuritic and diffuse plaques. Small dots *represent diffuse plaques, and the* larger circles *represent neuritic plaques. CA numbers = hippocampal fields; other numbers = Brodmann areas (35 = perirhinal cortex; 36 = perirhinal cortex); Sub = subiculum; PSub = presubiculum and parasubiculum; EC = entorhinal cortex.*

found in some cases as old as age 88. We conclude that the initial formation of tangles and the earliest amyloid deposition in plaques are independent events.

Subsequently, however, there appears to be interaction between amyloid and neurofibrillary changes. The deposition of large numbers of plaques in a subset of nondemented cases (Group C) is associated not only with the development of dystrophic neurites within neuritic plaques, but also with an increase in both the number of tangles and the rate of tangle formation with age. Because the pattern of distribution of tangles is the same with or without plaques, the apparent effect of amyloid is to accelerate an age-related tauopathy, which is otherwise relatively slow.

We propose that the nondemented cases with neuritic plaques (Group C) represent preclinical AD. The existence of a preclinical group must be postulated because the CDR = 0.5 cases, at the threshold of very mild dementia, all contain large numbers of tangles and plaques.[8,9] Because these lesions accumulate relatively slowly, the disease process must begin at an earlier stage, before clinical detection is possible. As expected for preclinical AD cases, the cases in Group C closely resemble CDR = 0.5 cases in the number and type of plaques and tangles. As recognized by the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) criteria for diagnosis of AD,[18,19] neuritic plaques provide an especially good indicator of AD, because they represent the conjunction of amyloid deposition and neurofibrillary change.

Relation to Other Studies

An important aspect of this study was that the premortem cognitive status of each case was carefully assessed clinically. Recognition of very mildly demented cases (CDR = 0.5) assured that the CDR = 0 cases were

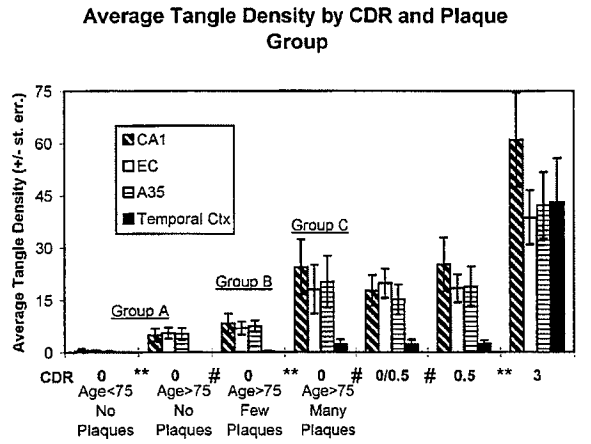

*Fig 7. Graphs of tangle density in hippocampal field CA1, the entorhinal cortex (EC), the perirhinal cortex (area 35, A35), and the temporal neocortex (Ctx), in cases grouped by CDR or within CDR = 0, into plaque Groups A, B, and C. There is a highly significant increase in tangle density for all brain areas between the younger and older cases in Group A, between Group B and Group C, and between CDR = 0.5 and CDR = 3 cases, but there is no significant difference between the other groups (**p < 0.001; #p > 0.1, for all comparisons between the same areas in adjacent groups; one-tailed t test). Note the large increase in the tangle density in the temporal cortex in the CDR = 3 cases.*

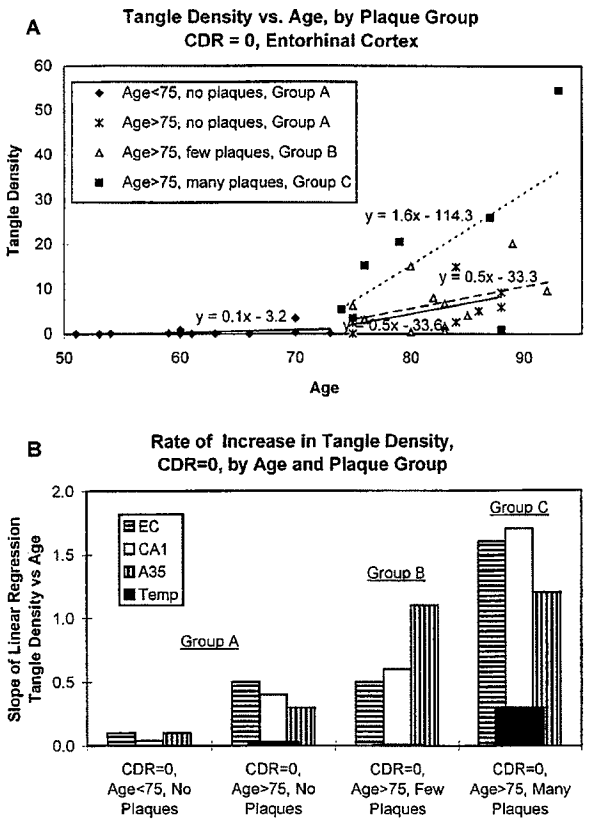

Fig 8. (A) Graph of tangle density against age in the entorhinal cortex in CDR = 0 cases. The cases are divided into Groups A, B, and C according to the presence or type of plaques found, and Group A is subdivided into younger and older cases. For each set of cases, a "best fit" linear regression line was calculated and drawn. The slope of this line, representing the increase in tangle density with age, increases between young and old cases without plaques (Group A), and between Group B and Group C. (B) Graphs of the rate of increase in tangle density with age calculated from the slope of linear regressions for Groups A, B, and C. There is an increase in the rate of tangle formation both with age (between younger and older cases in Group A) and with increasing plaque deposition (between cases with age over 75 years in Groups A, B, and C). EC = entorhinal cortex; CA1 = hippocampal field CA1; A35 = Brodmann area 35, perirhinal cortex; Temp = temporal neocortex.

truly free of cognitive change. In a smaller previous study that used the CDR,[15] the authors also speculated that 2 of 15 CDR = 0 cases containing substantial numbers of neuritic and diffuse plaques represented preclinical AD.

In a recent large study (2,661 cases), Braak and Braak[20] analyzed stages of AD-related lesions in relation to age, based on a previous study[21] that defined three neuropathological stages of amyloid deposition and six stages of neurofibrillary changes. In this study, the cognitive status of the cases was not carefully determined, and the amyloid and neurofibrillary stages are not closely related to each other or to the presence or level of dementia. Despite this, the spatial patterns and progression of amyloid and neurofibrillary changes that underlie these stages are very similar to those described here and previously.[9] An important observation in the study by Braak and Braak[20] was that neurofibrillary changes and plaque deposition may begin at young ages, even before age 30. Subsequently, the prevalence of both markers steadily increases with age.

There are several differences between the detailed results of the study by Braak and Braak[20] and the present observations, but there is also considerable agreement in important respects. In separate commentaries, Duyckaerts and Hauw[22] and Silverman and colleagues[23] calculated from the data of Braak and Braak[20] that the incidence of neurofibrillary stages I/II would begin virtually at birth and would reach 50% prevalence at about age 48. The earliest amyloid stage reached 50% prevalence 25 years later, at about age 73. The important conclusion from both these results and the present study is that the earliest neurofibrillary changes occur well before the earliest amyloid deposition. The calculations also indicate that there is a 35- to 40-year gap between earliest neurofibrillary stage I/II and the intermediate stage III/IV,[22,23] indicating that early neurofi-

brillary changes develop very slowly. Further, the development of amyloid occurs before the later, more severe neurofibrillary stages (Braak amyloid stages A and B rise in prevalence before neurofibrillary stages III/IV, and the late Braak amyloid stage C occurs before the late neurofibrillary stages V/VI). In agreement with the present results, therefore, these observations indicate that mild neurofibrillary changes begin before amyloid deposition, but severe neurofibrillary changes occur only after amyloid deposition. This supports the hypothesis presented here that amyloid deposition exacerbates the mild neurofibrillary changes seen in aging.

What Marks the Beginning of AD?

The early and virtually ubiquitous formation of tangles has led to the suggesting that tangles represent the earliest stage of AD (eg, by Braak and Braak[20]). If this is the case, AD is inevitable and may begin in the first decades of life. Tangle formation is closely correlated with cell loss, and there is considerable opinion that any tangle formation reflects pathological change.[24] For example, the early formation of tangles in the entorhinal cortex closely parallels cell loss in very mildly demented (CDR = 0.5) cases.[6] In contrast, in the superior temporal sulcus where plaques develop early in AD but tangles are formed later, cell loss occurs only in late AD.[25,26] Furthermore, the recent genetic observations in frontotemporal dementia and parkinsonism linked to chromosome 17 indicate that genetic alterations in tau by itself can result in neurodegeneration and dementia.[27,28]

Tangle formation during nondemented aging does not appear to be associated with age-related cell loss, however. Despite tangles in the entorhinal cortex and hippocampal field CA1, no cell loss has been identified in these structures as a function of nondemented aging.[5,6] Although this may be related to the difficulty of recognizing small amounts of cell loss, it would appear that age-related tangle formation is too slow to produce significant cell death during current life spans. We conclude that age-related tangle formation, although a mild form of tauopathy, does not by itself represent a process that would inevitably progress to AD.

In contrast, several observations in Down syndrome and familial forms of AD indicate that genetic factors resulting in changes in β-amyloid are sufficient to cause AD, including tangles and other neurofibrillary changes.[17] These observations provide strong evidence that β-amyloid can produce or exacerbate neurofibrillary changes, at least after the initial stages of amyloid deposition. Furthermore, the most distinct indication of the onset of dementia (in CDR = 0.5 cases) is a substantial increase in plaques.[11] As discussed above, most CDR = 0 cases do not have large numbers of plaques, and the small number of nondemented cases with substantial numbers of plaques can be recognized as preclinical AD. If, as indicated by the present data, extensive development of plaques accelerates age-related tangle formation, then amyloid deposition presumably converts the ubiquitous but slow neurofibrillary changes during aging into a disorder that leads inexorably to the severe stages of AD. The mechanisms by which β-amyloid might affect tangle formation are unclear but may include disturbances in calcium homeostasis, inflammatory reactions, and oxidative stress.

Finally, it should be asked whether the patches of diffuse amyloid plaques that are seen in pathologically less affected nondemented cases represent a still earlier stage in AD. Such plaques are not seen in all aging cases, at least well into the ninth decade, but where they do occur, a progression can be recognized from cases with few, very small patches of diffuse plaques to cases with more numerous and larger patches. The preclinical cases with extensive plaques, both neuritic and diffuse, appear to represent the continuation of this progression.

Note Added in Proof

Another study published since this paper was accepted for publication has also identified preclinical AD cases neuropathologically from 31 nondemented aged subjects (CDR = 0; age range, 72–102 years), based on the presence of neuritic plaques (CERAD "Possible AD").[29] Tangles were not used as the defining characteristic, and all the cases studied had some tangles (at least Braak stage 1). As a group, the preclinical cases had substantially more tangles and other neurofibrillary changes (average Braak stage, 2.3) than "normal" aging cases (average Braak stage, 1.3). These results agree well with the observations presented here.

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Causes of death associated with psychiatric illness

P. Prior, C. Hassall and K. W. Cross

Abstract

Background A prospective cohort analysis of mortality, among entrants to a population-based psychiatric case register, was undertaken to identify specific causes of death responsible for the increased risk of mortality previously reported in this large group of unselected patients.
Methods The analysis was based on a study population of 16871 cases, aged 15–89 years, from Worcester and Kidderminster Health Districts, entering the case register between 1974 and 1984 and generating a total of 85 073 patient-years (PYR) of observation. The underlying cause of death was coded to the relevant revision of the International Classification of Diseases (ICD). Numbers of deaths observed in the study population were compared with the number of deaths expected on the basis of mortality rates for England and Wales. Comparisons were made for eight main causes of death, aggregated at Chapter level of the ICD, and 11 categories of psychiatric diagnoses. Two indices of mortality were used for evaluation: relative risk (RR) = observed deaths/expected deaths; and excess mortality rate (EMR) = (observed − expected deaths)/PYR.
Results RRs were significantly raised for accidents, including suicides, as anticipated, and for various main causes of death. The increased risk of accidental death was found across the majority of the 11 psychiatric diagnostic groups although the EMRs were low at less than 5/1000 PYR. Deaths from respiratory disorders gave rise to the highest RRs after accidental deaths, and were responsible for substantial excess mortality among in-patients and patients with psychotic illnesses (especially dementia). The largest numbers of deaths of both sexes were due to diseases of the circulatory system, with a 40 per cent excess of observed over expected values in the whole series. The excess was due mainly to deaths of in-patients and of patients with psychotic diagnoses. No excess of deaths owing to neoplasms was found for either in-patients or out-patient groups.
Conclusions The findings that psychiatric illness is associated with an increased risk of death from 'natural' causes and that the level of risk was related to the severity and to the diagnostic category of the illness have implications for patterns of care and use of resources.

Keywords: psychiatric, case register, mortality, causes

Introduction

The psychiatric case register which formed the basis of this study was described in a previous report.[1] Briefly, the case register was a complete record of every patient using the psychiatric services in the catchment area (Worcester and Kidderminster Health Districts). Data recorded comprised not only the usual personal characteristics (sex, date of birth, area of residence, treatment, etc.) but also details of each contact with the ten psychiatric services available. Hence the data base gave a complete record of all psychiatric patients in a defined geographical area with a known population, and their use of the services.

A preliminary study[1] of mortality of all patients using the psychiatric services provided by the two health districts over a ten-year period revealed that deaths among these patients exceeded those expected for the general population by 80 per cent, and that the relative risk was maximal during the first year after registration and was significantly raised in both sexes and in patients of all age groups.

This large series of unselected psychiatric patients from defined geographical areas with known populations also provides the opportunity to study mortality by service use and diagnostic group. Thus it was shown that the excess mortality of 'in-patients' (i.e. those patients who experienced at least one episode of psychiatric in-patient care) both in relative and absolute terms exceeded those of 'out-patients' (i.e.

Department of Public Health and Epidemiology, The Medical School, University of Birmingham, Edgbaston, Birmingham B15 2TT.

P. PRIOR, Research Fellow

C. HASSALL, Senior Research Fellow

K. W. CROSS, Senior Lecturer

Address correspondence to Dr P. Prior, Centre for Cancer Epidemiology, Christie Hospital NHS Trust, Kinnaird Road, Withington, Manchester M20 4QL.

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the remainder). Differences in the excess mortality of patients with different psychiatric diagnoses, and the related different patterns with respect to sex, age and time after registration were illustrated by considering two diagnostic groups of patients: those with dementia and those with schizophrenia and paranoid psychosis.

It was clear that an analysis with respect to cause of death was essential to pursue some of the findings from this preliminary study. For example, it seemed likely that accidental deaths and suicide would prove to be a major factor in the excess of deaths of patients, but the extent of the contributions of this cause and indeed of other causes needs to be established. This paper is therefore concerned with analysis by cause of death of this series of psychiatric patients. Separate analyses have again been made of 'in-patients' and 'out-patients', and results are also given for patients in various diagnostic groups including the two mentioned above.

Material and method

The Worcester psychiatric case register which formed the basis of this study was described in the previous report.[1] A total of 16 871 patients aged between 15 and 89 years, registered between 1 January 1974 and 31 December 1984, have been followed-up until death or to 31 December 1985, when the analysis was terminated. The names of those who had died were submitted to the Office of Population Censuses and Surveys (OPCS) and death certificates were obtained for 97 per cent. Causes were coded to rubrics of the International Classification of Diseases (ICD) 8 or 9 according to year of death, but those referable to deaths in 1984 and 1985 were coded back to the rules as operative in 1981, for compatibility with the last quinquennial mortality rate used in the analysis. The numbers of deaths under each Chapter of the ICD that might be expected to occur in a given series were computed from sex- and age-specific 'person-years' (PYR) at risk, and sex-, age- and ICD Chapter-specific mortality rates for England and Wales. Quinquennial rates for estimating expected numbers were derived from annual publications of deaths and populations for 1969–1983 (OPCS, Mortality Statistics, Series DH5). It should be noted that throughout this paper the term 'accidental' deaths will include deaths attributable to all rubrics within Chapter XVII of the ICD, i.e. accidents, poisonings and violence. Two summary indices were used to assess the level of mortality in the series: a relative risk (RR) defined as a standardized mortality ratio, obtained from observed/expected numbers; and an excess mortality rate (EMR) defined as (observed minus expected/1000 PYR). The former is a measure of the risk of death in the patient series relative to the risk in the general population of the same sex and age constitution; the latter is taken as a measure of mortality attributable to the psychiatric illness or factors associated with it.

The following groups of patients have been investigated:

(1) In-patients (5930 cases);
Out-patients:
(i) one-day service (3271 cases);
(ii) 1 + days service (7669 cases).

(2) Psychotics - ICD 290–299:
(i) dementia – ICD 290;
(ii) affective psychosis – ICD 296;
(iii) schizophrenia and paranoid psychosis – ICD 295, 297.

(3) Alcoholism and drug dependence – ICD 291, 303–4.

(4) Non-psychotics:
(i) depression – ICD 300.4, 311 + 316.8 (8th Revision);
(ii) anxiety states – ICD 300.0;
(iii) personality disorders – ICD 301–2.

The distinction between out-patients who received a service on one day only and the remainder calls for comment. The former comprise a group of patients who experienced only a single contact with one of the psychiatric services: in some cases, the contact was made to assess whether or not the patient was mentally ill (with negative results); in others, a domiciliary visit was made to a physically ill (usually elderly) patient to assess whether he or she had an organic psychosis. This group of patients was therefore very heterogeneous and has been included only for completeness of the analysis. Such patients are not included in the analysis by psychiatric diagnosis.

Significance testing for individual RRs assumed that the observed numbers followed a Poisson distribution. When the expected number of deaths was less than 50 the exact probability of obtaining the observed number or more by chance was computed directly from a Poisson distribution with mean equal to the expected number. For larger expected values the distributions were assumed to approximate the Normal (i.e. with variance equals mean). For both Poisson and normally distributed estimates, two-tailed significance levels ($p < 0.05$, $p < 0.01$ and $p < 0.001$) have been used. The more stringent two-tailed tests of significance were used to make some allowance for spuriously 'significant' results which may arise when carrying out multiple testing. The 95 per cent confidence intervals (95 per cent CI) for RRs were obtained from Byar's approximation[2] when deaths numbered less than 50. For more than 50

deaths the Normal approximation was again invoked but, in this instance, taking the observed number as the mean.

Results

Total series

Considering all male patients (Table 1) there was an 85 per cent increase in mortality compared with the general population. Relative risks (RRs) were significantly raised for patients with causes of death subsumed under ICD Chapters of mental disorders (RR = 7·43), nervous diseases (3·53), diseases of the circulatory system (1·37), respiratory diseases (3·57), diseases of digestive system (2·34), and accidental deaths including suicides (4·96). It is noteworthy that the RR for malignant neoplasms was less than unity.

For all female patients there was a 75 per cent increase in mortality (Table 1). Similar RRs as for males were obtained for mental disorders (7·62), diseases of the circulatory system (1·41) and respiratory diseases (3·11). The RRs for females for nervous diseases (2·00), diseases of the digestive system (1·26) and accidental deaths (3·91) were substantially lower than for men, and of these three causes only the RR for accidental deaths was highly significant. However, the RRs for endocrine, nutritional and metabolic diseases, and diseases of the genito-urinary tract were significant at the 1 per cent level, and that for diseases of the nervous system at the 5 per cent level. The observed and expected deaths from malignant neoplasms were almost identical.

The overall excess death rates were 12 and 10 per 1000 PYR for males and females, respectively. For each sex the EMR for diseases of the respiratory system was maximal, followed by that for diseases of the circulatory system. 'Accidental' deaths contributed 2 and 1 per 1000 PYR to the male and female overall excess rates, respectively.

In-patients

Table 2 gives corresponding results for patients who had at some time received in-patient care. The overall relative risks were 2·24 (95 per cent CI 2·05–2·43) and 2·06 (95 per cent CI 1·91–2·21) for males and females, respectively, and the patterns of risk by ICD Chapter were essentially the same as for the total series but with increased RRs and EMRs. The overall male EMR was 25 per 1000 PYR with respiratory diseases (11), circulatory diseases (6) and accidental deaths (4) being the major contributors. Deaths from diseases subsumed under these three Chapters also accounted for the major part of the excess female deaths (overall EMR = 20).

Out-patients

Patients who had not received in-patient care at any time have been divided into those who only used a psychiatric service on one day and the remainder. Results for both groups are given in Table 3.

For male one-day service patients a relative risk of 1·85 was obtained, most of the excess being due to

TABLE 1 Relative risk and excess mortality rates by sex and ICD Chapter; total series

	Males (n = 6945)				Females (n = 9926)			
ICD Chapter	O	RR	95% CI	EMR	O	RR	95% CI	EMR
II, Neoplasms	101	0·89	0·72–1·06	—	133	0·99	0·82–1·12	—
III, Endocrine, nutrition and metabolic	7	1·67	0·67–3·44	<1	18	2·15**	1·27–3·40	<1
V, Mental disorders	15	7·43***	4·15–12·3	<1	41	7·62***	5·47–10·3	<1
VI, Nervous system	19	3·53***	2·13–5·52	<1	16	2·00*	1·14–3·25	<1
VII, Circulatory system	328	1·37***	1·23–1·52	3	481	1·41***	1·28–1·53	3
VIII, Respiratory system	264	3·57***	3·14–4·00	5	309	3·11***	2·77–3·46	4
IX, Digestive system	28	2·34**	1·55–3·38	<1	26	1·26	0·82–1·84	<1
X, Genito-urinary system	12	1·79	0·92–3·13	<1	19	1·99**	1·20–3·11	<1
E XVII, Accidental death	97	4·96***	3·97–5·94	2	75	3·91***	3·02–4·79	1
Remainder	17	2·35**	1·37–3·76	<1	22	1·35	0·85–2·04	<1
NK	9				22			
All causes	897	1·85***	1·73–1·97	12	1162	1·75***	1·65–1·85	10

O, Observed deaths; RR, relative risk; EMR, excess mortality rate per 1000 PYR; NK, cause of death not known.
*p < 0·05; **p < 0·01; ***p < 0·001.

TABLE 2 Relative risk and excess mortality rates by sex and ICD Chapter; in-patients

	Males (n=2470)			Females (n=3456)		
ICD Chapter	O	RR	EMR	O	RR	EMR
II	65	1·12	<1	71	1·06	<1
III	6	2·79*	<1	12	2·73**	<1
V	10	9·62***	1	32	11·47***	2
VI	9	3·41**	1	9	2·27*	<1
VII	198	1·57***	6	280	1·54***	5
VIII	183	4·45***	11	211	4·04***	9
IX	15	2·45**	1	16	1·49	<1
X	7	1·89	<1	10	2·01	<1
E XVII	57	7·48***	4	51	5·81***	2
Remainder	12	3·35***	<1	12	1·47	<1
NK	4			8		
All causes	566	2·24***	25	712	2·06***	20
95% CI		(2·05–2·43)			(1·91–2·21)	

*p<0·05; **p<0·01; ***p<0·001.

accidental deaths (RR=3·67, 2·00–6·16), respiratory diseases (RR=2·75, 1·86–3·93) and diseases of the circulatory system (RR=1·60, 1·19–2·01); together, these contributed 8 to the overall EMR of 9 per 1000 PYR.

One-day service female patients had a relative risk of 1·54 and an EMR of 7 per 1000 PYR. Deaths from circulatory diseases and from diseases of the respiratory system gave rise to RRs of 1·41 (1·11–1·71) and 2·41 (1·76–3·23), respectively, and largely accounted for the excess of mortality. The maximum RR occurred for mental disorders (4·95, 1·60–11·55) but, although highly significant, only five deaths were observed.

Out-patients who received services on more than one day experienced lower relative risks and smaller excess mortality rates than the above group. The overall male RR was 1·23 and significant RRs were obtained only for respiratory diseases (2·36, 1·71–3·01), accidental deaths (3·20, 2·09–4·69), mental disorders (6·06, 1·63–15·52), and nervous diseases (3·21, 1·62–9·67). The

TABLE 3 Relative risks and excess mortality rates by sex and ICD Chapter; out-patients

	One-day service						1 + day service					
	Males (n=1440)			Females (n=1831)			Males (n=3034)			Females (n=4635)		
ICD Chapter	O	RR	EMR	O	RR	EMR	O	RR	EMR	O	RR	EMR
II	15	0·88	—	17	0·82	—	21	0·52	—	45	0·94	—
III	0	—	—	5	3·67*	<1	1	0·71	—	1	0·38	—
V	1	3·13	<1	5	4·95**	<1	4	6·06**	<1	4	2·53	<1
VI	4	4·61**	<1	2	1·50	<1	6	3·21*	<1	5	1·85	<1
VII	58	1·60***	3	85	1·41**	3	72	0·93	—	115	1·15	1
VIII	30	2·75***	3	45	2·41***	3	51	2·36***	2	52	1·82***	1
IX	5	2·69	<1	1	0·28	—	8	2·01**	<1	9	1·39	<1
X	5	4·96**	<1	1	0·60	—	0	—	—	8	2·78*	<1
E XVII	14	3·67***	2	7	2·01	<1	26	3·20***	1	17	2·45*	<1
Remainder	2	1·71	<1	5	1·68	<1	3	1·16	<1	6	1·17	—
NK	3			4			2			9		
All causes	137	1·85***	9	177	1·54***	7	194	1·23**	2	271	1·33***	3
95% CI		(1·54–2·16)			(1·36–1·73)			(1·06–1·41)			(1·17–1·49)	

*p<0·05; **p<0·01; ***p<0·001.

overall female RR (1·33) differed little from the male value, but the RRs for respiratory disease (1·82, 1·33–2·53) and accidental deaths (2·45, 1·43–3·92) were lower. The only other ICD Chapter with a significant RR was diseases of the genito-urinary system (2·78, 1·19–5·44).

Psychoses (patients with more than one day of service use)

For all male psychotic patients the overall RR was 2·48 and the excess annual mortality rate was 47 per 1000 PYR (Table 4). Excess deaths attributable to diseases of the respiratory and circulatory systems largely accounted for the latter rate. In addition to these two Chapters, significant RRs were obtained for accidental deaths (5·66, 3·63–8·42) and mental disorders (16·47, 9·00–27·6). Diseases of the digestive and nervous systems were also significant, accounting for 21 deaths but contributing only 3 per 1000 PYR to the overall EMR. The same picture emerged for all female psychotic patients, with values of RRs and EMRs being generally somewhat smaller than for males. Exceptions to this parallel were the significant female RR for diseases of the genito-urinary tract (2·37, 1·18–4·24) and the non-significance of the RR for diseases of the digestive system (0·92).

Selected psychotic diagnoses

Dementia

For male patients the overall RR was 3·00 and significant RRs were obtained for mental disorders, diseases of the circulatory system and of the respiratory system (Table 5). Although the numbers were small, deaths from endocrine, nutritional and metabolic disorders, diseases of the digestive system and of the nervous system also gave rise to significant RRs. The pattern of risk for female dementia patients was very similar, although the RRs were somewhat smaller, and those for endocrine, nutritional and metabolic disorders, and for diseases of the digestive system were not significant. The overall male and female excess mortality rates were very high: 181 and 108 per 1000 PYR, respectively, largely owing to excess deaths from mental disorders, diseases of the circulatory system and of the respiratory system. Notably, there were comparatively few accidental deaths of patients of either sex with this condition.

Affective psychoses

The overall RR of 1·76 for males was significantly high (Table 6). Nearly half the observed deaths were due to diseases of the circulatory system (RR = 1·69, 1·16–2·39). There were only ten accidental deaths, although the RR (8·85, 4·24–16·28) was highly significant with the EMR (5) contributing one-third of the overall value. The 12 male deaths from malignant neoplasms only marginally exceeded the expected number (9·4). For females, the overall RR (1·39) was also significant; however, it was less than that for males, and the EMR (7) was about half the male rate. The RR for accidental deaths (7·34, 3·91–12·56) was similar to the male value. The RR for respiratory diseases (1·89, 1·10–3·03) was significant at only the 5 per cent level, whereas the small excess for the circulatory system was not found to be significant.

TABLE 4 Relative risk and excess mortality rates by sex and ICD Chapter; all psychoses

	Males (n = 1393)			Females (n = 2466)		
ICD Chapter	O	RR	EMR	O	RR	EMR
II	37	0·91	—	55	1·01	—
III	4	2·58	<1	7	1·81	<1
V	14	16·47***	2	35	12·68***	3
VI	8	4·30*	1	10	2·94**	1
VII	170	1·81***	13	265	1·55***	9
VIII	176	5·22***	24	211	4·15***	15
IX	13	2·89**	1	9	0·92	—
X	5	1·64	<1	11	2·37*	1
E XV11	24	5·66***	3	27	3·78***	2
Remainder	8	3·10*	<1	11	1·48	<1
NK	4			7		
All causes	463	2·48***	47	648	2·05***	31
95% CI		(2·25–2·70)			(1·90–2·21)	

*$p < 0·05$; **$p < 0·01$; ***$p < 0·001$.

TABLE 5 Relative risk and excess mortality rates by sex and ICD Chapter; dementia

	Males (n=468)			Females (n=846)		
ICD Chapter	O	RR	EMR	O	RR	EMR
II	9	0·48*	—	18	0·81	—
III	4	5·29*	3	2	1·07	<1
V	12	25·58***	11	32	19·68***	14
VI	5	5·62**	4	5	3·15*	2
VII	97	2·06***	48	162	1·77***	32
VIII	131	6·88***	109	156	5·39***	58
IX	7	3·16*	5	3	0·60	—
X	3	1·75	1	6	2·42	2
E XVII	4	2·94	3	8	2·50*	2
Remainder	10	3·37	7	3	0·78	<1
NK	1			4		
All causes	280	3·00***	181	399	2·46***	180
95% CI		(2·65–3·35)			(2·22–2·69)	

*$p<0·05$; **$p<0·01$; ***$p<0·001$.

Schizophrenia or paranoid psychosis

Male patients had a relative risk of 1·28 (non-significant) and the eight accidental deaths provided the only significant RR (RR=7·41, 3·19–14·6) and the only EMR (4) worthy of mention. On the other hand, female patients had a significant overall RR (1·61). Deaths from circulatory diseases accounted for half the total deaths, although the RR (1·56, 1·04–2·24) was significant at only the 5 per cent level. The RR for respiratory diseases (2·53, 1·35–4·33) was more significant and the deaths subsumed under these two Chapters together accounted for most of the EMR (9) for female patients with this psychiatric diagnosis.

Miscellaneous psychoses

The mortality from all causes was significantly high in males (RR=2·64, 2·09–3·19) and the EMR was substantial (65 per 1000 PYR). Deaths from diseases of the respiratory (RR=5·10, 3·46–7·24) and circulatory (RR=1·90, 1·30–2·69) systems largely accounted for the overall excess deaths. Although very small numbers were involved, the RR for nervous disorders (RR=9·25, 1·89–27·39) was also significant. For female patients the overall RR and EMR were smaller (RR=1·98, 1·58–2·38, EMR=23). Only diseases of the respiratory system (RR=3·22, 2·09–4·76, EMR=8) gave rise to a substantial number of deaths. Very small

TABLE 6 Relative risks and excess mortality rates by sex and ICD Chapter

	Affective pyschoses						Schizophrenia or paranoid psychosis					
	Males (n=357)			Females (n=733)			Males (n=327)			Females (n=418)		
ICD Chapter	O	RR	EMR	O	RR	EMR	O	RR	EMR	O	RR	EMR
II	12	1·28	1	17	1·09	<1	3	0·55	—	8	0·93	—
VII	32	1·69***	7	39	1·11	1	9	0·81	—	29	1·56*	4
VIII	8	1·50	1	17	1·89*	2	6	1·84	1	13	2·53**	3
IX	3	3·27	1	2	0·93	—	1	1·77	21	2	1·73	<1
E XVII	10	8·85***	5	13	7·34***	3	8	7·41***	4	2	1·91	<1
Remainder	0	—	—	6	1·30	<1	2	1·67	<1	5	1·88	<1
NK	1			1			—			1		
All causes	66	1·76***	15	95	1·39**	7	29	1·28	6	60	1·61***	9
95% CI		(1·34–2·19)			(1·11–1·67)			(0·86–1·84)			(1·11–2·13)	

*$p<0·05$; **$p<0·01$; ***$p<0·001$.

numbers of deaths attributable to ICD Chapters mental disorders, nervous diseases and diseases of the genito-urinary system gave rise to moderately raised RRs but the confidence intervals were wide.

Alcoholism and drug dependence

The overall RR was significantly raised for males (RR = 2·03). The increase was due mainly to diseases of the respiratory system (RR = 4·71, 2·43–8·22), digestive system (RR = 8·05, 2·60–18·82) and accidental deaths (RR = 6·44, 2·93–12·20). Both the overall RR (3·02) and EMR (14) for females were higher than for males, with high RRs for diseases of the circulatory system (2·56, 1·28–4·59) and of the digestive system (RR = 21·62), but the latter referred to only seven deaths. A small excess of respiratory system deaths was also observed.

Non-psychotic disorders (patients with more than one day of service use)

The overall relative risk for 2889 males was significantly raised [O = 190, RR = 1·17, 1·01–1·34, $p < 0·05$, EMR = 2] and for female patients (O = 222, RR = 1·28, 1·11–1·44, $p < 0·05$, EMR = 3). The most significant RRs were obtained for accidental deaths to males (O = 45, RR = 5·29, 3·86–7·08, $p < 0·001$), and to females (O = 35, RR = 5·22, 3·63–7·25, $p < 0·001$); the EMR of 2 per 1000 PYR was the same for both sexes. Diseases of the respiratory system was the only other ICD Chapter of significance for females (O = 31, RR = 1·48, 1·01–2·10, $p < 0·05$, EMR < 1). Although the RR for males was similar (O = 29, RR = 1·42, 0·95–2·04, EMR < 1), it did not achieve statistical significance.

Three specific non-psychotic diagnoses have been considered: anxiety states, depression and personality disorders. Of these, significantly raised RRs for all causes were obtained only for depression for males (O = 116, RR = 1·33, 1·09–1·57, $p < 0·01$, EMR = 6) and for females (O = 151, RR = 1·39, 1·17–1·61, $p < 0·001$, EMR = 4). Accidental deaths were also high in this group for males (O = 19, RR = 6·79, 4·08–10·60, EMR = 4) and for females (O = 23, RR = 6·98, 4·42–10·46, EMR = 2). Only accidental deaths were of significance among 549 male patients with a diagnosis of anxiety state (O = 6, RR = 4·45, 1·63–9·49, $p < 0·01$, EMR = 2) and 634 males with personality disorders (O = 10, RR = 5·03, 2·41–9·25, $p < 0·001$, EMR = 2).

Discussion

Most studies of mortality of psychiatric patients have been confined to selected groups, for example, those with a given psychiatric diagnosis or long-stay in-patients. This study is of a total unselected population of psychiatric patients who, for the most part, made their first contact with the psychiatric services during an 11-year period, and for whom complete data of their psychiatric care was available. The previously reported excess of observed deaths over expectation was evident for various causes of death after aggregation at Chapter level of the ICD.

It was anticipated that some of the excess mortality of both in-patients and out-patients would be due to accidental death including suicide. This has been confirmed and shown to be true for several psychiatric diagnostic groups. Relative risks were significantly raised for 16 of the 22 sex and diagnostic groups; the exceptions were: dementia (male); schizophrenia and paranoid psychosis (female); the miscellaneous group of psychoses (males and females); alcoholism and drug dependence (females) and personality disorder (females). For these six sex- diagnostic groups the numbers of deaths were very small (< 5). Both male and female patients with depression had high values (> 5) of relative risk, as did those suffering from other non-psychotic disorders, namely, alcohol and drug dependence and personality disorders (males). Despite the high relative risks, the excess mortality rates for all diagnostic groups here considered were very small, and although there was some variation between diagnostic categories, differences between males and females (the former having higher values in most instances) were the predominant feature of the findings for this measure of mortality.

Causes of death subsumed under ICD Chapters III, V–IX and Chapter X (males only) also made substantial contributions to the increase of mortality (measured in excess or relative terms or both) of patients in the psychiatric categories here considered. In the total series, the maximum relative risk was that for mental disorders; however, few (56) deaths were recorded as such and the excess mortality was less than 1 per 1000 PYR. The majority (42) of these deaths were of patients who had received in-patient care; 44 were suffering from dementia. Future studies may disclose even higher rates, particularly for dementia, because of the change of rules for coding causes of death on certificates post 1984, when dementia, appearing in Part II of the death certificate (contributory cause), may in some instances be coded as the underlying cause of death.

Deaths from respiratory diseases accounted for 28 per cent of all deaths and gave rise to the maximum excess mortality rates of all Chapters in the whole series, and to the highest relative risks after accidental deaths and mental disorders. This was a major group of causes of death especially for in-patients and for

TABLE 7 Relative risks and excess mortality rates by sex and ICD Chapter

	Miscellaneous psychoses						Alcoholism and drug dependence					
	Males (n = 241)			Females (n = 469)			Males (n = 596)			Females (n = 288)		
ICD Chapter	O	RR	EMR	O	RR	EMR	O	RR	EMR	O	RR	EMR
II	12	1·66	7	12	1·53	2	9	1·39	<1	1	0·31	—
V	1	6·67**	1	3	7·25*	1	—	—	—	1	20·74	<1
VI	3	9·25**	3	3	5·90*	1	—	—	—	—	—	—
VII	32	1·90**	18	35	1·35**	4	10	0·84	—	11	2·56**	5
VIII	31	5·10***	30	25	3·22***	8	12	4·71***	4	4	4·12*	2
IX	2	2·52	1	2	1·38	<1	5	8·05***	2	7	21·62***	5
X	1	1·83	<1	4	5·74*	2	1	4·25	<1	1	7·90	<1
E XVII	2	2·99	2	4	3·50	1	9	6·44***	3	2	5·21	1
Remainder	2	2·74	2	4	2·31	1	2	3·33	<1	2	5·13	1
NK	2			2			1			1		
All causes	88	2·64***	65	94	1·98***	23	49	2·03***	9	30	3·02***	14
95% CI		(2·09–3·19)			(1·58–2·38)			(1·05–2·68)			(2·04–4·31)	

*p < 0·05; **p < 0·01; ***p < 0·001.

patients with psychotic illnesses, resulting in substantial excess mortality; this was particularly true for dementia. Patients who suffered from alcoholism and drug dependence also had significantly raised relative risks of death from respiratory disease.

The ICD Chapter VII – diseases of the circulatory system – provided the largest number of deaths of both sexes. Although very highly significant because of the numbers involved, the relative risks for the whole series were rather small (1·4 for both sexes). Both in-patients and out-patients (with a one-day service), had high risks for diseases included in this Chapter, as did all psychotic patients combined; those patients with dementia and the other individual psychotic diagnoses here considered were notable in this respect. Out-patients with more than one day of service did not suffer an excess of circulatory system deaths.

The results for deaths from neoplasms call for special mention in that no significant excess over expectation was found for any of the groups here considered. Similar findings have been obtained by others for selected psychiatric populations; for example, by Sims and Prior[3] in respect of severely neurotic patients in the United Kingdom, by Casadebaig and Quemada[4] for psychiatric in-patients in France, and by Mortenssen[5] for schizophrenic in-patients in Denmark.

The increased relative risks of psychiatric in-patient deaths from natural causes (i.e. other than accidental deaths) found in our study has also been reported by other workers from national studies in France,[5] Netherlands[6] and Norway;[7] the last two papers were in reference to long-stay in-patient populations which have been excluded from our analysis. We might therefore infer that premature mortality is a general feature of the more severe forms of mental illness.

Few studies have been made of psychiatric out-patients and these have usually been based upon small numbers.[8,9] In our study of much larger numbers, there was a pronounced excess of deaths from natural causes over expectations for patients with a 'one-day' service. These were patients for whom the first contact with the psychiatric services (when they were registered) proved to be their only contact during the study period. This often took the form of a psychiatric assessment of a patient with concurrent physical illness. It is not surprising, therefore, that raised mortality should be observed in this group. The reluctance of psychiatrists to admit patients with primary physical problems to psychiatric care, and the concern of consultants in general hospitals to discharge patients as soon as possible after treatment for physical conditions, led to large numbers of assessments. Many of these patients aged 45 years or over died within 12 months of their assessments from circulatory and respiratory conditions.

Three-quarters of the 465 deaths of those (7669) out-patients who received more than one day's service were from neoplasms, and circulatory and respiratory diseases. However, only patients who died from respiratory diseases significantly exceeded those expected from the experience of the general population. In fact, only half the number of males died from neoplasms compared with expectation, most of the deficit being due to the relatively small number of

deaths from respiratory cancer; this finding may be due to inconclusive investigation of the patients' physical conditions and probably contributed towards the excess of deaths from respiratory diseases.

This study has demonstrated that the excess mortality from natural causes occurs across a broad spectrum of patients with psychiatric disorders with a gradient which parallels the severity of the disorder: from the highest for organic psychotic conditions to the lowest for neurotic conditions which did not require inpatient care. Furthermore, most of this excess mortality was from common conditions – cardiovascular and respiratory diseases – and hence is of considerable importance for public health.

Improvement in the health and well-being of the mentally ill is one of the key areas named in *Health of the nation.*[10] We have shown that there is a considerable burden of premature mortality in people with mental health problems and, therefore, room for improvement. Strategies for the general population in combating the common causes of death should also be applied to the mentally ill. They may, however, prove more difficult to implement in individuals who, by reason of their condition, are perhaps less accessible or receptive to health education initiatives. The mentally ill may also have increased exposure to known causes of premature death, such as tobacco, alcohol and other drug abuse. Although the patients in our series received good community care, the increased mortality from natural causes, and the implied co-morbidity, suggests that health professionals should be alerted to their need for general medical care.

For all these circumstances the reduction in premature mortality among psychiatric patients presents a formidable challenge to the public health services, and our data provide a basis for assessing the efficacy of any public health policies.

Acknowledgement

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Imaging of amyloid β in Alzheimer's disease with ^{18}F-BAY94-9172, a novel PET tracer: proof of mechanism

Christopher C Rowe, Uwe Ackerman, William Browne, Rachel Mulligan, Kerryn L Pike, Graeme O'Keefe, Henry Tochon-Danguy, Gordon Chan, Salvatore U Berlangieri, Gareth Jones, Kerryn L Dickinson-Rowe, Hank P Kung, Wei Zhang, Mei Ping Kung, Daniel Skovronsky, Thomas Dyrks, Gerhard Holl, Sabine Krause, Matthias Friebe, Lutz Lehman, Stefanie Lindemann, Ludger M Dinkelborg, Colin L Masters, Victor L Villemagne

Summary

Background **Amyloid-β (Aβ) plaque formation is a hallmark of Alzheimer's disease (AD) and precedes the onset of dementia. Aβ imaging should allow earlier diagnosis, but clinical application is hindered by the short decay half-life of current Aβ-specific ligands. ^{18}F-BAY94-9172 is an Aβ ligand that, due to the half-life of ^{18}F, is suitable for clinical use. We thus studied the effectiveness of this ligand in identifying patients with AD.**

Methods **15 patients with mild AD, 15 healthy elderly controls, and five individuals with frontotemporal lobar degeneration (FTLD) were studied. ^{18}F-BAY94-9172 binding was quantified by use of the standardised uptake value ratio (SUVR), which was calculated for the neocortex by use of the cerebellum as reference region. SUVR images were visually rated as normal or AD.**

Findings **^{18}F-BAY94-9172 binding matched the reported post-mortem distribution of Aβ plaques. All AD patients showed widespread neocortical binding, which was greater in the precuneus/posterior cingulate and frontal cortex than in the lateral temporal and parietal cortex. There was relative sparing of sensorimotor, occipital, and medial temporal cortex. Healthy controls and FTLD patients showed only white-matter binding, although three controls and one FTLD patient had mild uptake in frontal and precuneus cortex. At 90–120 min after injection, higher neocortical SUVR was observed in AD patients (2·0 [SD 0·3]) than in healthy controls (1·3 [SD 0·2]; p<0·0001) or FTLD patients (1·2 [SD 0·2]; p=0·009). Visual interpretation was 100% sensitive and 90% specific for detection of AD.**

Interpretation **^{18}F-BAY94-9172 PET discriminates between AD and FTLD or healthy controls and might facilitate integration of Aβ imaging into clinical practice.**

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Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, Victoria, Australia (C C Rowe MD, U Ackerman PhD, W Browne MD, R Mulligan PhD, K L Pike PhD, G O'Keefe PhD, H Tochon-Danguy PhD, G Chan PhD, S U Berlangieri MD, G Jones, K L Dickinson-Rowe BSc, V L Villemagne MD); **Department of Medicine, University of Melbourne, Parkville, Victoria, Australia** (C C Rowe); **Department of Radiology, University of Pennsylvania** (H P Kung PhD, W Zhang PhD, M P Kung PhD), **and AVID Radiopharmaceuticals, Philadelphia, PA, USA** (D Skovronsky MD); **Bayer Schering Pharma, Berlin, Germany** (T Dyrks PhD, G Holl MD, S Krause PhD, M Friebe PhD, L Lehman PhD, S Lindemann MD, L M Dinkelborg PhD); **and Department of Pathology, University of Melbourne, and Mental Health Research Institute of Victoria, Parkville, Victoria, Australia** (C L Masters MD, V L Villemagne)

Correspondence to: Christopher Rowe, Department of Nuclear Medicine, Centre for PET, Austin Health, 145 Studley Road, Heidelberg, Victoria 3084, Australia **christopher.rowe@austin.org.au**

Introduction

Amyloid-β (Aβ) imaging with PET allows assessment in vivo of Aβ deposition in the brain, providing an important new tool for the assessment of the causes, diagnosis, and future treatment of dementias, in which Aβ may play a part. Studies with ^{11}C-labelled Pittsburgh compound B (2-[4´-(methylamino)phenyl]-6-hydrobenzothiazole; PIB), the most specific and widely used PET Aβ ligand, indicate that Aβ imaging may allow earlier diagnosis of Alzheimer's disease (AD) and accurate differential diagnosis of the dementias.[1–5] ^{11}C-PIB studies show robust cortical binding in almost all AD patients,[2,6,7] and correlate well with a reduction in CSF $A\beta_{42}$.[8] Binding also correlates with the rate of cerebral atrophy as measured by MRI,[9] and with episodic memory impairment in apparently normal elderly individuals and in patients with mild cognitive impairment.[10] Increased ^{11}C-PIB binding may also be predictive of conversion of mild cognitive impairment to AD.[11] Furthermore, comparison of the diagnostic use of Aβ imaging versus ^{18}F-fluorodeoxyglucose PET indicates greater accuracy for distinguishing patients with mild AD from elderly controls.[12]

Subsequent to recent advances in imaging and CSF analysis, Dubois and colleagues[13] proposed that the research criteria for the diagnosis of probable AD should be revised to allow earlier diagnosis and therapeutic intervention. The authors of this position statement argue that dementia is not required for the diagnosis of AD if there is a clear history of progressive cognitive decline, objective evidence from psychometric tests of episodic memory impairment, and characteristic abnormalities in the CSF or in neuroimaging studies. The latter includes the imaging of Aβ with appropriate PET tracers. Thus, as the criteria for the diagnosis of AD evolve, Aβ imaging is likely to have an increasingly important role in clinical practice, provided it is accessible and affordable.

Unfortunately, the 20 min radioactive decay half-life of ^{11}C limits the use of ^{11}C-PIB to centres with an on-site cyclotron and ^{11}C radiochemistry expertise. Consequently, access to ^{11}C-PIB PET is restricted and the high cost of studies is prohibitive for routine clinical use. To overcome these limitations, a tracer for imaging Aβ that can be labelled with ^{18}F is required. The 110 min radioactive decay half-life of ^{18}F allows centralised production and regional distribution as currently practised worldwide in the supply of ^{18}F-fluorodeoxyglucose for clinical use.

Barrio and colleagues[14] have developed an ^{18}F-labelled tracer that shows binding to both Aβ plaques and neurofibrillary tangles in vitro,[15] and report separation of patients with AD from healthy controls with PET imaging.[16] However, the analysis required a 2 h continuous scan and only showed 9% higher cortical uptake in AD. By comparison, ^{11}C-PIB shows a 70% increase in cortical binding in AD,[2,7] and ^{11}C-PIB images can be accurately

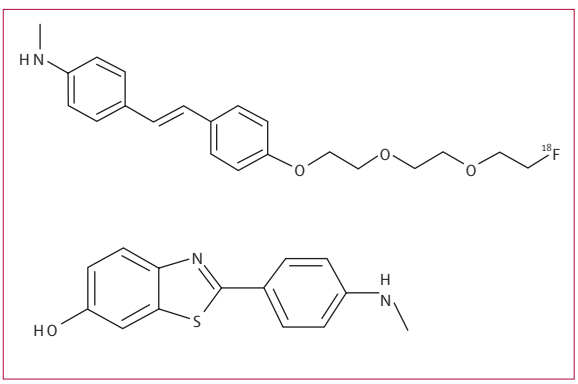

Figure 1: **Chemical structure of ^{18}F-BAY94-9172 (top) and ^{11}C-PIB**
Both are small planar molecules with extended aromatic rings and alkyl-amino substitution.

read without quantification and acquired with less than 30 min of PET camera time.[12] An ^{18}F tracer with characteristics similar to those of ^{11}C-PIB is needed. Structural and pharmacological evidence supports the claim that a stilbene derivative should have similar specificity to a thioflavin derivative (ie, PIB) for Aβ aggregates.[17,18] Thus, ^{18}F-BAY94-9172 or trans-4-(*N*-methylamino)-4´-{2-[2-(2-[^{18}F]fluoro-ethoxy)-ethoxy]-ethoxy}-stilbene (also known as ^{18}F-AV1/ZK), which shares common structural features to PIB (figure 1), has been developed. ^{18}F-BAY94-9172 and ^{11}C-PIB are small planar molecules with extended aromatic systems and alkyl-amino substitution. They compete pharmacologically for the same binding site on amyloid aggregates with similar affinity, and in human brain sections they show the same pattern of labelling of Aβ plaques.[17,18] Furthermore, another stilbene, ^{11}C-SB13 (^{11}C-4-*N*-methylamino-4´-hydroxy-stilbene), has shown the same regional brain distribution pattern as ^{11}C-PIB when studied in the same population of AD patient and age-matched healthy controls.[19]

See Online for webfigure 1

^{18}F-BAY94-9172 has been shown to bind avidly to neuritic and diffuse Aβ plaques and to cerebral amyloid angiopathy in vitro; it does not show appreciable labelling of tangles, Pick bodies, Lewy bodies, or glial cytoplasmic inclusions. In brain homogenates from patients with AD, BAY94-9172 was found to bind with high affinity (K_i=6·7±0·3 nM), and in AD tissue sections, ^{18}F-BAY94-9172 selectively labelled Aβ plaques.[17] At tracer concentrations, BAY94-9172 did not show binding to post-mortem cortex from patients with frontotemporal dementia, or in post-mortem brain tissue from a variety of neurodegenerative diseases, including tauopathies and α-synucleinopathies. Images of ^{18}F-BAY94-9172 binding to brain slices from patients with AD, frontotemporal lobar degeneration, and normal brain obtained with PhosphorImager plates are shown in webfigure 1. After injection into Tg2576 transgenic mice, ex-vivo brain sections showed localisation of ^{18}F-BAY94-9172 in regions with Aβ plaques as confirmed by thioflavin binding.[18] In normal mice, ^{18}F-BAY94-9172 rapidly entered the brain with 8·14% injected dose per gram and washed out to 2·14% injected dose per gram within 2 h.

Preclinical toxicity studies in several animal species showed a good safety profile with no observable effects at 100 times the expected human mass dose. On the basis of these studies, we deemed ^{18}F-BAY94-9172 to be a suitable agent for human studies.

Region	Healthy controls (n=15)	Alzheimer's disease (n=15)	Effect size	p*
Dorsolateral prefrontal	1·23 (0·21)	1·95 (0·33)	2·61	<0·0001
Ventrolateral prefrontal	1·32 (0·20)	2·12 (0·32)	2·99	<0·0001
Orbitofrontal	1·34 (0·20)	2·09 (0·31)	2·86	<0·0001
Gyrus rectus	1·37 (0·24)	2·15 (0·37)	2·49	<0·0001
Anterior cingulate	1·32 (0·23)	2·05 (0·32)	2·61	<0·0001
Posterior cingulate	1·27 (0·19)	2·14 (0·38)	2·91	<0·0001
Parietal	1·21 (0·15)	1·95 (0·31)	3·06	<0·0001
Occipital	1·36 (0·15)	1·84 (0·26)	2·27	<0·0001
Lateral temporal	1·30 (0·18)	2·05 (0·27)	3·30	<0·0001
Mesial temporal	1·24 (0·14)	1·47 (0·14)	1·68	<0·0001
Caudate nuclei	1·34 (0·23)	2·05 (0·43)	2·07	<0·0001
Putamen	1·30 (0·15)	1·89 (0·35)	2·21	<0·0001
Thalamus	1·41 (0·18)	1·65 (0·40)	0·79	0·042
Midbrain	1·69 (0·15)	1·83 (0·27)	0·64	0·094
Pons	1·93 (0·17)	1·99 (0·30)	0·23	0·53
White matter	1·93 (0·18)	1·89 (0·45)	–0·11	0·89
Neocortex†	1·29 (0·17)	2·02 (0·28)	3·14	<0·0001

Data are mean (SD). *Unpaired Student's *t* test (p<0·0031 is significant after correction for multiple comparisons). †Neocortex comprises the average SUVR for frontal, parietal, cingulate, occipital, and lateral temporal cortices.

Table: **Regional standardised uptake value ratios ($SUVR_{90-120}$) in healthy controls and patients with Alzheimer's disease**

Methods

Participants

15 healthy elderly controls, 15 patients who met the NINDS-ADRDA criteria for probable AD and the DSM-IV criteria for dementia of Alzheimer's type, and five patients who met the consensus criteria for frontotemporal lobar degeneration (FTLD) were enrolled in the study. Patients with AD and FTLD were recruited from the Austin Health Memory Disorders Clinic (Heidelberg, Victoria, Australia) if they met the inclusion and exclusion criteria and were willing to participate in the study. Healthy controls were recruited by advertisement in the community. The study was approved by the Austin Health Human Research Ethics Committee. Written informed consent was obtained from all individuals before participation and also from the next of kin or carer for the patients with dementia.

All participants were aged over 60 years, spoke fluent English, and had completed at least 7 years of education. No participant had a history or physical or imaging findings of other neurological or psychiatric illness, current or recent drug or chronic alcohol use or dependence, or any significant other disease or unstable medical condition.

Safety monitoring consisted of clinical observation and intermittent measurement of vital signs for 3 h starting immediately before tracer injection. Vital signs, haematology, and biochemistry testing were done 1 week after injection and compared with baseline. Participants were asked about possible adverse events 3 h, 24 h, and 1 week after injection.

MRI and psychometric examination were completed within 4 weeks of the ^{18}F-BAY94-9172 scan. MRI consisted of a 3-dimensional (3D) T1-weighted MPRAGE and a T2-weighted turbospin-echo sequence. Participants were given the mini-mental state examination (MMSE), the clinical dementia rating (CDR) scale, and a battery of neuropsychological tests to ensure that participants fulfilled the diagnostic criteria for AD or normality. Healthy controls were excluded if any score fell below 1 SD of the published mean for that test. All probable AD patients had episodic memory scores below 2 SD of the published mean. Venous samples were taken at frequent intervals throughout the scan. Total radioactivity in plasma was measured and metabolites were detected by high-performance liquid chromatography (HPLC).

^{18}F-BAY94-9172 synthesis

Labelling was done in the Austin Health Centre for PET immediately before injection. Avid Radiopharmaceuticals, Inc (Philadelphia, PA, USA), supplied the precursor and cold standard for production of ^{18}F-BAY94-9172. Radiolabelling was achieved by an automated synthesis process using [^{18}F] potassium fluoride Kryptofix complex followed by acid hydrolysis and semi-preparative HPLC for purification. Standard Sep-pak reformulation produced the injectable product. Manufacturing time was 60 min. The final product had an average specific activity of 170 GBq/µmol and a radiochemical purity of 95%.

^{18}F-BAY94-9172 PET acquisition

PET scans were acquired using a 3D GSO Philips Allegro scanner in the Austin Health Centre for PET. A thermoplastic face mask was used to minimise head movement. A 2 min transmission scan using a rotating ^{137}Cs source was done for attenuation correction immediately before each imaging period. A slow intravenous bolus of 300 MBq of ^{18}F-BAY94-9172 was given over 30 s followed by a 60 min list-mode emission acquisition in 3D mode. List-mode raw data were sorted off-line into four 30 s, nine 1 min, three 3 min, four 5 min, and two 10 min frames. Further imaging was done at 90–120 min and 135–165 min after injection with 10 min frames. One normal participant and three AD patients refused the final scan period because of discomfort or fatigue. Images were reconstructed using a 3D RAMLA algorithm.

Image analysis

Co-registration of the PET images with each individual's MRI scan was done. Regions of interest (ROI) were then

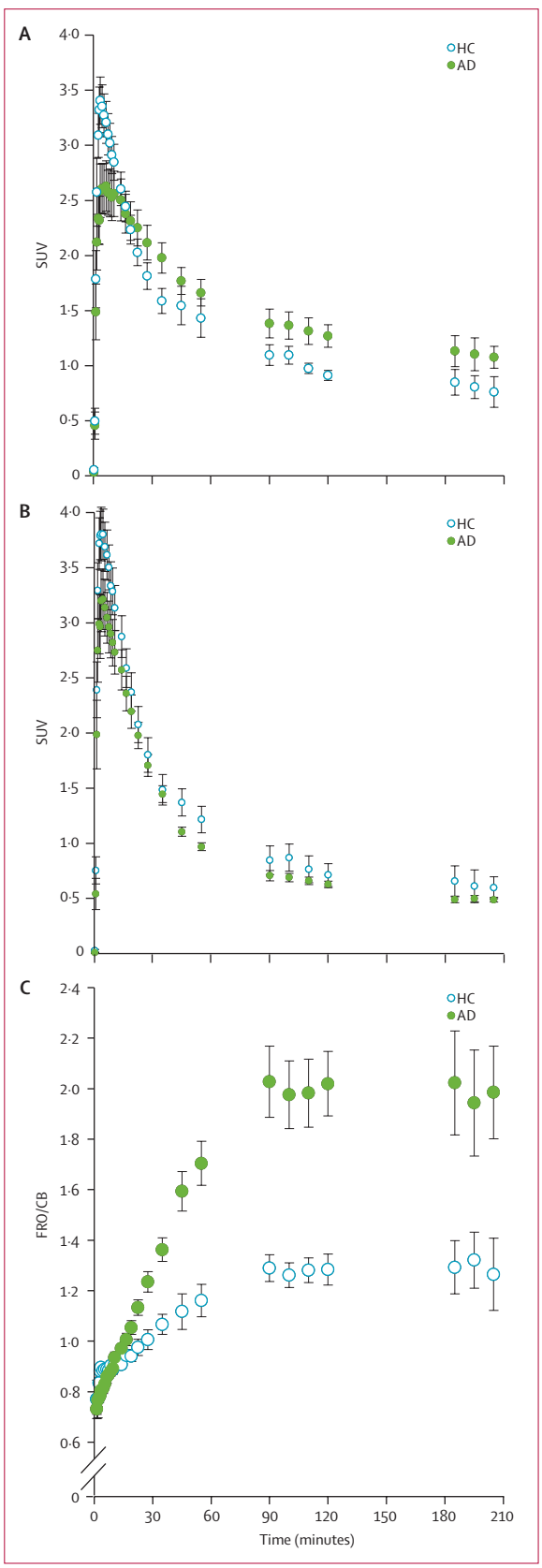

Figure 2: **Time-activity curves (decay corrected) for ^{18}F-BAY94-9172 in patients with Alzheimer's disease (AD) and age-matched healthy controls (HC)**
(A) Frontal cortex; (B) cerebellar cortex; and (C) frontal to cerebellar ratio. Error bars (SD) are shown.

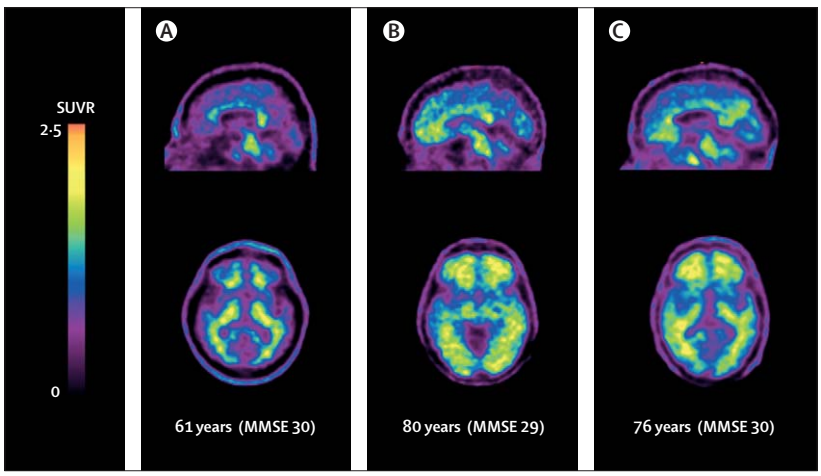

Figure 3: **Transaxial and midsagittal PET images obtained 90–120 min after injection of 300 MBq ^{18}F-BAY94-9172 in three healthy controls**
Image (A) is typical of 12 healthy controls with no cortical binding. Extensive white-matter binding is most apparent in the corpus callosum, peri-thalamic area, pons, and centrum semi-ovale. (B) and (C) are images of two healthy controls who showed mild frontal and precuneus binding and were interpreted as probable AD by a blinded reader.

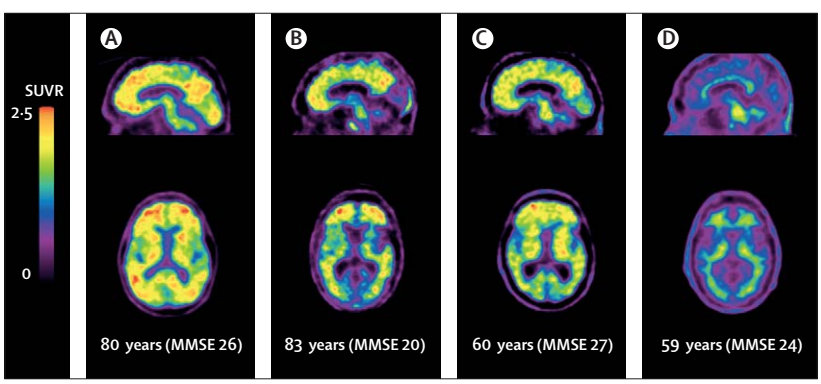

Figure 4: **^{18}F-BAY94-9172 images from three patients with AD and one patient with FTLD**
There is cortical binding in frontal, posterior cingulate/precuneus, and lateral temporal areas with relative sparing of occipital and sensorimotor cortex in AD patients (A–C). By contrast, there is no cortical binding in the FTLD patient (D).

See Online for webfigure 2

drawn on the individual MRI. Mean radioactivity values were obtained from ROI for cortical, subcortical, and cerebellar regions (table), and decay-corrected time-activity curves were generated over 165 min from the 28 frames. White-matter ROIs were placed at the centrum semiovale, and the cerebellar regions were placed over the cerebellar cortex, taking care to avoid white matter. In two cases, MRI could not be obtained and ROI were drawn directly on to the PET images by an operator blind to the clinical status of the individuals. No correction for partial volume was applied to the PET data.

The standardised uptake values (SUV), defined as the decay-corrected brain radioactivity concentration and normalised for injected dose and bodyweight, was calculated for all regions. These were then used to derive the SUV ratio (SUVR), which was referenced to cerebellar cortex at a time soon after the neocortical to cerebellar tracer-binding ratio reached an apparent steady state. Neocortical Aβ burden was expressed as the average SUVR of the area-weighted mean for the following cortical ROIs: frontal (consisting of dorsolateral prefrontal, ventrolateral prefrontal, and orbitofrontal regions), superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate.

The distribution volume ratio (DVR) was determined through graphical analysis of the 165 min time-activity curves (28 data points).[20] To avoid arterial blood sampling, a simplified approach was applied by use of the cerebellar cortex, a region relatively unaffected by Aβ deposition in early AD, as input function. This approach has not been validated against an arterial plasma activity input curve for ^{18}F-BAY94-9172, but has worked well in ^{11}C-PIB studies and has provided good distinction between AD patients and healthy controls.[2,12,20,21] Neocortical DVR was calculated with the same regions used for the neocortical SUVR.

Images were generated from the 90–120 min data for visual inspection on a Philips workstation and displayed with a rainbow colour scale. The colour scale was adjusted so that cerebellar white matter was yellow, as previously described for reading ^{11}C-PIB images.[12] A mid-sagittal slice and transverse slices at the level of the cerebellar white matter and the thalamus from all 35 individuals are displayed in this way in webfigure 2. A nuclear-medicine physician with experience in interpretation of ^{11}C-PIB scans, and blind to diagnosis and all other clinical information, classified the ^{18}F-BAY94-9172 images as "normal" or "probable AD" on the basis of the presence (green to red) or absence (blue to black) of binding in cerebral cortex. A 2×2 contingency analysis was used to determine the test sensitivity and specificity of visual interpretation of ^{18}F-BAY94-9172 in differentiating probable AD from non-AD (ie, the combination of healthy controls and FTLD patients).

Data are presented as mean±SD, unless otherwise stated. Statistical analyses were done using a Student's *t* test with correction for multiple comparisons. Effect size was measured with Cohen's *d*. Correlations were assessed by Pearson correlation coefficient. All data were analysed with Minitab software.

Role of the funding source

The funding sources had no role in study design, data collection, data analyses, and data interpretation. Bayer Schering Pharma did not contribute to the manuscript other than to provide preclinical information in response to the reviewers' comments at the authors' request. The corresponding author had full access to all the data in this study and had final responsibility for the decision to submit for publication.

Results

15 healthy controls (eight men and seven women; age 68·8±6·0 years; MMSE 29·5±1·0; CDR 0·0), 15 patients with probable AD (10 men and five women; age 69·5±10·0 years; MMSE 23·3±4·0; CDR 1·0), and five patients with

FTLD (three men and two women; age 67·4±9·0 years; MMSE 24·6±2·0; CDR 1·0) were recruited and studied between September, 2006, and September, 2007. All recruited individuals completed the study and are included in the analysis. Three of the FTLD patients met criteria for frontotemporal dementia and two for semantic dementia. No adverse events related to the study drug were observed or reported by the participants after the ^{18}F-BAY94-9172 scan.

Initial brain uptake of ^{18}F-BAY94-9172 was slightly higher in controls than in AD patients in all areas examined. Clearance was slower from the neocortex in AD patients than in controls, although there was no significant difference in clearance from the cerebellar cortex between AD patients and healthy controls (figure 2). SUVs for the cerebellar cortex late in the scan when ^{18}F-BAY94-9172 binding reaches an apparent steady state were not significantly different between AD patients and healthy controls, validating its selection as a reference region. The ratio of cortical to cerebellar binding became constant in AD patients and healthy controls by 90 min after the injection of tracer (figure 2). Analysis of venous plasma samples by HPLC showed that 12% of the compound remained at 20 min and 5% at 60 min after injection.

^{18}F-BAY94-9172 binding was present in the white matter (figure 3) in all healthy controls. In two healthy individuals, an 80-year-old man and a 76-year-old woman, both with no family history of dementia and no subjective or objective memory complaints, mild binding was seen in the orbitofrontal cortex and posterior cingulate/precuneus cortex. In another control, a 63-year-old man with a strong family history of AD, there was mild diffuse cortical binding with occipital sparing. The scans from the two men were read as "probable AD" by the reporting clinician (figure 3).

All AD patients showed extensive cortical ^{18}F-BAY94-9172 uptake that was greater in the frontal and posterior cingulate/precuneus cortex than in the lateral temporal and parietal cortex (figure 4). There was relative sparing of occipital, primary sensorimotor, and mesial temporal cortex with no appreciable binding in cerebellar cortex.

Four of the five FTLD patients had no cortical binding. One FTLD patient, a 74-year-old woman with semantic dementia, showed mild frontal binding of ^{18}F-BAY94-9172, but the scan was read as normal by the reporting clinician.

Blinded reading of the images obtained 90–120 min after injection correctly distinguished AD patients from controls and FTLD patients in all cases except for the two healthy controls discussed above. These healthy controls were misclassified as probable AD. The sensitivity of ^{18}F-BAY94-9172 PET for the detection of AD against diagnosis based on clinical criteria was 100% with a specificity of 90%.

The SUVR was calculated from the data acquired over the 90–120 min post-injection period because the ratio of binding in the cortical regions to that in the cerebellar cortex reached a plateau by 90 min. The table shows the SUVR and effect size for the 15 healthy controls compared with the 15 AD patients for each of the regions assessed. The SUVR was significantly greater in AD patients in all cortical regions and the striatum. The individual neocortical SUVR values of all the participants are shown in figure 5. Neocortical SUVR in healthy controls was 1·29±0·17 compared with 2·02±0·28 in AD patients ($p<0·0001$; effect size $d=3·14$). All the FTLD patients had neocortical SUVR similar to healthy controls and there was no overlap with the AD patients (figure 5). Neocortical SUVR correlated inversely with MMSE when all individuals were analysed together ($r=0·66$, $p=0·0001$), but there was no correlation within diagnostic groups (eg, in AD patients, $r=0·06$, $p=0·84$).

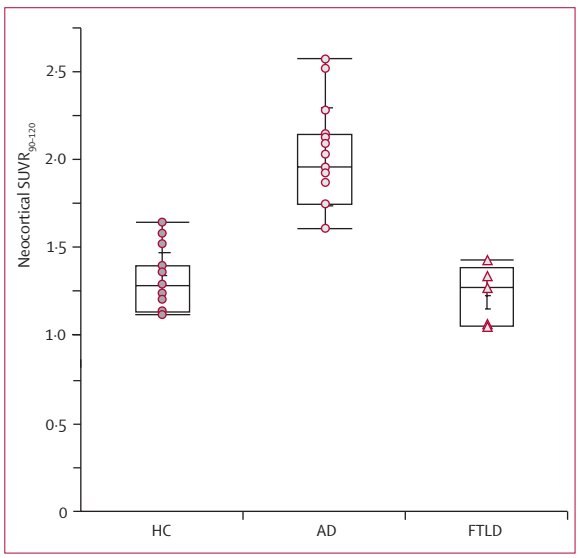

Figure 5: **Neocortical SUVR 90–120 min values in 15 healthy controls (HC), 15 AD patients, and five FTLD patients**
Each dot represents one individual. Box plots show the median value and interquartile range; the small horizontal lines show 1 SD above and below the mean.

Three healthy controls did not have the initial dynamic scan, which prevented the calculation of DVRs. In the remaining participants, a significantly higher DVR was found in AD patients in all cortical regions and in the striatum. The neocortical DVR was 1·71±0·24 in AD patients versus 1·21±0·17 in healthy controls ($p<0·0001$, Cohen's effect size $d=2·41$). SUVRs showed higher values in AD patients compared with healthy controls than did DVRs, but the rank order of regional values was identical. Both measures indicated that the greatest binding was in the frontal and precuneus cortex, whereas the greatest effect size between AD patients and healthy controls was in the lateral temporal and parietal cortex. SUVRs correlated strongly with DVRs in all cortical regions including the composite neocortical region ($r=0·98$, $p<0·0001$).

Discussion

^{18}F-BAY94-9172 binding matched the reported histopathological distribution of neuritic plaques in AD, corresponding closely to stage C of Braak's Aβ deposition categories.[22,23] The cortical binding of ^{18}F-BAY94-9172 provided robust separation of individuals with AD from healthy elderly controls and patients with FTLD. This separation was achieved either with visual image interpretation or a simple semiquantitative measure, the ratio of binding in neocortex to cerebellar grey matter expressed as SUVR. Furthermore, these results were obtained with only 30 min of scan acquisition, which began 90 min after injection of the tracer. Such properties indicate that ^{18}F-BAY94-9172 PET might be suitable for use in clinical practice. The acquisition time allows economical use of a PET camera and should be tolerated by elderly patients. Shorter scanning times are feasible but need validation. Furthermore, the decay half-life of ^{18}F makes centralised production with distribution to multiple PET sites possible, thereby improving access to Aβ imaging while simultaneously reducing the cost.

Our results with ^{18}F-BAY94-9172 PET compare favourably with those reported in ^{11}C-PIB PET studies.[1–12] The distribution of ^{18}F-BAY94-9172 binding is almost identical to that reported for ^{11}C-PIB, but the degree of binding is slightly less. The mean neocortical SUVR for ^{18}F-BAY94-9172 in AD patients was 57% greater than in healthy controls. Our previously reported experience with ^{11}C-PIB with the same equipment and quantitative methods is that binding is 70% higher on average in AD patients than in healthy controls.[2] Despite this finding, ^{18}F-BAY94-9172 yielded similarly large effect size and accuracy figures to those reported with ^{11}C-PIB for distinction of AD patients from healthy controls and FTLD patients.[2,21]

FTLD accounts for about 15–20% of all dementia cases.[24] The frontal (behavioural) and the temporal (semantic) forms of FTLD rarely have Aβ plaques at post-mortem examination.[24] Therefore the ability to image Aβ may allow distinction of AD from FTLD with great accuracy.[2,5] Four of our FTLD patients (two with frontotemporal dementia and two with semantic dementia) had no grey-matter ^{18}F-BAY94-9172 retention, allowing them to be easily distinguished from AD patients. One had mild frontal binding, but was read as normal by the blinded reviewer and had a neocortical SUVR within the normal range. ^{18}F-BAY94-9172 shares many structural and pharmacological properties with thioflavin-T derivatives such as PIB. PIB does have some affinity for tau, or even α-synuclein, in human brain specimens when applied at much higher concentration than those achieved during PET studies.[25,26] ^{18}F-BAY94-9172 may also display some affinity for tau under certain circumstances, and further work in this area is thus warranted. The rapid rate of metabolism of ^{18}F-BAY94-9172 is similar to that of PIB.[21] Some of the metabolites of BAY94-9172 are lipophilic and therefore may contribute to background brain radioactivity. Further characterisation of the metabolites is in progress.

Three ^{18}F-BAY94-9172 scans showed cortical binding among the 15 healthy controls (20%) in this study and two of these were read as "probable AD" by the blinded reviewer. This is consistent with ^{11}C-PIB studies that have reported positive scans in up to 23% of normal elderly individuals,[1,2] and with post-mortem studies that have reported moderate numbers of Aβ plaques in the cerebral cortex of more than a quarter of non-demented people aged over 75 years.[27,28] The reported post-mortem frequency of Aβ deposition in non-demented people at a given age is similar to the incidence of AD in people aged 5–10 years older, suggesting that Aβ deposition precedes the dementia of AD by this time period.[22,29,30] Further evidence that Aβ deposition precedes the clinical expression of AD is provided by the relation between episodic memory function, the first cognitive domain to decline in AD, and ^{11}C-PIB binding in non-demented elderly individuals.[10] Longitudinal studies are underway to determine whether apparently healthy individuals with cortical binding of Aβ ligands such as ^{11}C-PIB and ^{18}F-BAY94-9172 will develop the clinical features of AD, and thus the true specificity of Aβ imaging for very early, even preclinical diagnosis of AD.[31] Such a tool would open up new possibilities for early intervention and prevention of clinical AD.[32]

Our results suggest that ^{18}F-BAY94-9172 can reliably detect Aβ deposition and thereby aid early diagnosis, differential diagnosis, and therapeutic monitoring in AD. ^{18}F-BAY94-9172 provides images of similar appearance to ^{11}C-PIB without the inherent limitation of the 20 min half-life that makes use of ^{11}C-PIB potentially problematic in clinical practice. Further validation of ^{18}F-BAY94-9172 is required, including full characterisation of the metabolism and kinetics to determine the most precise and appropriate quantification method for applications such as disease and therapeutic monitoring. The development of ^{18}F-BAY94-9172 promises to be an important step towards the integration of Aβ imaging into clinical practice and towards meeting the desired goal of earlier diagnosis of AD to assist the development of preventive therapeutics and early intervention.

Contributors

HPK, WZ, MPK, and DS discovered and characterised BA94-9172 (previously known as AV-1). TD, GH, SK, MF, SL, LMD, and LL undertook further preclinical development of the compound. CCR, UA, WB, RM, KLP, GO'K, HT-D, GC, SUB, GJ, KLD-R, CLM, and VLV designed, performed, and analysed this study of BA94-9172 in human beings.

Conflicts of interest

As employees or co-owners of Avid Radiopharmaceuticals Inc, HPK, WZ, MPK, and DS receive payment and royalties from the sale of intellectual property rights to BA94-9172. TD, GH, SK, MF, SL, LMD, and LL are employees of Bayer Schering Pharma, which recently sublicensed the rights to AV-1 from Avid Radiopharmaceuticals Inc. CCR, GO'K and VLV provide external consultant services to Bayer Schering Pharma. The other authors have no conflicts of interest.

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Imaging β-amyloid burden in aging and dementia

C.C. Rowe, MD
S. Ng, MBBS
U. Ackermann, PhD
S.J. Gong, PhD
K. Pike, BSc
G. Savage, PhD
T.F. Cowie, BSc, MBA
K.L. Dickinson, BSc
P. Maruff, PhD
D. Darby, PhD
C. Smith, MSc
M. Woodward, FRACP
J. Merory, FRACP
H. Tochon-Danguy, PhD
G. O'Keefe, PhD
W.E. Klunk, MD
C.A. Mathis, PhD
J.C. Price, PhD
C.L. Masters, MD
V.L. Villemagne, MD

CME

Address correspondence and reprint requests to Dr. C.C. Rowe, Department of Nuclear Medicine, Centre for PET, Austin Health, 145 Studley Rd., Heidelberg, Victoria 3084, Australia
christopher.rowe@austin.org.au

ABSTRACT Objective: To compare brain β-amyloid (Aβ) burden measured with [^{11}C]Pittsburgh Compound B (PIB) PET in normal aging, Alzheimer disease (AD), and other dementias. **Methods:** Thirty-three subjects with dementia (17 AD, 10 dementia with Lewy bodies [DLB], 6 frontotemporal dementia [FTD]), 9 subjects with mild cognitive impairment (MCI), and 27 age-matched healthy control subjects (HCs) were studied. Aβ burden was quantified using PIB distribution volume ratio. **Results:** Cortical PIB binding was markedly elevated in every AD subject regardless of disease severity, generally lower and more variable in DLB, and absent in FTD, whereas subjects with MCI presented either an "AD-like" (60%) or normal pattern. Binding was greatest in the precuneus/posterior cingulate, frontal cortex, and caudate nuclei, followed by lateral temporal and parietal cortex. Six HCs (22%) showed cortical uptake despite normal neuropsychological scores. PIB binding did not correlate with dementia severity in AD or DLB but was higher in subjects with an *APOE*-ε4 allele. In DLB, binding correlated inversely with the interval from onset of cognitive impairment to diagnosis. **Conclusions:** Pittsburgh Compound B PET findings match histopathologic reports of β-amyloid (Aβ) distribution in aging and dementia. Noninvasive longitudinal studies to better understand the role of amyloid deposition in the course of neurodegeneration and to determine if Aβ deposition in nondemented subjects is preclinical AD are now feasible. Our findings also suggest that Aβ may influence the development of dementia with Lewy bodies, and therefore strategies to reduce Aβ may benefit this condition. **NEUROLOGY 2007;68:1718–1725**

Histopathologic studies show extensive cortical β-amyloid (Aβ) deposition in Alzheimer disease (AD), but it may also be found in asymptomatic elderly persons, adults with Down syndrome, and in dementia with Lewy bodies (DLB). In Down syndrome, Aβ deposition begins over a decade prior to the dementia that develops in the majority of persons with this condition.[1] Asymptomatic cortical Aβ deposition in elderly individuals is well documented with one-fourth or more of the nondemented population age over 75 years having moderate numbers of neuritic plaques in the cerebral cortex.[2,3] The neuropathologic findings in DLB, a condition that may account for up to 15% of dementia, frequently includes Aβ plaques and neurofibrillary tangles (NFTs).[4-6] Consequently, the term "Lewy body variant of AD" is preferred by some authors.[7] "Pure DLB" with no Aβ accumulation is seen in only 10 to 20% of clinically diagnosed cases.[4,8-12] Frontotemporal dementia (FTD) accounts for another 15 to 20% of dementia.[13] The frontal (behavioral) and the temporal (semantic) forms of FTD rarely have Aβ plaque at post mortem.[13] Hence, the ability to image Aβ may allow distinction of AD from FTD and give new insights into the role of Aβ in DLB.

(*N*-Methyl-[^{11}C])2-(4′-methylamino-phenyl)-6-hydroxy-benzothiazole ([^{11}C]6-OH-BTA-1), also known as "Pittsburgh Compound B" ([^{11}C]PIB), a carbon-11-labeled derivative of the thioflavin-T amyloid dye, binds with high affinity and high specificity to neuritic Aβ

From the Department of Nuclear Medicine (C.C.R., S.N., U.A., S.J.G., K.L.D., C.S., H.T.-D., G.O.,V.L.V.), Centre for PET, Austin Health, Heidelberg, Departments of Medicine and Aged Care (C.C.R, M.W., J.M.), Austin Health, University of Melbourne, School of Psychology (K.P., G.S.), Psychiatry and Psychological Medicine, Monash University, Melbourne, Department of Pathology (T.F.C., C.L.M., V.L.V.), University of Melbourne, Cogstate Pty Ltd.(P.M., D.D.), Melbourne, and Mental Health Research Institute of Victoria (C.L.M., V.L.V.), Parkville, Victoria, Australia; and Departments of Radiology and Psychiatry (W.E.K., C.A.M., J.C.P.), University of Pittsburgh, PA.

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Table 1 Group mean clinical data

	HC, n = 27	MCI, n = 9	AD, n = 17	DLB, n = 10	FTD, n = 6
Age (range), y	72.6 ± 6.9 (59–84)	73.3 ± 10.9 (50–83)	74.0 ± 11.3 (56–91)	72.0 ± 5.4 (63–81)	71.5 ± 9.4 (59–81)
Female/male	13:14	7:2	9:8	2:8	1:5
Education, y	12.5 ± 3.5	11.8 ± 4.3	12.3 ± 4.8	9.3 ± 0.9	11.8 ± 8.3
MMSE	29.2 ± 0.9	26.7 ± 1.6	22.1 ± 5.5*	20.8 ± 7.2*	25.7 ± 3.4
CDR	0.0 ± 0.0	0.3 ± 0.2	1.2 ± 0.7*	1.6 ± 0.8*	0.7± 0.3*
APOE ε2/3	6	2			
APOE ε 3/3	13	3	7	2	4
APOE ε 2/4	1		2		
APOE ε 3/4	6	1	5	6	2
APOE ε 4/4	1	3	2	1	

Values expressed as means ± SD.
*Significant results compared with controls ($p < 0.05$).
HC = healthy controls; MCI = mild cognitive impairment; AD = Alzheimer disease; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating.

plaques.[14,15] PIB does not show significant binding to diffuse plaque, NFT, or "pure" DLB brain homogenates.[16] Human PET studies have shown robust cortical binding in AD patients[17-21] and correlation with the rate of cerebral atrophy in AD subjects,[22] with decreased CSF $A\beta_{1-42}$ in both demented and nondemented subjects[23] and with parieto-temporal hypometabolism.[24]

In this study we sought to compare [^{11}C]PIB PET as a biomarker for Aβ burden in AD, DLB, FTD, mild cognitive impairment (MCI), and normal elderly persons with previously established neuropathologic findings in these conditions and with clinical features.

METHODS Twenty-seven elderly individuals with well documented normal cognitive function, 17 patients with mild to moderate AD, 10 patients with DLB, 6 patients with FTD, and 9 subjects with MCI were recruited for the study (table 1). Normal volunteers were recruited from a cohort of subjects participating in the longitudinal Healthy Aging Study at the Mental Health Research Institute of Victoria and had shown normal cognitive performance on neuropsychological tasks that included California Verbal Learning Test (CVLT II), Rey figure, Logical Memory, verbal and categorical fluency, Boston Naming Task, and digit span. All subjects in the current study were assessed with this neuropsychological test battery, the Mini-Mental State Examination (MMSE),[25] and the Clinical Dementia Rating[26] within 1 week of the PIB scan. All AD patients met National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD,[27] whereas all subjects in the DLB group met the consensus criteria for probable DLB of cognitive fluctuation, visual hallucinations, and parkinsonism.[4] FTD subjects had characteristic clinical presentations[13] and frontal lobe or temporal lobe atrophy on MRI with concordant hypometabolism on fluorodeoxyglucose PET. MCI subjects met the Petersen criteria of subjective and objective cognitive difficulties, predominantly affecting memory, in the absence of dementia or significant functional loss.[28] All patients were recruited from the Austin Health Memory Disorders and Neurobehavioral Clinics.

Written informed consent for participation in this study was obtained prior to the scan. Approval for the study was obtained from the Austin Health Human Research Ethics Committee.

All subjects underwent a three-dimensional spoiled gradient echo T1-weighed MRI acquisition for screening and subsequent co-registration with the PET images.

APOE genotype was determined by PCR amplification of genomic DNA.

Production of [^{11}C]PIB was performed in the Centre for PET, Austin Hospital, using the one-step [^{11}C]methyl triflate approach.[29] The average radiochemical yield was 30% after a synthesis time of 45 minutes with a radiochemical purity of >98% and a specific activity of 30 ± 7.5 GBq/μmol. Each subject received 375 ± 18 MBq [^{11}C]PIB by IV injection over 1 minute. Imaging was performed with a Phillips Allegro PET camera. A rotation transmission sinogram acquisition in three-dimensional mode with a single ^{137}Cs point source was performed before the injection of the radiotracer for attenuation correction. A 90-minute list-mode emission acquisition was performed in three-dimensional mode after injection of PIB. List-mode raw data were sorted off line into 4 × 30-second, 9 × 1-minute, 3 × 3-minute, 10 × 6-minute, and 2 × 10-minute frames. The sorted sinograms were reconstructed using a three-dimensional RAMLA algorithm.

Co-registration of the PET images with each individual's MRI was performed with SPM2 (Statistical Parametric Mapping, MRC Cognition and Brain Sciences Unit).[30] For registration purposes, the initial frames of the dynamic PET studies were summed. The early frames of the study reflect regional blood flow allowing an easy co-registration with the MRI. Regions of interest (ROIs) were then drawn on the individual MRI. Mean radioactivity values were obtained from ROIs for cortical, subcortical, and cerebellar regions as listed in table 2, and decay-corrected time–activity curves were generated. White matter ROIs were placed at the centrum semiovale, and

Table 2 PIB DVR values (means ± SD) in aging healthy controls, subjects with MCI, and patients with dementia

Region	HC, n = 27	MCI, n = 9	AD, n = 17	DLB, n = 10	FTD, n = 6
Neocortex*	1.2 ± 0.2	1.6 ± 0.4†‡	2.0 ± 0.2†	1.7 ± 0.3†‡	1.1 ± 0.1‡
Dorsolateral prefrontal	1.12 ± 0.20	1.45 ± 0.40†‡	2.02 ± 0.30†	1.64 ± 0.42†‡	1.03 ± 0.14‡
Ventrolateral Prefrontal	1.20 ± 0.24	1.61 ± 0.54†‡	2.18 ± 0.29†	1.81 ± 0.40†‡	1.07 ± 0.13‡
Orbitofrontal	1.22 ± 0.21	1.67 ± 0.52†‡	2.10 ± 0.28†	1.74 ± 0.37†‡	1.12 ± 0.10‡
Gyrus rectus	1.30 ± 0.27	1.71 ± 0.48†‡	2.19 ± 0.38†	1.96 ± 0.57†	1.16 ± 0.14‡
Post. cingulate gyrus	1.27 ± 0.24	1.72 ± 0.54†‡	2.19 ± 0.26†	1.72 ± 0.41†‡	1.10 ± 0.05‡
Ant. cingulate gyrus	1.27 ± 0.26	1.65 ± 0.44†‡	2.16 ± 0.26†	1.78 ± 0.41†	1.13 ± 0.09‡
Superior parietal	1.10 ± 0.18	1.49 ± 0.41†‡	1.93 ± 0.19†	1.49 ± 0.26†‡	1.07 ± 0.10‡
Lateral occipital	1.21 ± 0.11	1.35 ± 0.17‡	1.56 ± 0.19†	1.43 ± 0.21†	1.21 ± 0.07‡
Lateral temporal	1.19 ± 0.18	1.50 ± 0.37†‡	1.90 ± 0.22†	1.61 ± 0.35†‡	1.15 ± 0.11‡
Mesial temporal	1.16 ± 0.11	1.23 ± 0.17	1.35 ± 0.13†	1.29 ± 0.15†	1.02 ± 0.12‡
Caudate nucleus	1.30 ± 0.21	1.64 ± 0.43†‡	2.16 ± 0.37†	1.76 ± 0.37†	1.22 ± 0.10‡
Putamen	1.31 ± 0.16	1.51 ± 0.29‡	1.97 ± 0.30†	1.67 ± 0.28†	1.21 ± 0.10‡
Thalamus	1.57 ± 0.30	1.66 ± 0.19	1.86 ± 0.34†	1.68 ± 0.19	1.45 ± 0.12
Midbrain	1.59 ± 0.13	1.64 ± 0.12	1.63 ± 0.18	1.58 ± 0.12	1.51 ± 0.16
White matter	1.39 ± 0.19	1.25 ± 0.24	1.36 ± 0.24	1.33 ± 0.36	1.29 ± 0.15

*Neocortex comprises the average DVR values for frontal, parietal, cingulate, occipital, and lateral temporal cortices, subsequently shown independently in the table.
†Significant results vs controls ($p < 0.05$).
‡Significant results for DLB and FTD vs AD ($p < 0.05$).
PIB = Pittsburgh Compound B; DVR = distribution volume ratio; MCI = mild cognitive impairment; HC = healthy control subject; AD = Alzheimer disease; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia.

the cerebellar regions were placed over the cerebellar cortex, taking care to avoid white matter. The orbitofrontal ROI included both the mesial and lateral aspects (including superior, middle, and inferior frontal gyri). No correction for partial volume was applied to the PET data.

Distribution volume ratios (DVRs) were determined through graphical analysis.[31] To avoid arterial blood sampling, a simplified approach was applied using the cerebellar cortex, a region relatively unaffected by amyloid deposition, as input function.[17,20,31] Besides regional DVR values, the mean of the DVRs for frontal, cingulate, parietal, lateral temporal, and occipital cortex was calculated and termed the neocortical DVR. DVR images were created for visual inspection with a rainbow color scale.

Standardized uptake value (SUV), defined as the decay-corrected brain radioactivity concentration, normalized for injected dose and body weight, was calculated for the cerebellar cortex late in the scan when PIB binding reaches apparent steady state[20,32] to compare binding in the reference region with age, diagnosis, and cognitive status.

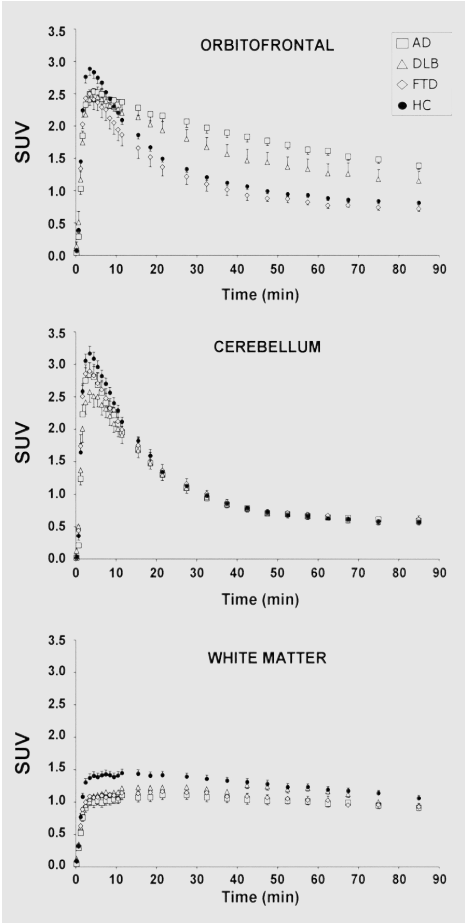
Statistical evaluations were performed using a Wilcoxon signed-ranks test followed by a Dunnet test to compare each group with controls and a Tukey–Kramer highly significant difference test to establish differences between group means. Pearson product–moment correlation analyses were conducted between the neocortical DVR and clinical features. Data are presented as means ± SD unless otherwise stated.

RESULTS Clinical data. The subject groups were well matched for age and for years of education (table 1). Most cases of AD were of mild severity with a mean CDR score of 1.2 and mean MMSE score of 22. DLB subjects had slightly greater cognitive impairment with mean MMSE of 21 and CDR of 1.6. All control subjects had a CDR score of 0 and MMSE of >27, whereas all MCI subjects had a CDR score of 0 or 0.5 and MMSE of >24.

[^{11}C]PIB distribution. Brain radioactivity peaked between 3 and 6 minutes post injection, and the binding appeared to be reversible with rapid washout from all areas in controls other than white matter (figure 1). [^{11}C]PIB cleared fastest from cerebellar cortex, and the rate was the same for all groups, consistent with the absence of significant Aβ in this region in all subjects (figure 1). The SUV measurements in the cerebellar cortex showed no difference between subject groups and no correlation with age or with dementia severity in the AD subjects as assessed by MMSE ($r = 0.11$, $p = 0.21$) or CDR ($r = -0.08$, $p = 0.74$).

On visual inspection of the DVR images, all AD subjects showed marked cortical PIB binding, greatest in the precuneus/posterior cingulate and frontal cortex and the caudate nuclei, followed by lateral temporal and parietal cortex. Occipital, sensorimotor, medial temporal, and thalamic gray matter was less affected (figure 2). Cerebellar cortex showed no uptake. Most DLB subjects also showed increased PIB binding, similar in distribution to AD (figure 2).

Figure 1 Time-activity curves



Time-activity curves demonstrating uptake and clearance of [^{11}C]Pittsburgh Compound B (PIB) in frontal cortex, cerebellar cortex, and white matter. There is greater retention of PIB in the frontal cortex in Alzheimer disease and to a lesser extent in dementia with Lewy bodies than in frontotemporal dementia or normal elderly control subjects. In contrast, clearance is identical in the cerebellar cortex, demonstrating that this is an appropriate reference region. There were no significant differences between groups in the clearance from white matter. SUV = standardized uptake value.

However, the degree of binding was generally lower and varied widely between DLB subjects ranging from normal to AD levels (figure 3). One DLB subject and all six FTD subjects had no gray matter PIB binding.

PIB binding in MCI subjects either clustered in an "AD-like" (n = 5) pattern that was indistinguishable from AD subjects or had normal binding (n = 4) (figure 3).

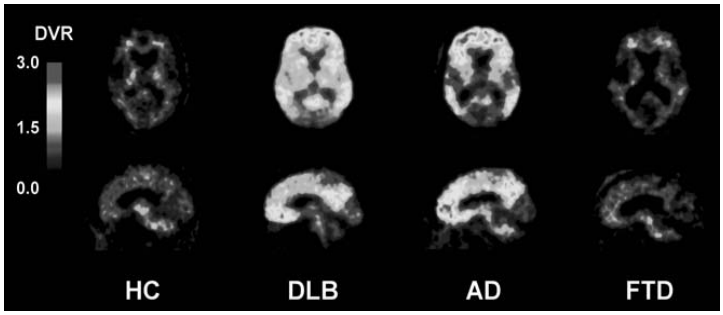
Twenty-one HCs showed no binding in cortical or subcortical gray matter, and their scans were clearly distinguishable from those of subjects with AD (figure 2). However, six (22% of HCs) showed a range of increased [^{11}C]PIB binding in gray matter (figure 3). Four of these six had binding in orbitofrontal cortex with variable involvement of cingulate, precuneus, and temporal cortex, a pattern similar to that seen in AD and that resembles the stages of Aβ deposition (figure 4).[33] One subject showed isolated binding in the right occipital lobe, and one displayed focal areas of binding in several cortical regions.

Regional DVR values confirmed higher binding in neocortical areas in AD and DLB patients when compared with HC subjects and no cortical binding in FTD (table 2). DVR values clustered in MCI to either the normal or the AD range (figure 3). In contrast to the 70 to 80% greater frontal and precuneus DVR in AD over controls, binding in the medial temporal region was only increased by 14% in AD.

Correlation with clinical features. ***Diagnosis.*** The PIB scans of all AD subjects could be readily distinguished from normal studies both visually and by neocortical DVR values. A cut-off value for the neocortical DVR defined as 2 SD greater than the HC mean detected all AD while including one HC. Three HCs could not be distinguished from AD by visual inspection and their DVR values were very close to those of the AD subjects. Three other HCs showed cortical PIB binding of clearly lesser degree and extent than seen in AD. PIB scans were able to distinguish all FTD subjects from AD subjects. PIB scans were not able to reliably distinguish DLB or MCI from AD other than in those cases with no or low cortical binding.

Age. The six HCs with increased PIB binding on visual inspection were older than the other HCs (78.5 vs 72.2 years; $p = 0.03$). On correlational anal-

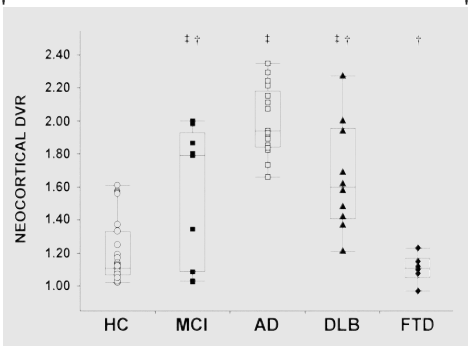
Figure 2 In vivo imaging of β-amyloid (Aβ) burden in aging and dementia



Representative distribution volume ratio (DVR) PET transaxial images (top) and sagittal images (bottom) of a 73-year-old healthy control (HC) subject (Mini-Mental State Examination [MMSE] = 30), a 78-year-old patient with dementia with Lewy bodies (DLB) (MMSE = 19), an 82-year-old patient with Alzheimer disease (AD; MMSE = 22), and an 80-year-old patient with frontotemporal dementia (FTD; MMSE = 25). DVR PET images show clear differences when comparing HC or FTD subjects with DLB or AD patients, with nonspecific Pittsburgh Compound B (PIB) binding in white matter in the HC and FTD subjects compared with PIB binding in the frontal, temporal, and posterior cingulate/precuneus cortex of the AD and DLB patients.

Box-and-whiskers plot displaying median and 1st and 99th percentiles of neocortical β-amyloid (Aβ) burden as quantified by [11C]Pittsburgh Compound B distribution volume ratio for Alzheimer disease (AD; □), dementia with Lewy bodies (DLB; ▲), frontotemporal dementia (FTD; ◆), mild cognitive impairment (MCI; ■), and healthy control (HC; ○). †Significant results for MCI, DLB, and FTD vs AD ($p < 0.05$). ‡Significant results vs controls ($p < 0.05$).

Figure 3 Box-and-whiskers plot



ysis, there was a nonsignificant trend toward greater neocortical DVR with increasing age in the HC ($r = 0.3$); however, there was no correlation when all subjects were combined or examined by disease groups.

Rate of disease onset. In the DLB subjects, high neocortical DVR correlated with shorter time between the onset of cognitive impairment and development of the diagnostic clinical features ($r = -0.75$, $p = 0.01$) (figure 5). Of all cortical areas, this correlation was strongest in the posterior cingulate cortex ($r = -0.8$, $p = 0.005$). There was no correlation in the AD group between neocortical DVR and time from onset of cognitive decline to diagnosis ($r = -0.06$, $p = 0.9$).

Cognitive status. Both the CDR and the MMSE correlated with neocortical DVR when all subjects were pooled (CDR: $r = 0.49$, $p < 0.001$; MMSE: $r = -0.42$, $p < 0.005$). However, there was no correlation in any group when analyzed separately. For example, in the AD group, there was no correlation between PIB DVR and MMSE score ($r = 0.06$, $p = 0.81$) or with specific domains of cognitive function such as episodic memory (CVLT II short delay recall $r = -0.32$, $p = 0.30$).

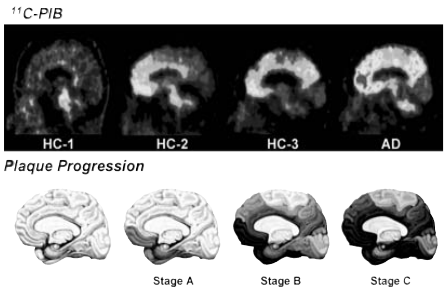
The cognitive performance of the HCs with cortical PIB binding compared with those without was not significantly different. The mean MMSE was 29 for both groups, and all subjects performed within the expected range for age and education on neuropsychological tasks. There was a minor but nonsignificant reduction in performance on several cognitive tests in those with PIB binding such as for the CVLT II long delay (9.8 ± 3.1 vs 11.8 ± 2.8). Likewise, no difference in cognitive deficits was observed between MCI subjects with and without cortical PIB binding.

APOE status. An *APOE* ε4 allele was present in 56% of AD, 78% of DLB, 44% of MCI, 33% of FTD, and 30% of HC subjects (table 1). With all subjects combined, the presence of an *APOE* ε4 allele was associated with higher PIB binding (neocortical DVR 1.61 ± 0.41 vs 1.38 ± 0.39, $p = 0.02$). Within groups there was no significant difference.

Medication. Ten of the 17 AD subjects were taking acetylcholine esterase inhibitor medication at the time of the PIB scan. Those on this medication showed no difference in PIB DVR vs the other AD subjects (1.97 ± 0.21 vs 2.05 ± 0.2; $p = 0.45$).

Representative sagittal PET images showing the regional uptake of [11C]Pittsburgh Compound B (PIB), reflecting β-amyloid (Aβ) burden in the brain, in three asymptomatic healthy age-matched control subjects (HC 1 to 3) and one patient with Alzheimer disease (AD; top), and schematics showing the stages of Aβ deposition in the human brain as proposed by Braak and Braak (bottom).[33] Twenty-two percent of HCs had PIB binding ranging from stages A to C. All AD subjects matched stage C.

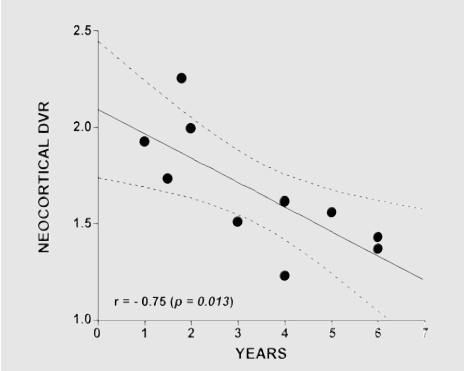
Figure 4 Representative sagittal PET images



DISCUSSION In vivo amyloid imaging with PET is allowing new insights into Aβ deposition in the brain, facilitating research into the causes, diagnosis, and future treatment of dementias where Aβ may play a role. In this study we have demonstrated that extensive Aβ deposition is present in the neocortex and caudate nuclei of all patients with AD, even when the severity of the disease is classified as mild. This is consistent with postmortem studies that suggest the deposition of Aβ is well advanced prior to the onset of dementia. Support for this hypothesis is provided by our observation of cortical PIB binding in 22% of the normal elderly subjects in this study. This accords well with the reported prevalence of AD at age 85 years of 15 to 25% and postmortem reports that 30% of nondemented older persons over age 75 have moderate numbers of neuritic plaques in the cerebral cortex.[2,34] The mean age of our normal cohort was 73 years and the mean age of those normal subjects with cortical PIB binding was 78 years. In a recent study of nondemented subjects, PIB binding was found in 3 of the 20 subjects over age 65.[35] These subjects showed no difference in cognitive performance vs those with no PIB uptake. Our HCs with PIB binding also showed no significant reduction in cognitive performance, though there was a trend on several measures that may have reached significance with larger subject numbers. A recent report of neuropathologic findings in 134 elderly persons without cognitive impairment found a slight but significant reduction in episodic memory test scores in those with moderate

Relationship between neocortical Pittsburgh Compound B distribution volume ratio and time elapsed (expressed in years) between first sign of cognitive impairment recalled by caregiver and development of the diagnostic clinical features of dementia with Lewy bodies ($r = -0.75$, $p = 0.013$). Dotted lines represent 95% confidence limits for the linear regression.

Figure 5 Relationship between neocortical Pittsburgh Compound B distributional volume ratio and time elapsed



numbers of neuritic plaques.[3] It is possible that PIB PET is detecting preclinical AD. Longitudinal observation of a large cohort of cognitively normal elderly subjects studied with PIB PET is required to confirm or refute this hypothesis.

We did not find a correlation between the Aβ burden and the severity of dementia in the AD cases. Neuropathologic reports are not consistent on this question, with studies reporting greater plaque density with worsening dementia,[36-38] no correlation,[2] or a correlation only in those under age 75.[39] Some have found a correlation with levels of soluble but not insoluble Aβ.[40] Our data suggest that Aβ deposition is an early event and likely to occur prior to demonstrable cognitive impairment with little subsequent change in Aβ burden. A recent report on PIB PET repeated 2 years apart in 16 AD subjects supports this interpretation, finding no change between scans.[41] The authors did find a correlation between the degree of PIB binding on the first scan and the likelihood of progression over this 2-year period. Caution is required in interpreting the apparent lack of correlation between PIB binding and dementia severity observed in our study. Studies to date, including ours, have not corrected the PET data for atrophy. Partial volume effects,[42] where increasing cortical atrophy results in an apparent reduction in radioactivity, could mask an increase in binding over time or with increasing dementia severity. Lack of sufficient cases with moderate or severe dementia and relatively small subject numbers may also result in failure to detect a correlation. Increased PIB binding in the cerebellar reference region would mask an increase in cortical binding. There are reports of Aβ in the cerebellum in advanced AD predominantly in diffuse plaques to which fibrillar dyes and PIB related compounds bind poorly.[16,43,44] Our SUV measurement of cerebellar PIB binding and our time–activity curves for cerebellar cortex found no evidence of increased uptake in AD with age or with increasing severity of dementia.

PIB binding in our AD patients closely matched the reported histopathologic distribution of neuritic plaques.[33,45,46] In all of the AD subjects in our study, the distribution of Aβ as measured by [^{11}C]PIB binding was extensive and corresponded closely to stage C of the Braak Aβ deposition categories (figure 4).[33,45] The high binding of PIB in the caudate nucleus has been observed by other groups.[17,35] Neuropathologic studies have reported high levels of Aβ in the caudate, less in the putamen, and little in the globus pallidus.[46,47]

The relatively small increase in binding in the medial temporal lobe agrees with the histopathologic observation that in mildly demented patients, the plaque density in the hippocampus is one-third that in the orbital cortex.[2] In our affected normal elderly subjects, the area that most frequently displayed PIB binding was the orbitofrontal cortex followed closely by the posterior cingulate/precuneus, consistent with the neuropathologic stages of neuritic plaque deposition.[33,45] White matter binding was observed in all subjects, and though it is likely to represent nonspecific binding, no explanation for it has yet emerged.

In vitro studies indicate that PIB binding is highly specific for Aβ when using a tracer dose at nanomolar concentration, and our robust difference between the binding in AD vs HC and FTD shows that this specificity holds for in vivo studies. At the nanomolar concentrations attainable in human PET studies, [^{11}C]PIB and related benzothiazole derivatives bind at 10-fold higher levels to AD frontal cortex homogenates of extracellular plaque and perivascular Aβ than the background binding observed in amyloid-free control brain frontal cortex.[16] Under these same conditions, benzothiazole compounds do not produce detectable binding to brain homogenates from the frontal cortex of pure DLB brain.[16]

In this study, PIB binding was consistent with the histopathologic observation that the density of classic Aβ deposits is significantly lower in the cortex of DLB subjects compared with AD and absent in a small proportion of DLB.[4,8-12,48]

Our observation that higher Aβ burden is associated with more rapid development of the full DLB phenotype has not been previously reported. Data suggest that Aβ may influence the development of DLB. The cortical Aβ deposits in PD with dementia, a condition with many similarities to DLB, are asso-

ciated with extensive α-synuclein lesions and higher levels of insoluble α-synuclein.[49] Further evidence comes from studies in transgenic mice. Crossbreeding of mice that develop α-synuclein related lesions with mice that develop cerebral Aβ deposits results in greater aggregation of α-synuclein and exacerbation of α-synuclein-dependent neuronal injury.[50] These data suggest a possible role for Aβ in DLB. An alternative explanation is that factors favoring amyloid deposition also promote synuclein pathology. Either way, our findings suggest that strategies to reduce Aβ may also be of benefit in DLB. Forty to sixty percent of subjects with MCI progress to AD.[28] Longitudinal follow-up studies will determine if the two well differentiated patterns of PIB binding observed in our MCI subjects reliably predict those who will progress to AD.

None of the FTD subjects in our study showed cortical PIB binding. This suggests that PIB PET may assist the differential diagnosis of AD from FTD.

A potential limitation of our study is the reliance on clinical diagnosis as the "gold standard" rather than neuropathology. Consequently, we aimed for specificity rather than sensitivity, selecting only those subjects with characteristic clinical presentations supported by appropriate structural and functional imaging findings. For example, all the DLB subjects had all of the three consensus diagnostic features of persistent visual hallucinations, parkinsonism, and fluctuation in cognition. Neuropathologic studies have shown that the presence of two or more of these features results in a specificity of greater than 85% for DLB.[4] Our observation that all of the AD subjects had extensive PIB uptake and none of the FTD subjects had PIB uptake indicates that our approach to subject selection produced reasonably pure cohorts. At this time postmortem confirmation of the diagnoses is available in only one subject. This patient had a clinical diagnosis of DLB and had high cortical PIB binding indistinguishable from the AD subjects. Postmortem neuropathologic examination confirmed the presence of large numbers of cortical neuritic Aβ plaques, Lewy bodies, and NFTs. Another limitation of our study is the relatively small number of subjects with DLB and MCI with great variability in PIB binding. Therefore, though PIB PET images correlate well with neuropathologic observations of the incidence and distribution of Aβ plaques in aging and neurodegenerative diseases in this study, confirmation with larger sample sizes is warranted before it can be claimed that in vivo imaging of Aβ will allow more accurate and specific diagnosis of dementia.

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Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion

Philip Scheltens, Nick Fox, Frederik Barkhof, and Charles De Carli

Neuroimaging is increasingly used to aid diagnosis in dementia. The traditional view that imaging is important solely as means of excluding treatable causes of dementia is maintained by many guidelines. These conditions however, account for a tiny proportion (<1%) of all causes of dementia. Over the past few years it has been recognised that a more accurate diagnosis and prognosis is important for patients and their families. The different pathological processes that produce cerebral dysfunction at a cellular level also produce macroscopic effects that can be detected in vivo with imaging. Clinically useful measures that distinguish between neurodegenerative disorders at an early stage are still awaited. The most likely future use of structural imaging will be the identification of patients at risk for Alzheimer's disease or with preclinical Alzheimer's disease. For magnetic resonance imaging (MRI) this will mean focusing on those areas that are affected earliest in the disease; ie, entorhinal cortex and hippocampus, using high resolution structural MRI or sophisticated brain mapping techniques. Imaging research is also likely to focus on measuring progression and detecting therapeutic effect. As such, MRI is already become an indispensable tool in clinical trials in dementia.

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Dementia, the progressive impairment of many cognitive domains, can be produced by a large number of pathological processes. These underlying processes can be difficult to distinguish from each other clinically, particularly in their early stages. Only a few of the causes of dementia can be identified by laboratory tests. Screening blood tests, such as syphilis serology and measures of thyroid function or vitamin B12, are widely used, but the yield from these tests is very low. As a result, there has been increasing use of neuroimaging to aid diagnosis in dementia. Traditionally, imaging was thought to be important only as a means of excluding treatable causes of dementia. These disorders account for a tiny proportion (< 1%) of all causes of dementia; far more common are Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia.[1] In the past, the prevailing attitude to the diagnosis of these disorders was that they were difficult to diagnose with any certainty and that in any case there was little point in making an attempt because there was no treatment. During the past few years, this attitude has changed, with the recognition that more accurate diagnosis and prognosis are important for patients and their families. A specific diagnosis is increasingly influencing management, whether it is in the use of acetylcholinesterase inhibitors in Alzheimer's disease and dementia with Lewy bodies, the modification of vascular risk factors in vascular dementia, or caution in the use of neuroleptics in dementia with Lewy bodies or frontotemporal dementia. The possibility of disease-slowing therapies will further increase the need for an earlier and more accurate diagnosis in dementia.[2] The different pathological processes that produce cerebral dysfunction at a cellular level also produce macroscopic effects that can be detected in vivo with imaging. For these reasons, neuroimaging in general, and magnetic resonance imaging (MRI) in particular, are increasingly being regarded as an essential part of the investigation of a patient with dementia. This review deals with the changing roles of structural MRI in dementia, its value in particular disorders, its limitations, and its potential.

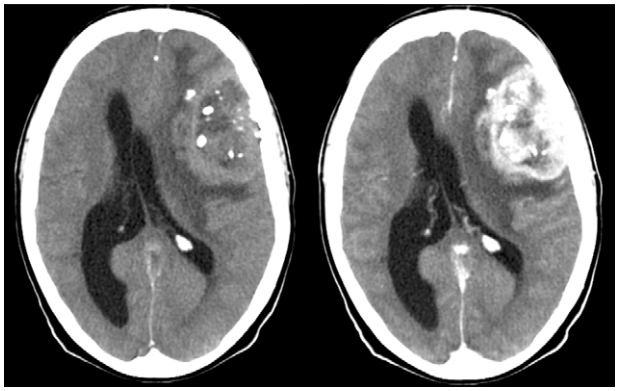

Figure 1. 71-year-old woman with rapidly progressive dementia. CT scan before (left) and after (right) contrast enhancement shows a huge space-occupying lesion. The pathological diagnosis was glioma.

The exclusionary approach

Traditionally, computed tomography (CT) and MRI were used to exclude other abnormalities that were potentially

PS is at the Department of Neurology and Alzheimer Centre and FB is at the Department of Diagnostic Radiology and Image Analysis Centre, Vrije Universiteit Medical Centre, Amsterdam, Netherlands. NF is a member of the Dementia Research Group at the Institute of Neurology, University College London, UK. CdC is at the University of California–Davis, Alzheimer's Disease Center, Sacramento, CA, USA.

Correspondence: Dr Philip Scheltens, Department of Neurology/Alzheimer Centre, Vrije Universiteit Medical Centre, PO Box 7057, 1007 MB Amsterdam, Netherlands. Tel +31 20 4440742; fax +31 20 4440715; email p.scheltens@vumc.nl

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Table 1. Visual and linear measurements of atrophy in the medial temporal lobe on MRI in dementia

Ref	Individuals studied	Field strength (T)	Slice thickness (mm)	Anatomy assessment	Results
19	28 AD, 28 controls	1·5	1·3	Radial width of temporal horn corrected for age	Largest width sensitivity 75%, specificity 93%
23	21 AD, 21 controls	0·6	5	Coronal, 0–4 scale	Sensitivity 81%, specificity 67%
24	34 AD, 39 controls	1·5	3–5	0–4 rating scale plus linear assessment	Sensitivity 41%, specificity 90%
25	26 AD, 21 controls	1·5	1	Linear measurement	Sensitivity 81%, specificity 96%
26	130 controls, 72 MCI, 73 mild AD, 130 AD	1·5	6	Axial, 0–3 rating scale; k=0·92	Sensitivity 95%, specificity 85% on discriminant analysis
27	77 AD, 61 depression, 44 other dementias, 40 controls	0·3	5·1	Coronal, 0–3 scale, anterior hippocampal atrophy best	Sensitivity 83%, specificity 80% *vs* controls and 89% *vs* other dementias
28	10 AD, 41 controls	0·6	5	Coronal, 0–4 scale	Sensitivity 70%, specificity 76%
29	39 AD, 15 other dementias, 33 controls	1·0	3	Coronal, linear measurements	Left hippocampal height: sensitivity 79%, specificity 69%
30	28 AD, 26 DLB, 24 vascular dementia, 26 controls	1·0	5	Coronal, visual 0–4 scale	AD *vs* controls: sensitivity 100%, specificity 96% DLB *vs* AD: sensitivity 38%
31	24 AD, 15 controls	0·3	5·1	Coronal, visual 0–3 scale	Sensitivity 92%, specificity 93%
32	41 AD, 36 other dementias, 66 controls	1·5	2·8	Coronal, 0–4 scale	Sensitivity 95%, specificity 96% *vs* controls and 85% *vs* other dementias
33	38 AD, 21 controls	1·5	5	Coronal, 0–4 scale	CDR 0·5: sensitivity 58%, specificity 81% CDR 1: sensitivity 79%, specificity 81% CDR 2: sensitivity 83%, specificity 95%.

AD=Alzheimer's disease; MCI=mild cognitive impairment; DLB=dementia with Lewy bodies; CDR=clinical dementia rating.

amenable to (surgical) treatment, such as a tumour (figure 1), haematoma, or hydrocephalus. The yield of such a procedure is probably less than 1%. In Farina and co-workers' study[3] of use of CT in 513 patients referred to a memory clinic, 362 were found to be demented. A potentially reversible cause of dementia was detected in only 26 (7·2%). However, CT did not reveal findings that had not been discovered clinically in any patient. Foster and colleagues[4] carried out a systematic review on the use of CT in dementia. Comparing costs and outcome, they concluded that the most cost-effective approach would be scanning of all patients under 65 years of age and treatment of only those with subdural haematoma. Treatment of apparent normal-pressure hydrocephalus actually reduced quality-adjusted survival. Chui and colleagues[5] also found that imaging did not reveal reversible disease in many cases, but directed diagnostic revisions that had an influence on care of the patient.

The inclusive approach

Imaging is increasingly being used to add positive or negative predictive value in the diagnosis of the more common dementing illnesses. The development of diagnostic clinical criteria has improved diagnostic accuracy, but it is still far from perfect. From clinicopathological correlation, the accuracy of criteria for Alzheimer's disease[6,7] is limited and depends on the expertise of the clinical centre, with specificity ranging between 76% and 88%, and sensitivity between 53% and 65%.[6–8] In population settings, reflecting more closely the common practice in non-specialised centres, the neuropathological confirmation rate of "probable" Alzheimer's disease is as low as 65%.[9] Varma and colleagues[10] found a very low specificity of 23% when using the criteria of the National Institute of Neurological Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) to distinguish patients with Alzheimer's disease from those with frontotemporal dementia. Diagnostic clinical criteria have also been developed for frontotemporal, vascular, and Lewy-body dementias.[11–13] The diagnostic accuracy of these criteria needs to be further defined. Neuroimaging is increasingly being used to add support to a clinical diagnosis. Imaging already forms an essential part of some clinical criteria for vascular dementia. Imaging evidence of cerebral atrophy, especially if progressive, has long been cited in criteria for Alzheimer's disease as lending support to this diagnosis. Similarly, frontal and temporal atrophy form part of the supporting evidence in consensus criteria for frontotemporal dementia. The value of imaging in dementia in clinical practice (ie, outside the research setting) is still not well defined. Nonetheless, there is clear potential for research findings to be used in routine clinical practice, and the recent advice from the American Academy of Neurology recommends that neuroimaging (CT or MRI) should be done in all cases of dementia.[14]

Medial-temporal-lobe atrophy

Neuropathological studies have implicated the medial temporal lobe as an early site of pathological involvement in Alzheimer's disease (consistent with the characteristic amnestic presentation in this disorder), and many imaging studies have therefore focused on this part of the brain. Although visibility of the medial temporal lobe is limited on CT, some CT studies have used assessments of structures in

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Table 2. Visual assessment of medial-temporal-lobe atrophy

Score	Width of choroid fissure	Width of temporal horn	Height of hippocampus
0	Normal	Normal	Normal
1	↑	Normal	Normal
2	↑↑	↑	↓↓
3	↑↑↑	↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓

↑=increased, ↓=decreased. Reproduced with permission of BMJ Publishing Group.[23]

this region with success.[15–17] The technique of Jobst and co-workers[15] required slices of 3 mm or thinner, oriented parallel to the medial temporal lobe, and skilful handling of the calliper. Studies in which this technique was used showed sensitivities between 70% and 92% and specificities between 80% and 95% in differentiating patients with Alzheimer's disease from controls.[18] However, the patients in these studies were moderately demented. An attempt to replicate these results by Frisoni and colleagues[19] gave maximum sensitivity of 74% (with specificity set at 95%). In addition, they found the reliability of the technique quite low, with intraclass correlation coefficients of 0·74 within raters and 0·78 between raters. Interestingly, they experimented with the measurement of the radial width of the temporal horn of the lateral ventricle and found that this feature had higher sensitivity (93%), specificity (97%), and reliability (intraclass coefficients between 0·94 and 0·98). More complex analytical tools such as volume measurements of the lateral and third ventricles on CT have never reached those values.[20]

The availability of MRI enabled the study of specific structures within the medial temporal lobe, such as the hippocampus itself, the parahippocampal gyrus, subiculum, entorhinal cortex, and amygdala. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) study group[21] and the work of Bobinski and colleagues[22] showed the close relations between atrophy on MRI of the temporal lobe in the living patient and necropsy findings of hippocampal atrophy. These structures have been measured with various tracing techniques and anatomical boundaries. Some studies have used linear or visual measurements.[19,23–33]

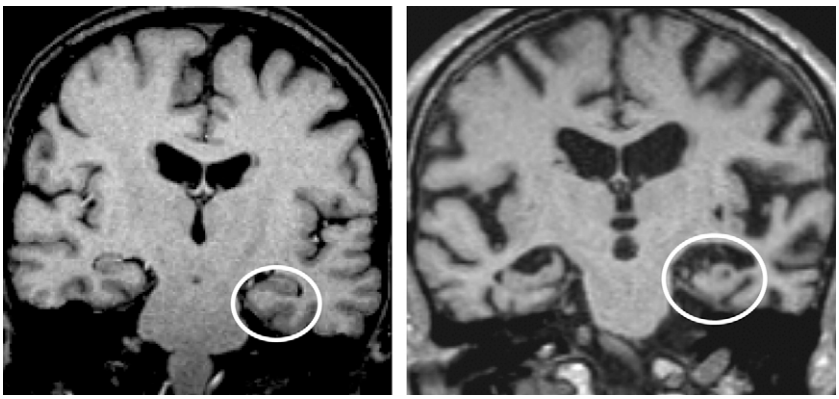

Figure 2. Coronal T1-weighted perpendicular to the long axis of the temporal lobe, indicating the absence (left) and presence (right) of medial-temporal-lobe atrophy.

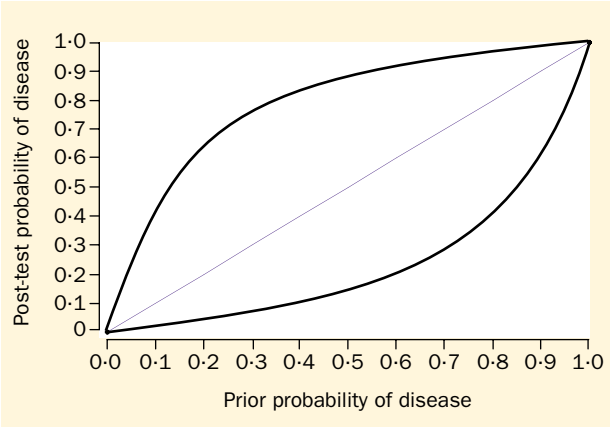

Figure 3. Post-test probability of disease with a test of sensitivity 85% and specificity 88% for any given pretest probability (prevalence of disease). The upper curve shows the incremental diagnostic gain from a positive result of a test (ie, presence of hippocampal atrophy on MRI) and the lower curve shows that from a negative result (ie, presence of hippocampal atrophy on MRI).

Because of their supposedly (but debatably) greater accuracy and reliability, other studies have used volume measures of structures in the medial temporal lobe. Comparative studies have found good correlations between these assessment techniques.[31,34] Table 1 lists the pertinent studies that have used these clinically applicable measurements for diagnostic purposes in dementia.

Most of the studies listed involved selected groups of patients. Thus, application of the results to the large and diverse group of patients encountered in clinical practice is difficult. Also, different techniques were used to assess medial-temporal-lobe atrophy. Several studies used a qualitative method that involves a visual rating scale, in most cases of 4 or 5 points, ranging from absent to severe atrophy (table 2, figure 2).[23,24,28] Frisoni and co-workers[25] used a compound score of linear measurements that included the temporal horn. Pucci and colleagues[29] found the best discriminating variable to be simply the height of the left hippocampus. In a novel approach, Frisoni and co-workers[19] used the radial width of the temporal horn of the lateral ventricle on axial MRI as measured with a calliper on paper printouts. Visual assessment is much less time-consuming than volumetry and easily applicable in clinical practice.[34] The drawback may be a larger between-rater variability.[35] From table 1 the weighted (corrected for number of people in the study) sensitivity and specificity for detection of mild to moderate Alzheimer's disease compared with controls can be calculated as 85% and 88%, respectively. Thus, we can conclude that atrophy of the medial temporal lobe is quite sensitive for Alzheimer's disease, but the absence of such atrophy is more specific for normal ageing.[36] The practical implications of

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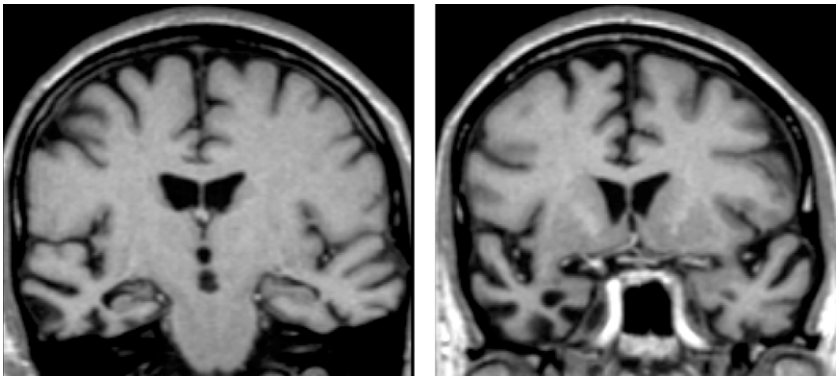

Figure 4. Coronal T1-weighted images of a patient with frontotemporal dementia, showing asymmetrical atrophy of the right temporal lobe including the hippocampus.

the results given in table 1 can be seen in figure 3, which shows the incremental diagnostic gain of a positive and negative result of a test (ie, presence or absence of hippocampal atrophy on MRI) at any given pretest chance (prevalence of disease). For instance, in the case of a pretest probability of Alzheimer's disease in a clinical setting of 0·60 (which is in line with the sensitivity values for the NINCDS-ADRDA criteria as mentioned above), a positive result adds 0·31 to give a post-test probability of 0·91 and a negative result lowers the post-test probability to 0·20.

Frontotemporal atrophy

Neary and colleagues[7] listed frontal and temporal atrophy as supportive diagnostic features for frontotemporal dementia, but absence of these features does not rule out this diagnosis. Asymmetrical, predominantly left-sided perisylvian atrophy characterises progressive non-fluent aphasia; asymmetrical anterior-temporal-lobe atrophy is diagnostic of semantic aphasia. In both disorders, with time, atrophy becomes more widespread but generally remains asymmetrical (figure 4). In Galton and colleagues' study[37] of 30 patients with Alzheimer's disease, 17 with semantic dementia, 13 with the frontal variant of frontotemporal dementia, and 18 controls, a new visual scale was used; it was based on atrophy of the temporal pole, parahippocampal gyrus, and lateral temporal gyri, and it could be helpful in distinguishing Alzheimer's disease from semantic dementia, because the latter disorder shows significantly more atrophy in all these regions in both hemispheres. In addition to asymmetry, a strong anterior to posterior gradient of atrophy within the temporal lobe also suggests a diagnosis of frontotemporal dementia rather than Alzheimer's disease.[38]

Vascular dementia

Criteria for vascular dementia include definitions of dementia, vascular disease, and a relation between the two. Vascular disease can be diagnosed on clinical grounds, on the basis of information from neuroimaging (CT and MRI), or on both. In the diagnostic and statistical manual of mental disorders, fourth revision (DSM-IV) criteria for vascular dementia,[4] imaging evidence of cerebrovascular disease is exemplified as multiple infarctions involving cortex and underlying white matter that are judged to be causally related to the disturbance. The criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) for ischaemic vascular dementia were the first formulated in the format possible/probable/definite vascular dementia.[39] The criteria are restricted to dementia caused by ischaemic vascular disease, but leave room for multi-infarct dementia, dementia after a single stroke, and Binswanger's syndrome

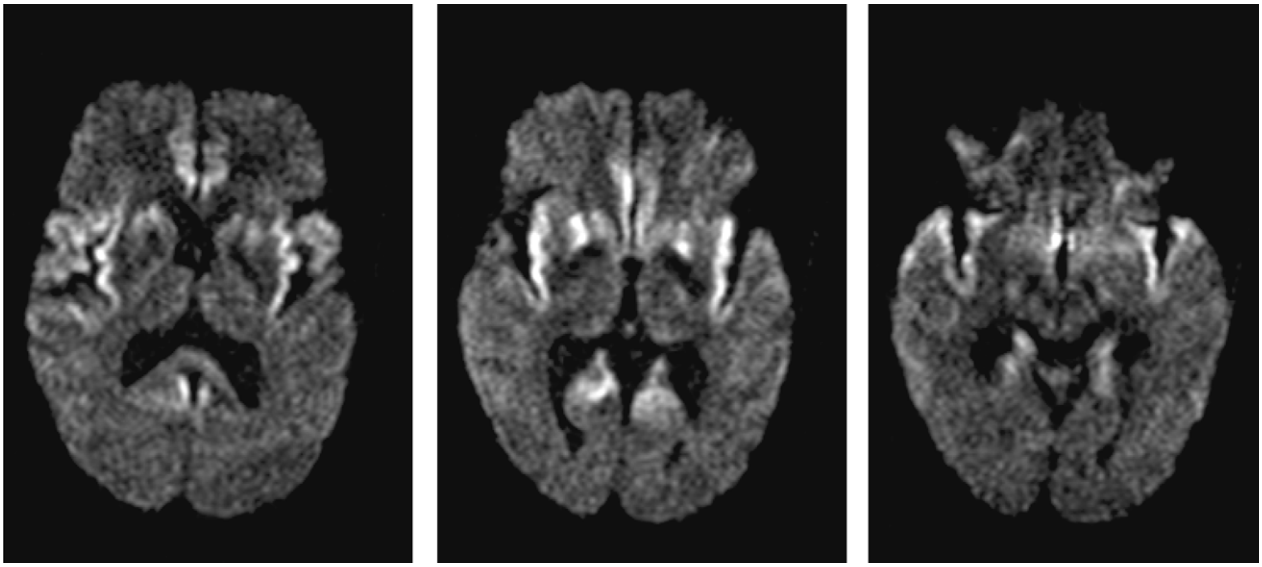

Figure 5. Three consecutive diffusion-weighted MRI slices of a 42-year-old patient with Creutzfeldt-Jakob disease, showing focal high-signal abnormalities in both temporal lobes.

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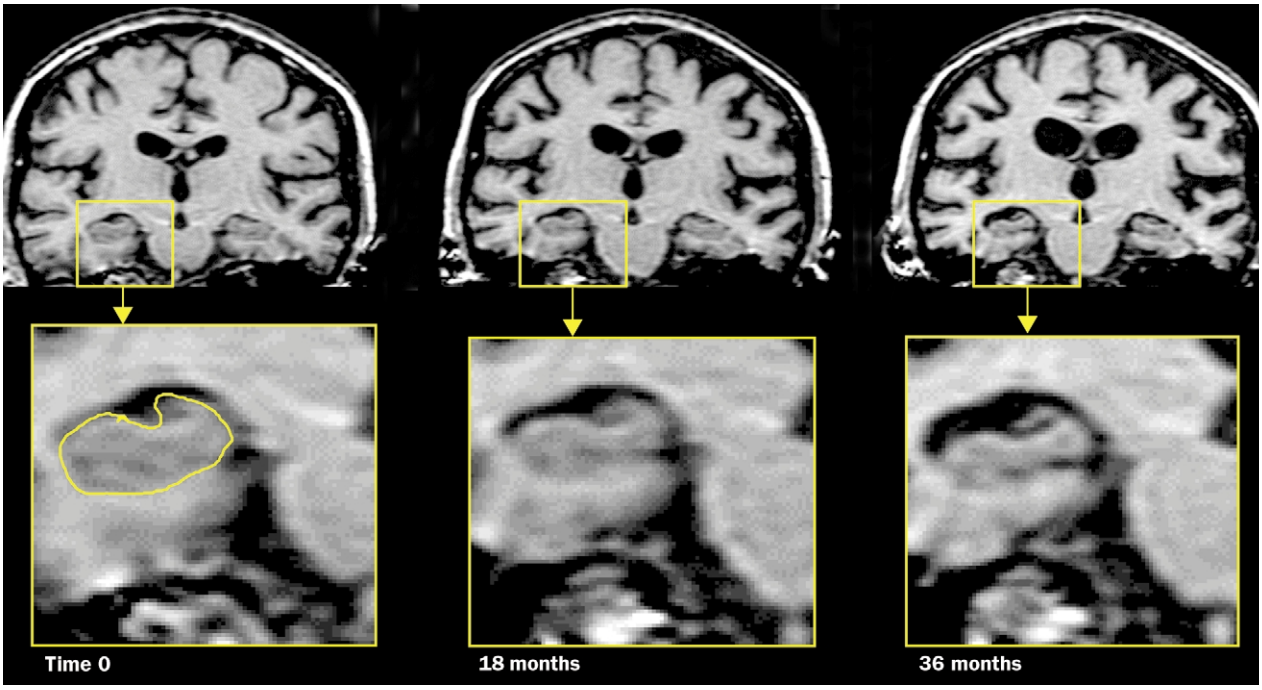

Figure 6. Serial coronal MRI of an individual with Alzheimer's disease. Progressive hippocampal atrophy is clearly shown (magnified region outlined in yellow) but the pronounced sulcal and ventricular enlargement is evidence of continuing generalised atrophy.

(widespread microvascular damage to the deep white matter, for which explicit criteria are provided). Vascular disease is defined both clinically and in terms of neuroimaging results. The documentation of a temporal relation between the dementia and stroke is taken as indicative of a causal relation.

In the National Institute for Neurological Disorders and Stroke–Association pour la Recherche et L'Enseignement en Neurosciences (NINDS–AIREN) international work group criteria for vascular dementia, brain imaging is thought to be essential for the diagnosis, and without it vascular dementia will be "possible" at best.[12] In addition, the criteria specify the vascular territories that are relevant for vascular dementia. These include large-vessel strokes, such as bilateral infarcts in the area of the anterior cerebral artery, infarcts in the area of the posterior cerebral artery, association areas, or in the watershed regions. In the presence of findings restricted to small-vessel disease, some discussion may arise as to whether the patient meets these criteria. Although the exact nature of white-matter changes on CT and MRI is still debated, periventricular and deep white-matter changes on CT and MRI are generally believed to represent damage in which vascular changes may have an important role. MRI is far more sensitive in this respect than CT, but CT is more specific, especially for symptomatic cerebrovascular disease. The NINDS-AIREN criteria state that white-matter changes alone may be sufficient to cause dementia when 25% or more of the white matter is involved. Although this proportion is set purely arbitrarily, it accords with the findings of most studies that only severe white-matter disease is associated with cognitive dysfunction.[40] Our recent study suggested that most patients with vascular dementia diagnosed by the NINDS-AIREN criteria have small-vessel disease only.[41] This conclusion led a group of investigators to formulate specific criteria for subcortical vascular dementia.[42] In practice, to diagnose this disorder, a practicable and clinically valid rating scale has to be used. In a review on existing rating

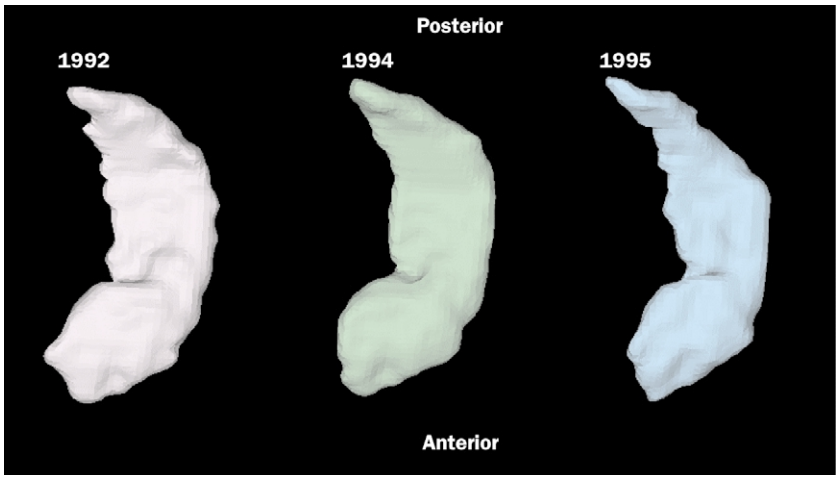

Figure 7. These volume-rendered hippocampi (medial view) have been created by manual outlining of the left hippocampus on serial MRI of a patient with early Alzheimer's disease. Progressive atrophy (8% per year) is shown from 1992 to 1995.

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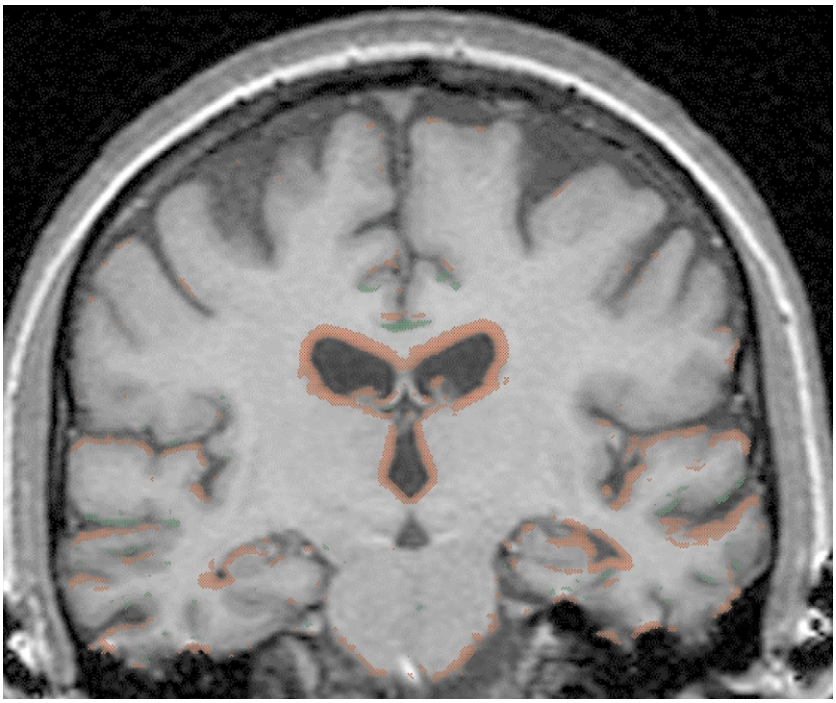

Figure 8. Registered serial (1-year interval) MRI reveals widespread tissue loss (in red) in this patient with Alzheimer's disease.

scales in 1998, we concluded that the ideal rating scale did not exist.[43] On the initiative of the European Task Force on Age Related White Matter Changes (ARWMC), a scale was developed that is applicable to both CT and MRI and gives an estimate of the vascular burden in six regions of the brain (frontal, temporal, and parieto-occipital, left and right). The scale has acceptable reliability within and between raters.[44] Use of high grades of white-matter changes for a diagnosis of subcortical vascular dementia seems prudent, however, as suggested by Erkinjunti and colleagues.[42] With the ARWMC scale, for example, a score of 3 in at least two regions and a score of 2 in two other regions could be sufficient.

Identification of vascular disease

As with Alzheimer's disease, the prevalence of cerebrovascular disease, both symptomatic and clinically silent, increases greatly with age, and many pathological studies find concomitant cerebral infarction in patients with definite Alzheimer's disease.[45] Even small concurrent infarctions significantly increase the likelihood of expressed dementia, suggesting a synergistic effect. Current research aims to elucidate the potential interaction between Alzheimer's disease, cerebrovascular disease, and expressed dementia. Many studies have shown that silent cerebrovascular brain injury is associated with diminished cognitive performance in older people.[46–48] More recent data have also suggested that evidence of cerebrovascular disease on brain imaging is associated with an increased risk of mild cognitive impairment and conversion of such impairment to dementia.[49,50] In addition, brain-imaging evidence of cerebrovascular disease may influence the clinical presentation and neurobiology of Alzheimer's disease.[51–56] Given that concurrent cerebrovascular disease may be amenable to targeted interventions potentially ameliorating disease progression, brain imaging may prove important to clinical care of the demented patient with coexisting cerebrovascular disease. Preliminary evidence from trials of antihypertensive treatment in older people supports this notion, although further prospective clinical trials involving brain imaging are necessary.[57]

Miscellany

In addition to the above, specific imaging signs may include bilateral caudate atrophy in Huntington's disease, hyperintense signal in the putamen in sporadic Creutzfeldt-Jakob disease, and hyperintense singnal change in the pulvinar in variant Creutzfeldt-Jakob disease.[58] Diffusion-weighted MRI shows (the earliest) focal changes in Creutzfeldt-Jakob disease not yet apparent on fluid attenuated inversion recovery (FLAIR) images, which may widely involve the cortex (figure 5).[59] Normal-pressure hydrocephalus is a questionable disease entity, and whether such a patient would benefit from a shunting procedure may be difficult to decide. Vanneste concluded[60] that strict adherence to clinical and MRI criteria is important, with additional information from a positive—but not a negative—CSF tap and the occurrence of B-waves. These MRI criteria include widened ventricles with normal sulci and without white-matter pathology. Of more clinical relevance is dementia with Lewy bodies, possibly the third most common degenerative dementia. MRI has been reported to show medial-temporal-lobe atrophy in a lower frequency than in Alzheimer's disease, leading Barber and co-workers[30] to state that, "in the differentiation of dementia with Lewy bodies from Alzheimer's disease and vascular dementia the absence of medial-temporal-lobe atrophy is suggestive of a diagnosis of dementia with Lewy bodies".

Serial studies

Most imaging studies in dementia have been cross-sectional, a characteristic that reflects current clinical practice in which a single investigation is done to aid diagnosis. Serial imaging allows assessment of progression. The patient serves as his or her own reference baseline, and rates of change (eg, in atrophy) can then be calculated. In cases of diagnostic uncertainty, a follow-up scan may support a diagnosis of a degenerative dementia by showing continuing atrophy (figure 6). As long ago as the early 1980s, serial imaging studies (mainly CT) showed that when patients were rescanned after an interval of more than

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a year, rates of ventricular enlargement were significantly greater in Alzheimer's disease than in normal controls.[61,62] Rates of atrophy of the medial temporal lobe on CT are also increased in Alzheimer's disease.[63] By use of serial MRI, Jack and co-workers[64] showed that rates of hippocampal atrophy were significantly higher in Alzheimer's disease than in age-matched controls (mean rate 4·0% *vs* 1·6% per year; figure 7). Manual measurements such as these are time-consuming and have not entered routine clinical practice. Digital subtraction of serial-registered (positionally-matched) images allows small amounts of diffuse atrophy to be detected and displayed automatically (figure 8). Such methods have shown that rates of whole-brain atrophy are several times greater in Alzheimer's disease than in normal ageing (2·5 [SD 1·1] *vs* 0·4 [SD 0·4]% per year).[65] Furthermore, rates of cerebral atrophy are already increased in symptom-free individuals at risk of familial Alzheimer's disease who subsequently become clinically affected.[66,67] Analysis of the presymptomatic images suggests that atrophy rates increase first in the medial temporal lobe and posterior cingulate regions, but by the time a clinical diagnosis can be made atrophy is already generalised in most cases (figure 9). Serial imaging is likely to be increasingly used in clinical trials in the search for treatments that slow diseases such as Alzheimer's disease. Demonstration of a slowing in rates of cerebral atrophy would provide a strong suggestion that a therapy is actually slowing degeneration rather than simply providing short-term symptomatic relief. If and when such therapies are found, there will be even greater interest in making an accurate diagnosis earlier in these diseases, and MRI will be used to support these diagnoses.

Conclusion

Exclusion of structural lesions remains an important indication for CT or MRI in an individual with cognitive decline, particularly if the presentation is in any way unusual.[14] The ability of CT, if done appropriately with negative angulation and thin slices, and MRI to detect even subtle atrophy of the medial temporal lobe helps to diagnose Alzheimer's disease and differentiate it from normal ageing and non-dementia disorders (such as depression), but these imaging methods cannot rule out other dementias. The sensitivity of MRI to detect vascular pathology has boosted research into, and clinical recognition of, vascular dementia and aids tremendously in the distinction between Alzheimer's disease and vascular dementia; however, we have also learned that there are overlap syndromes between the two disorders, and operational definitions for "mixed" dementia, indicating the presence of both Alzheimer's disease and vascular dementia, are still lacking. Definite progress is being made in distinguishing normal ageing from neurodegeneration by use of serial imaging. The pattern of atrophy may indicate a focal dementia rather than Alzheimer's disease. Clinically useful measures that distinguish the different neurodegenerative disorders from each other at an early stage are still awaited. The most difficult differentiation remains that between Alzheimer's disease and dementia with Lewy bodies.

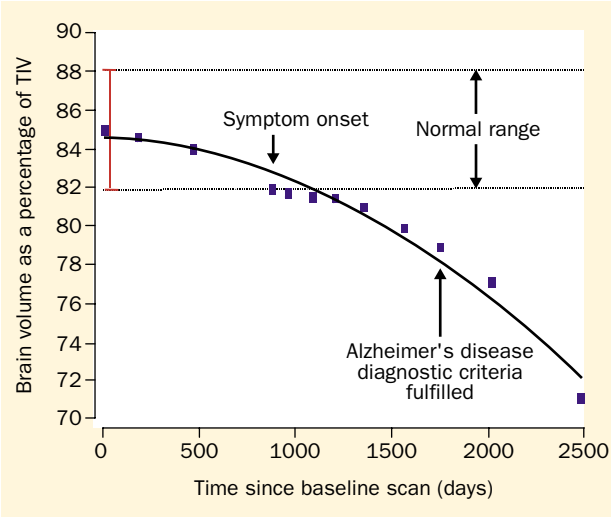

Figure 9. Serial MRI of an individual at risk of familial Alzheimer's disease shows progressive brain atrophy that preceded clinical diagnosis by several years. TIV=total intracranial volume.

Future perspectives

The most likely future use of imaging will be the identification of patients at risk of Alzheimer's disease or with preclinical Alzheimer's disease or mild cognitive impairment. For MRI, this use will involve focusing on the areas that are affected earliest in the disease (ie, entorhinal cortex and hippocampus) with high-resolution structural MRI.[68,69] Work from several research groups has shown that moderate medial-temporal-lobe atrophy, measured qualitatively or quantitatively, is a strong predictor (positive predictive value 80% and overall classification accuracy more than 90%) of development to Alzheimer's disease in people with mild cognitive impairment.[70–73] Medial-temporal-lobe atrophy predicts Alzheimer's disease in these individuals independently of age, memory function, and *APOE* genotype.[70]

With the ability to acquire rapidly high-contrast, high-spatial-resolution, three-dimensional brain images, several laboratories are experimenting with sophisticated brain-mapping algorithms.[74] This process allows an individual MRI to be compared with an "average" or "ideal" brain, enabling the detection of anatomical differences at one point in time as well as change in anatomical structure over repeated observations. When this process is applied to brain MRI from a group of patients with Alzheimer's disease, volume loss of the medial temporal and parietal regions is apparent.[75] A similar result is being achieved through voxel-based morphometry.[76] The first pilot study compared seven patients with Alzheimer's disease and seven controls, and showed grey-matter volume differences in both medial-temporal lobes, the left insula, and both caudate nuclei; these findings were partially replicated by another group.[77,78] A recent comparative study with this technique showed preservation of the medial temporal lobe, hippocampus, and amygdala in dementia with Lewy bodies compared with Alzheimer's disease.[79]

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Brain-mapping techniques can also be used to create automatic (or nearly automatic) brain region identification schemes. This approach has already been applied to estimation of hippocampal volume.[80] Further work, however, is necessary to elucidate fully the sensitivity and specificity of these procedures for diagnosis in the individual patient. If these methods are validated, these algorithms could be incorporated into regular brain-imaging protocols, giving clinicians important additional information when they are attempting to make an early and accurate diagnosis. Imaging research is also likely to focus on measurement of progression and detection of therapeutic effect. As such, MRI is already being used in clinical trials in mild cognitive impairment, Alzheimer's disease, and vascular dementia.

MRI is increasingly seen as an essential investigation in dementia. Until novel biomarkers are found that can reliably detect and track the underlying pathological processes in the different dementias, MRI will continue to play an important part in the diagnosis of patients with dementia and in research into treatments.

Search strategy and selection criteria

Studies were found by searches of the Medline database with the keywords: "Alzheimer's disease", "MRI", "hippocampus", "area and linear measurement", and "visual assessment". Studies were included if they used an objective clinical diagnostic reference for Alzheimer's disease as the gold standard, in most cases the NINCDS-ADRDA criteria and/or DSM-IV, with or without follow-up.

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Authors' contributions

The first draft of the article was made by PS. Subsequently all authors made revisions, added text, and worked on the final version.

Conflict of interest

None of the authors has a conflict of interest.

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INVITED COMMENTARY

Evaluating Dementia Using PET: How Do We Put into Clinical Perspective What We Know to Date?

Decreasing mortality, with consequent progressive aging of the mature adult population, has led to a rising prevalence of senile dementia. The condition is tremendously costly to patients, their families, and society in general. Alzheimer's disease (AD) in the United States affects over 4 million people, who incur associated yearly expenses of nearly $70 billion; when indirect costs such as the lost productivity of caregivers are considered, total annual expenditures approximate $100 billion. As the "baby boomers" approach senior citizen status in the 21st century, it has been estimated that over 14 million Americans will suffer from AD by 2050 (*1–4*).

Regional cerebral metabolic patterns of patients with dementia reflect pathophysiologic alterations, even before they lead to symptomatic expression (*5*). The use of PET in evaluating dementia has been studied since the early 1980s (*6–9*) and has been extensively reviewed in recent years (*10–14*). The best studied application of PET in dementia uses FDG to evaluate AD. Assessment of the diagnostic accuracy of PET, even for this application, however, has been hindered by the paucity of data involving scans of patients undergoing subsequent neuropathologic examination.

The article by Hoffman et al. (*15*) in this issue of *The Journal of Nuclear Medicine* addresses an issue of pressing clinical relevance: the establishment of reliable estimates of diagnostic accuracy of FDG PET (the present imaging modality of choice in the assessment of primary neurodegenerative dementias) for AD. In doing so, their article provides a substantial addition to the currently limited base of data in the peer-reviewed scientific literature on patients studied by both brain PET and pathologic analysis. The authors sampled patients at a university-based memory disorder clinic, staffed by board-certified neurologists who specialized in dementia evaluation; patients were included if their impairment of memory was objectively documentable but the diagnosis was "challenging or difficult" according to the evaluating clinicians. A nuclear medicine physician who was unaware of clinical information and who interpreted FDG PET was able to predict the ultimate diagnosis of AD in 13 of the 14 patients (92.9%) for whom that was the only evident neuropathology and for 14 of the 16 patients (87.5%) harboring AD-related changes in their brains. In comparison, a diagnosis of AD had been clinically suspected (considered probable) in 64.3% and 62.5%, respectively, and considered possible in another 14.3% and 12.5%, respectively. Thus, under the best of circumstances, AD would be clinically missed in 21% of these patients, whereas under those same circumstances, only 7% of AD cases would escape detection on FDG PET, even in the absence of knowledge of any other clinical information. Because of the lower diagnostic specificity found for FDG PET (75% vs. 100%), however, corresponding overall accuracies for clinical evaluation and PET were identical (86.4%). The difference in specificity was entirely accounted for by 2 cases—1 of Creutzfeldt-Jacob disease and 1 of Lewy Body disease—both with clinically evident diagnoses and associated with bilateral parietotemporal hypometabolism. Thus, if PET had been interpreted in light of the available clinical information (as would likely occur in its routine clinical application), rather than blindly (as done here to address a specific research question), a diagnostic specificity of 100% would pertain. FDG PET did correctly classify as non-AD the cases (1 each) of progressive supranuclear palsy, preamyloid, mesio-limbo cortical degeneration, and nonspecific neuronal degenerative change, as did clinical evaluation.

The most serious problem of the current investigation (*15*) is the inadequacy of its statistical strength to meaningfully assess specificity, because of the low number of patients included in the study who were found on histopathologic exam to be free of AD. This problem arises from the general difficulty, shared by all previous such studies, in obtaining sufficiently sizable samples of patients who have had brain PET and are followed to pathologic confirmation. Because of this, values are reported that would be substantially altered by shifts in the "truth tables" of just 1 or 2 patients. This statistical weakness can be appreciated quantitatively by considering that the 95% confidence interval (not reported by the Hoffman et al.) pertaining to the 75% specificity value ranges from 45% to 100%. In other words, the actual specificity for correctly identifying non-AD patients could range anywhere from essentially perfect to a coin flip, given the number and distribution of cases included in the study. Another shortcoming with this study, as presented, is that it is difficult to determine the appropriate setting to which it applies, because the degree of cognitive impairment of the patients examined is nowhere quantified (e.g., by Mini-

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For correspondence or reprints contact: Daniel H. Silverman, MD, PhD, Department of Molecular and Medical Pharmacology, UCLA School of Medicine, CHS AR-144, Los Angeles, CA 90095-6942.

Mental State Examination [MMSE] (*16*)) or otherwise described.

Despite its limitations, the study does provide data derived from compilation of the largest PET-studied autopsy–biopsy series yet reported, which agree with data of other analyses. In a recent review (*10*) that provided a pooled analysis of another 20 patients with dementia for which both PET and autopsy data were available (*17–19*), the sensitivity, specificity, and overall accuracy were 92%, 71%, and 85%, respectively. In a preliminary analysis of a larger (n = 70) multicenter, pooled population that included the current sample, along with those from several other institutions in the United States and Europe, corresponding values were 96%, 67%, and 87% (*20*). Those analyses agree with the values reported for the 22 cases in this study. Thus, diagnostic sensitivity has been found consistently to be quite high (range, 94% ± 2%), with specificity falling in the range of 71% ± 4%. With respect to each of those analyses, it should be kept in mind that the patient samples were not generally representative of people who undergo dementia evaluations but of particularly diagnostically challenging cases—the small subset of patients for whom both brain PET and biopsy–necropsy had been obtained to help establish the diagnosis. This could in turn affect the assessment of diagnostic specificity, causing it to be underestimated relative to a more routine clinical application of FDG PET in which a smaller proportion of non-AD patients would have, for example, Creutzfeldt-Jacob disease.

In addition to the diagnostic value FDG PET may have in evaluation of dementia, it may also serve explicitly as a prognostic tool to determine likelihood of deterioration of mental status in the period after the time of scanning. For example, relative hypometabolism of associative cortex can be used to predict whether cognitive decline will occur (at a pace faster than would be expected for healthy aging) over the several years after a PET evaluation (*21–23*). Moreover, the magnitude of decline over a 2-y period for some standardized measures of memory was recently found to correlate significantly with the degree of initial hypometabolism of inferior parietal, superior temporal, and posterior cingulate cortical regions (*24*), with Pearson correlation coefficients ranging as high as 0.71. In our experience, visually interpreted PET has had a prognostic sensitivity of 90%–93% and a prognostic specificity of 74%–77%, with an overall accuracy of 83%–85% for predicting pathologic clinical progression in the several years (up to 9 y; mean, 3 y) after the scan. This high sensitivity of FDG PET in patients with mild impairment (mean MMSE, 25/30) suggests that by the time a patient presents with symptoms of a progressive neurologic process, sufficient alteration of cortical activity generally has occurred to diminish metabolism of certain areas of the brain to an extent readily detectable on FDG images. At the same time, the lower specificity points to the existence of processes other than those poised to cause imminent cognitive deterioration capable of producing hypometabolic foci discernible with PET. This sensitivity–specificity situation, for clinical progression consequent to metabolically evident disease, bears resemblance to that pertaining to the well-established use of PET for evaluation of a solitary pulmonary nodule, where it is unusual for a focus that is not hypermetabolic to go on to demonstrate progressive growth at a rate indicating malignancy, although several benign diagnostic entities may cause focal hypermetabolism.

Ultimately, how much need there is for functional neuroimaging in the evaluation of dementia depends largely on the adequacy of a traditional diagnostic work-up without imaging. What does the primary scientific literature reveal regarding accuracy of clinical diagnosis? Considering the critical importance of this question, surprisingly few studies have addressed it systematically—with a representative patient mix and in a way capable of yielding measures of true sensitivity and specificity. In 1 study that was so designed, of 421 cognitively impaired patients being clinically followed, diagnostic comparisons were made for the first 58 who died (*25*). The patients' mean age was 79 y, and all but 3 subjects were at least 65 y. Histologic review revealed that nearly half (28/58) had neuropathologic hallmarks of AD, a diagnosis that was missed in 8 subjects. Conversely, the diagnosis of AD was made clinically in 8 of the 30 subjects who had no pathologic evidence for AD. The sensitivity, specificity, and overall accuracy were thus 71%, 73%, and 72%, respectively. Compared with PET studies, this represents a substantially lower sensitivity, at a comparable level of specificity; these numbers suggest that for every 100 patients with AD who are examined, PET would find about 20 whose diagnosis would have been missed by clinical evaluation. Few clinical diagnosis studies have provided an analysis that is stratified for severity, as would be needed to address the issue of diagnostic accuracy in the earlier stages of disease. One study that did specifically address the question of clinical detection of very-mild disease followed patients who initially appeared normal or minimally affected for an average of 4 y (*26*). Even by the end of this longitudinal follow-up period, a neurologist examiner detected AD in only 70% of the patients who were histologically positive. On the other end of the severity spectrum, 65 elderly patients with moderate to severe dementia were evaluated clinically and followed longitudinally until death (*27*). The mean duration of their symptoms was 8.9 y. Autopsies revealed that AD existed in 48 patients (10 of whom also had evidence of multiple infarcts). By the time those patients had reached this late stage of disease, sensitivity of AD diagnosis made clinically (45/48 = 94%) was similar to that made with PET at much earlier stages of disease, but 10 of the remaining 17 patients were also clinically (mis)diagnosed as having AD, indicating a specificity of only 41%. Another study was performed with 25 patients who had advanced-stage dementia; functional status had deteriorated to the point where they were living in a long-term care

facility. All of the patients met the *Diagnostic and Statistical Manual for Mental Disorders, third edition* (*28*), criteria for primary neurodegenerative disorder and National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for AD, yet only 68% were found on pathologic review to actually have AD. Most of the misdiagnosed cases were in younger patients. Finally, in a study of 54 patients with dementia who were not stratified by severity but included a good diagnostic mix (in descending frequency: AD, multiple infarct dementia, Parkinson's dementia, Creutzfeldt-Jakob disease, subcortical gliosis, progressive supranuclear palsy, and Huntington's disease), 2 independent neurologists agreed on the correct diagnosis in just 63% of cases; their average individual accuracy rate was 71.5% (*29*).

As well-articulated in the article by Hoffman et al. (*15*), the gold-standard pathologic diagnosis has not always turned out to be as unambiguous a determination as one might suppose. This is especially the case when pathologic diagnosis is based on biopsy, which allows only a small area of (what one hopes to be representative) tissue to be sampled; even when full brain autopsy is performed, the application of different histopathologic criteria can result in divergent diagnoses in a substantial proportion of cases. Efforts over the last decade to bring standardization to this field, however, have resulted in schemes of consensus criteria with much higher agreement among them, as discussed by Mirra et al., who applied 1 such scheme (*30*) in their study.

In conclusion, to place the above considerations in their wider clinical context, it is important to note that dementing illness in patients with mild cognitive dysfunction frequently is unrecognized and, consequently, goes untreated because of the difficulty in making an accurate clinical diagnosis in the early stages of dementia (*31*). This may have been less relevant at a time when little could be done to improve the cognitive symptoms of most patients with dementia. However, advances occurring over the last half-dozen years have changed that situation. For example, tacrine, donepezil, and rivastiamine have been cleared by the U.S. Food and Drug Administration for improving cognition or slowing intellectual decline associated with mild to moderate AD. There is evidence accumulating that such cholinesterase inhibitors can also improve global function and decrease the need for placement of patients in long-term care facilities (*32,33*) and that to derive maximal benefit, the use of these drugs should be initiated early in the course of disease. Moreover, both vitamin E and selegiline were recently demonstrated to delay progression of symptoms, in a double-blind, placebo-controlled, randomized, multicenter trial of 341 patients with moderate AD (*34*). In addition, patients predisposed to or with early signs of vascular dementia may modify their risk of progression with antihypertensive and antithrombotic medications or vascular surgery. In addition to the significant strides that have been made in the past decade in developing therapies for patients with AD, the present decade has opened with an improved understanding of etiologic factors, now being exploited in the development of more specifically targeted therapies aimed at arresting progression of AD (*35*). These 3 areas of advancement—better understanding of the basic neurodegenerative mechanisms, development of more effective therapies administered before significant irreversible neurodegeneration has occurred, and enhanced ability to establish accurate diagnoses early on—are concomitantly driving progress on each other's fronts. The immediate diagnostic challenge—to accurately identify minimally affected patients early enough to allow them to reap the greatest potential therapeutic benefits—will be met best by using the tools most well equipped to facilitate making the diagnosis with a high degree of sensitivity and overall accuracy at the earliest stage of disease. The current study bolsters the use of FDG PET, to improve accuracy of evaluation of patients with dementia, in meeting that challenge.

Daniel H.S. Silverman
Michael E. Phelps
University of California Los Angeles
School of Medicine
Los Angeles, California

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Evaluating Early Dementia With and Without Assessment of Regional Cerebral Metabolism by PET: A Comparison of Predicted Costs and Benefits

Daniel H.S. Silverman, MD, PhD[1]; Sanjiv S. Gambhir, MD, PhD[1,2]; Hsuan-Wen C. Huang, BSc[1]; Judy Schwimmer, MS, MBA[2]; Shanna Kim[1]; Gary W. Small, MD[1,3,4]; Joshua Chodosh, MD[4]; Johannes Czernin, MD[1]; and Michael E. Phelps, PhD[1,2]

[1]Department of Molecular and Medical Pharmacology and Ahmanson Biological Imaging Center, UCLA School of Medicine, University of California, Los Angeles, Los Angeles, California; [2]Department of Biomathematics and Crump Institute for Molecular Imaging, UCLA School of Medicine, University of California, Los Angeles, Los Angeles, California; [3]Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, University of California, Los Angeles, Los Angeles, California; and [4]Department of Internal Medicine and Center on Aging, UCLA School of Medicine, University of California, Los Angeles, Los Angeles, California

Evaluating dementia in patients with early symptoms of cognitive decline is clinically challenging. Growing evidence indicates that appropriate incorporation of PET into the clinical work-up can improve diagnostic and prognostic accuracy with respect to Alzheimer's disease (AD), the most common cause of dementia in the geriatric population. The precise diagnostic role of PET and its economic impact in this context, however, have not been systematically examined previously. **Methods:** We compared the relative value of 2 strategies for assessing whether early AD is responsible for cognitive symptoms in geriatric patients: (a) a conventional approach, based largely on establishing clinical criteria for the presence of dementia and excluding non-AD etiologies that could contribute to the patient's symptoms, and (b) a proposed approach using PET to examine regional cerebral metabolism and look for characteristic patterns of abnormal metabolism. The total costs (measured in dollars) and benefits (measured in number of accurate diagnoses) of diagnostic testing and clinical outcomes accruing to each strategy were calculated using formalized tools of decision analysis. The primary outcome measure by which the strategies were compared was the ratio of costs to benefits obtained following each approach. **Results:** Following the proposed approach led to improved accuracy in identifying early AD, without adding to the overall costs of diagnosis and treatment ($3,433 vs. $3,564 per patient approached by the proposed or conventional algorithm, respectively). The strategy making use of PET was associated with a reduced rate of false-negative and false-positive findings compared with the conventional approach (3.1% vs. 8.2% and 12.0% vs. 23.0%, respectively, at a prevalence of 51.6% in the studied symptomatic population) and a cost savings of $1,138 per correct diagnosis rendered ($4,047 vs. $5,185). The lower cost per unit benefit for the proposed strategy was maintained over a wide range of tested values for variables of sensitivity, specificity, costs of PET and long-term care, and varying approaches to the use of structural neuroimaging. **Conclusion:** Appropriate use of PET for evaluating early dementia in geriatric patients can add valuable information to the clinical work-up, without adding to the overall costs of evaluation and management, resulting in a greater number of patients being accurately diagnosed for the same level of financial expenditure. Thus, the opportunity exists for diminishing the morbidity of dementia economically, with earlier institution of more appropriate management in evaluated patients.

Key Words: Alzheimer's disease; dementia; PET; FDG; functional brain imaging; cost-to-benefit ratio; cost-effectiveness; decision tree; decision analysis

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Dementia exacts a huge toll on our health and welfare and, as mean life expectancy continues to rise, the magnitude of this problem is growing. It is estimated that 8% of people who are ≥65 y old suffer from the most common form of dementia, Alzheimer's disease (AD) (*1,2*). Disease prevalence climbs rapidly with age, and at least 30% of people who are ≥85 y old are afflicted with AD (*3,4*). An even larger number of caregivers and family members must cope with the emotional and practical burden of the disease's relentless and irreversible decline in cognition, functioning, and behavior. The disease also has enormous finan-

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For correspondence or reprints contact: Daniel H.S. Silverman, MD, PhD, Department of Molecular and Medical Pharmacology and Ahmanson Biological Imaging Center, CHS AR-144, UCLA School of Medicine, MC694215, University of California, Los Angeles, Los Angeles, CA 90095-6942.
E-mail: dsilver@ucla.edu

cial consequences on families and the larger society. In the United States alone, >$90 billion will be spent on AD-related expenses each year (*5,6*).

Dementia is generally defined by documented decline in multiple cognitive functions (e.g., memory, language, visuospatial ability), sufficiently severe to interfere with daily life in an alert patient (*1*). AD is a dementia syndrome that progresses insidiously, eventually altering memory, higher intellectual function, language, praxis, and visuospatial and other cognitive abilities. A definite diagnosis of AD can be made only by histopathologic examination of brain tissue, which rarely occurs before the patient's death (*7*). The identification and differential diagnosis of dementia are especially challenging in its early stages, partly because of the difficulty in distinguishing it from the mild decline in memory that can occur with normal aging and from mild cognitive manifestations of other neuropsychiatric conditions, such as depression. Systematic studies indicate that the frequency of unrecognized memory impairment or dementia could range from 50% to 90% of cases (*8,9*). Physicians frequently err by failing to make the diagnosis of AD when the disease is present and by diagnosing early AD when it is in fact absent (*8–13*). Given the large number of their older patients likely to become affected, physicians require more accurate and effective methods to work through the differential diagnosis of early symptoms of cognitive impairment.

This need for accurate diagnoses has become even more important now that several prescription medications for the treatment of mild to moderate AD are available. Controlled clinical trials have shown that cholinesterase inhibitors can improve, or delay decline in, memory and other cognitive functions in AD patients (*14–20*). These treatments can cut by more than half the proportion of patients requiring nursing home placement over a given period of time (*21,22*). Cholinergic (and other (*23*)) agents also have beneficial effects with respect to reducing behavioral problems, improving patients' functional abilities, and decreasing caregiver burden (*16,24–27*). Those studies that have examined the long-term effects of cholinesterase inhibitors indicate that drug treatment produces an average delay in cognitive decline in AD patients of 9–12 mo, relative to the time course of untreated patients (*26,28,29*), and a delay in the need for institutionalization of 18 mo on average (*30*). This may represent a substantial portion of the patients' remaining life expectancy. Moreover, delaying the institution of therapy by as little as 6 mo—in addition to carrying the inherent adverse consequence of depriving the patient of the short-term advantages of potentially enhanced mental activity and diminished cognitive decline during that time—may have long-term disadvantages as well (*16,26,31*). In a randomized, placebo-controlled trial of the cholinesterase inhibitor galantamine in patients with mild to moderate AD, Raskind et al. (*16*) found that the drug significantly improved cognitive function relative to the placebo after 6 mo of treatment; during an ensuing 6-mo open-label treatment period, the patients who were originally in the placebo group were also given active drug. At 1 y, better cognitive performance was seen in patients who began drug treatment from the beginning of the trial than in those who had been delayed with the placebo for 6 mo. Similar detrimental effects have also resulted from delaying the institution of therapy with either rivastigmine (*19*) or donepezil (*31*). Thus, the need is apparent for accurate and early diagnosis of AD.

Along with the advantages of allowing earlier institution of pharmacotherapy, early detection of AD offers several additional benefits. For example, many people may want to know about a poor prognosis while their memory losses are relatively mild to better plan for their future. This knowledge allows physicians, patients, and family members the opportunity to address safety issues as well as to identify surrogate decision makers and sources of caregiver support early in the disease process. Furthermore, such benefits have been shown to reduce the need for nursing home placement of patients with mild dementia by 82%, to delay nursing home placement of all AD patients by an average of 11 mo, and to generally enhance quality of life for patients and their families (*32*). Finally, early accurate diagnostic approaches may also help to avoid the costs, efforts, and frustrations associated with years of multiple diagnostic evaluations. As summarized by the U.S. Agency for Health Care Policy and Research in 1996, "early recognition of the condition has important benefits," and yet, "early-stage dementia is often unrecognized or misdiagnosed" (*33*).

A noninvasive neurobiologically based approach through molecular imaging with PET could be of great use in addressing this diagnostic challenge. Mounting evidence indicates that the dementing process of AD begins years before the clinician can confirm the diagnosis using conventional approaches to assessment (*34,35*) and that the associated cerebral changes can be detected by PET during these early stages of AD, and even preclinically (*36,37*). In a recent report by the members of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) (*38*), it was concluded that "PET scanning appears to have promise for use as an adjunct to clinical diagnosis [of AD]" on the basis of their review of published studies that showed diagnostic accuracies of 86%–100% for PET with ^{18}F-FDG, but they stopped short of directly endorsing PET in this context. Given that patients have the most to gain from effective therapeutic approaches that intervene as early as possible in the course of dementing illness—and that, on the one hand, conventional methods for evaluating those patients are inadequate for making reliable diagnostic and prognostic assessments in the early stages of their disease, whereas, on the other hand, PET can detect such disease even at the time of its earliest symptomatic expression—the question arises as to what is the most appropriate role for PET in the diagnostic process. On the basis of our own review and synthesis of the data available with which to address that question, we believe that PET is underused

for this purpose and have proposed applying it in a way that is more consonant with those data (*39–43*). In this study, we use formalized tools of decision analysis to compare the conventional approach, as guided especially by AAN reviews and recommendations, with an approach that attempts to take greater advantage of the direct cerebrometabolic information that imaging with PET can add to the diagnostic work-up of early dementia. We identify the sensitivity, specificity, and overall accuracy of each approach and assess the financial consequences of missed diagnoses. As our primary outcome measure, we compare the ratio of costs (measured in Medicare dollars) to benefits (measured in number of accurate diagnoses) accruing to each approach.

MATERIALS AND METHODS

Decision-Tree Analysis

The main endpoint measures (overall costs, number of accurate diagnoses, and cost per accurate diagnosis) were quantified from a payor perspective through established methods of decision analysis (*44–47*). This analysis involved 4 major components.

First, a decision-tree model was constructed to represent and compare 2 competing strategies: an algorithm reflecting current practice standards for expert evaluation of dementia (conventional algorithm) and the algorithm that we propose for evaluation of dementia (proposed algorithm). Dollar costs for medical care were assigned to each test and to each clinical outcome detailed in the model, as described below. The explicit probabilities for each of the branches in the decision tree were obtained as functions of explicitly defined variables (Table 1). The probabilities were computed using standard Bayesian analytic methods (*46*) where applicable. Essentially, diagnoses of AD were made with the conventional algorithm (Fig. 1) by documenting the presence of clinical criteria for dementia, followed by a deductive process of ruling out, or identifying and treating, other potentially confounding conditions (e.g., structural brain lesions, thyroid disease, depression). This represents the set of procedures recommended by the AAN (*38,56*) (and, in somewhat less comprehensively articulated fashion, by the American Association of Geriatric Psychiatry,

TABLE 1
Explicitly Modeled Variables of Decision-Tree Analysis

Algorithm	Variable	Value of variable in base-case analysis	Supporting literature or other justification
C, P	Prob. of initial comprehensive H&P (including neurologic examination)	1.00	Required part of evaluation
C, P	Prob. of needing CT or MRI	0.625, 1.00 initial evaluation (0.10 in comprehensive follow-up evaluation)	Set to be equal in both algorithms
C, P	Prob. of needing special tests or outside consultation (blue-shaded boxes in Figs. 1 and 2)	0.035 (initial evaluation only)	Refs. (*48,49*); set to be equal in both algorithms
C	Prob. of obtaining neuropsychologic testing	0.59	Ref. (*50*)
C	Prob. of having multiple cognitive domains affected (including patients undergoing neuropsychologic testing)	0.67 initial evaluation	Based on number of clinical dementias per documented AD case in Ref. (*10*) and adjusting AD prevalence to rate in Ref. (*50*)
		Additional 0.01 of remaining patients per month on follow-up evaluation	Based on conversion rates as documented in Refs. (*51,52*)
C	Prob. of functional decline (among those with multiple cognitive domains affected)	0.90	Estimate based on clinical experience (no published values found)
C, P	Prob. of potentially reversible cause of dementia evident on H&P or common laboratory tests	0.22	Refs. (*48,49,53,54*)
C, P	Prob. of identifying potentially reversible dementia by H&P or common laboratory tests and completely reversing it with therapy	0.045	Refs. (*48,49,53,55*)
C, P	Prob. of identifying potentially reversible dementia by CT or MRI, not found by H&P or common laboratory tests, and completely reversing it with therapy	0.00	Ref. (*53*)

C = conventional; P = proposed; Prob. = probability; H&P = history and physical examination; Ref. = reference.

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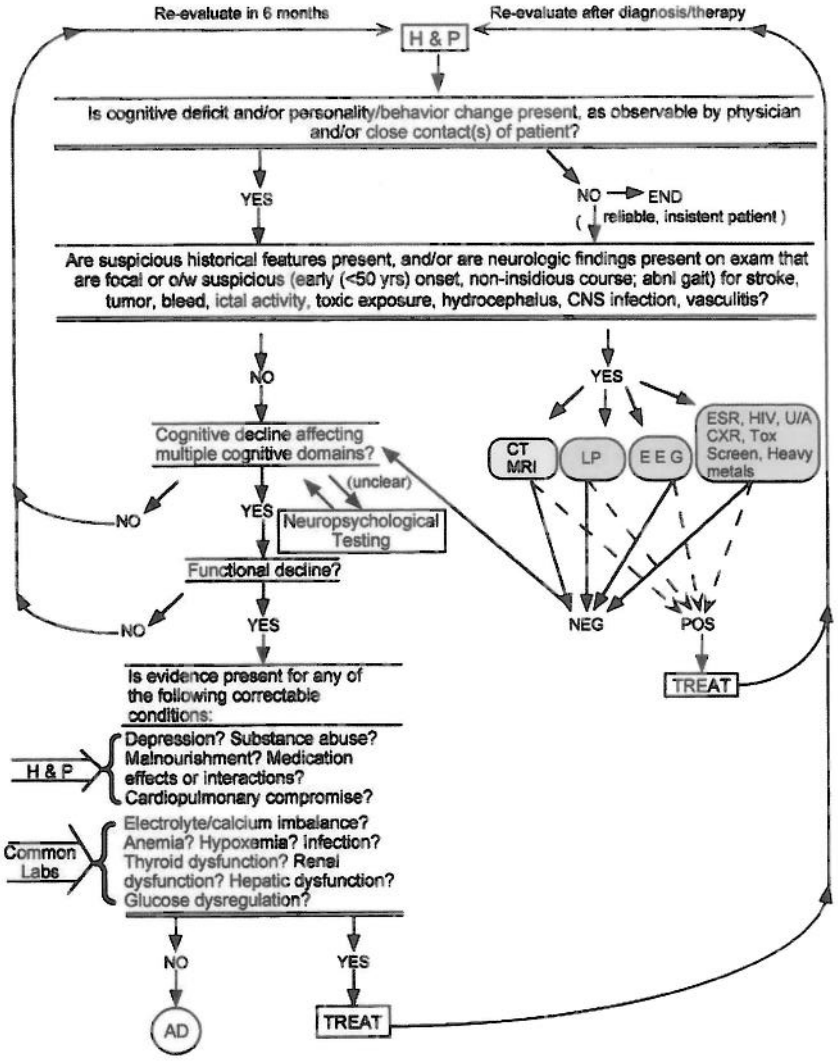

FIGURE 1. Conventional algorithm used for diagnosis of AD. H & P = history and physical examination; exam = examination; o/w = otherwise; abnl = abnormal; bleed = bleeding; CNS = central nervous system; LP = lumbar puncture; E E G = electroencephalogram; ESR = erythrocyte sedimentation rate; U/A = urinalysis; CXR = chest x-ray; Tox = toxicology; NEG = negative; POS = positive; Labs = laboratory tests.

Alzheimer's Association, and American Geriatrics Society (*1*) as well as the American Medical Association (*57*)).

In comparison, the proposed algorithm used FDG PET in the diagnostic work-up of patients with early cognitive symptoms when appropriate, as defined by explicitly formulated criteria (Fig. 2); diagnosis of AD depended on identification of a characteristic pattern of regional cerebral metabolism on PET scans. Note that Figure 2 is not intended to indicate all tests that can or should be done to fully evaluate all patients with cognitive impairment but, rather, represents the steps in the decision pathway that we used to determine whether a PET scan was obtained on patients presenting with symptoms that could represent the early manifestations of AD or related diseases. In particular, between 1994 and 2001, the position of the AAN shifted from recommending that CT or MRI studies should be ordered only for patients with a specific indication identified by history or examination (*56*) to recommending that they be ordered for essentially all patients undergoing initial evaluation for dementia (*38*). This shift occurred largely because of intervening empiric documentation (*50*) showing that clinically important conditions were sometimes found on CT or MRI in patients who did not have any of the previously recommended criteria for undergoing neuroimaging. Figure 2 should not be interpreted as being in support of the former position (*56*); it illustrates only those steps necessary for the evaluating physician to take before deciding whether to order FDG PET. Accordingly, in this analysis, we compared the conventional algorithm and the proposed algorithm with the frequency of structural neuroimaging set at levels determined by each set of AAN guidelines, and the comparison was always made in a balanced manner. For example, when MRI scans were obtained for 100% of patients in the conventional algorithm, they were also obtained for 100% of patients in the proposed algorithm with which it was being compared, and the associated costs comparably accrued to both algorithms.

Second, the medical literature was reviewed to determine reliable means and ranges for all modeled variables; these were specifically oriented, wherever time-stratified or severity-stratified data were available, toward evaluation of patients with clinical presentations indicating an early stage of cognitive decline. To minimize the chance of introducing any bias operating against the algorithm emulating AAN recommendations (Fig. 1) (*50,55,56*), we implemented the following policy: Whenever the values of

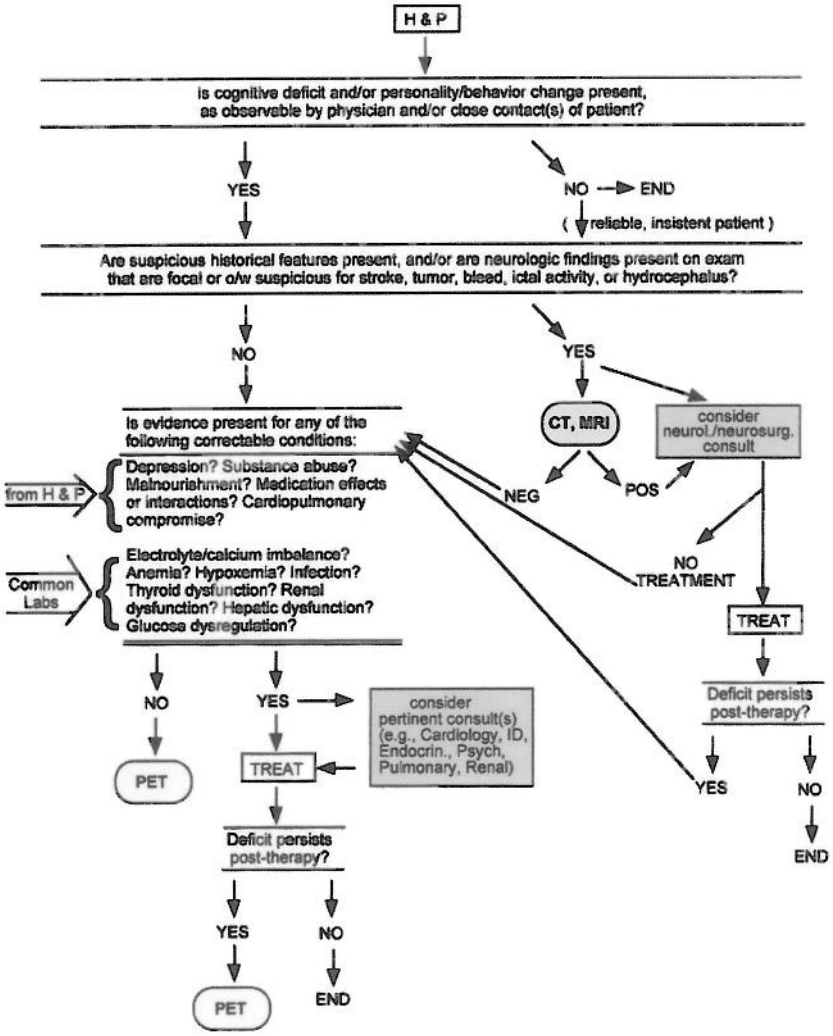

FIGURE 2. Proposed guidelines for determining when to obtain brain PET study in evaluation of geriatric patients with early symptoms of cognitive decline. H & P = history and physical examination; exam = examination; o/w = otherwise; bleed = bleeding; neurol. = neurologic; neurosurg. = neurosurgical; consult = consultation; NEG = negative; POS = positive; Labs = laboratory tests; ID = infectious disease; Endocrin. = endocrinology; Psych = psychology.

outcome-probability variables were ascertainable from the data presented in the AAN's own published practice parameter papers (*38,51,56*), or in the background paper for, or systematic study of, AAN parameters (*50,55*), those values were used for the decision analysis model. To obtain all other values, MEDLINE (MEDLARS On-Line) and BIOSIS (BioScience Information Service) databases were used to search for research articles published between 1985 and 2000. The results of the search were limited to human-related articles published in English. The search was conducted using the keyword "dementia," cross-referenced with 1 or more of the following other relevant terms: early diagnosis, early evaluation, Alzheimer or Alzheimer's, cognitive impairment, cognitive dysfunction, practice parameter, laboratory, delirium, depression, neuropsychological testing, CT, MRI, PET, sensitivity, specificity, follow-up, and reversible. Articles were required to include at least some patients who were geriatric (≥60 y old) and who had mild dementia (Mini-Mental State Examination scores of ≥20). Articles were excluded if they involved diagnostic work-ups lacking the majority of types of examinations used in the context of either the conventional or the proposed algorithm.

Values for all variables were tabulated along with the supporting literature sources (Tables 1–3) and were entered into the model at the appropriate branch points of the decision tree. The prevalence of AD in the study population used in the analysis was determined by applying the average diagnostic sensitivity and specificity values cited by the AAN in their most recent review of those data (*38*) to the distribution of final diagnoses resulting empirically from systematic application of the conventional algorithm (*50*), giving a calculated prevalence of 51.6% of patients studied. This estimate not only had the advantage of being derived from a realistic empiric situation but also accorded well with the theoretic principle that the most generally informative test of a diagnostic algorithm usually occurs when it is applied to patients from a population who, before diagnosis, are thought to possess an approximately equal chance of having or not having the disease of interest.

Cost values were defined using current Medicare reimbursement rates for all variables where those had been established and by explicitly stated methods and literature sources otherwise (Table 4). In particular, because Medicare reimbursement rates for PET with FDG were established for whole-body studies but not (at the time of our investigation) for dedicated brain studies, we calculated a Medicare-consistent cost for brain PET by multiplying the Medicare whole-body reimbursement rate by a factor (0.70)

TABLE 2
Sensitivity and Specificity of PET Compared with Neuropathologic Confirmation of Presence or Absence of AD

No. of patients	Major findings	Comments	Ref.
13 AD, 7 Non-AD	Sens = 92%, Spec = 71%	Pooled analysis across 3 studies (*58–60*) providing small groups of pathologically confirmed cases	(*39*)
16 AD, 6 Non-AD	AD identified in 13/14 (Sens = 93%) of AD-only and 1/2 AD-positive cases (overall Sens = 88%). Absence of AD confirmed in 4/6 cases (Spec = 67%)	Single-institution series of 22 pathologically confirmed cases; 14 patients had AD as only pathologic diagnosis, 1 had AD-positive Lewy bodies, 1 had AD-positive PSP	(*61*)
97 AD, 41 Non-AD	Sens = 94%, Spec = 73%. For subset of 55 patients with documented early (questionable or mild) dementia, Sens = 95% and Spec = 71%	Data represent current status of FIND-AD investigation, reported in Ref. (*43*)	(*43*)

Ref. = reference; AD = cognitively impaired secondary to AD; Non-AD = no AD identified on neuropathologic examination; Sens = sensitivity with respect to correctly identifying presence of AD; Spec = specificity with respect to correctly specifying that AD is absent; PSP = progressive supranuclear palsy; FIND-AD = FDG-PET International Nexus for Diagnosis of Alzheimer's and Other Dementias.

reflecting the ratio of reimbursement rates from private insurance companies that compensate our institution for dedicated brain and whole-body studies. This led to a brain PET cost of $1,661 for our base-case analysis (which is also similar to what our institution actually charges for those studies). No time-based cost discounting (*47*) was incorporated into the decision-tree model because all evaluations were assumed to be completed within 6 mo from the time of patients' initial presentation.

Third, overall cost for each strategy was calculated by summing the products of the branch-probability and cost values for every branch of each strategy. The expected number of accurate diagnoses for each strategy was calculated by determination and summation of path probabilities to all AD outcomes, coupled with sensitivity and specificity values obtained from reviewing the most pertinent literature, as detailed below. The blue-shaded portions of the algorithms indicate the role of specialized tests and consultations in dementia evaluations. Note that they were included in the diagrams for the sake of conceptual completeness but, as evident from our cost tabulations (Table 4), we only explicitly modeled the costs of their structural neuroimaging component. We did so because our review of the literature indicated that the frequency for needing other kinds of specialized evaluation in the context of dementia work-up was low, and their contribution toward establishing the final diagnosis was even lower. Thus, they would not be expected to impact significantly on our outcome measures (particularly because overall they would be used similarly in conventional and proposed algorithms). Calculations of cost savings between the competing strategies were determined by subtracting the expected cost per accurate diagnosis for the proposed algorithm from the expected cost per accurate diagnosis for the conventional algorithm (i.e., a higher overall cost per unit benefit for the proposed algorithm would yield a negative cost savings). This cost-savings method of comparing the costs per unit benefit accruing to each strategy was used in preference to the method of incremental computation of the summary measure (*47*) because of the presence of significant structural differences in the 2 strategies being analyzed rather than PET being used as a simple add-on test.

TABLE 3
Sensitivity and Specificity of Conventional Clinical Evaluation Compared with Neuropathologic Confirmation of Presence or Absence of AD

No. of patients	Major findings	Comments	Ref.
94 AD, 40 Non-AD	Sens = 83%, Spec = 55% Prob AD Sens = 85%, Spec = 50% Prob AD + Poss AD	Patients with new onset (<1 y) of symptoms of dementia when first seen; diagnoses based on average follow-up of 3.0 y	(*10*)
80 AD, 24 Non-AD	Sens = 49%, Spec = 100% Prob AD Sens = 96%, Spec = 61% Prob AD + Poss AD	40% of patients lived in long-term care facilities. Diagnoses based on annual assessments from time of referral until death. Followed for average of 2.3 y, at which time majority of patients were moderately or severely demented	(*63*)
68 AD, 12 Non-AD	Sens = 50%, Spec = 70% Prob AD	Diagnoses based on annual assessments from time of referral until death	(*64*)

Ref. = reference; AD = cognitively impaired secondary to AD; Non-AD = no AD identified on neuropathologic examination; Sens = sensitivity with respect to correctly identifying presence of AD; Spec = specificity with respect to correctly specifying that AD is absent; Prob AD = diagnosis of probable AD by National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria; Poss AD = diagnosis of possible AD by NINCDS–ADRDA criteria.

TABLE 4
Costs Accrued to Conventional (C) and Proposed (P) Algorithms

Algorithm	Item	Cost of item in base-case analysis	Medicare rate or other cost basis
C, P	H&P		
	Initial comprehensive	$149.47	Medicare
C	Follow-up (used to reassess for dementia in previously nondemented patient)	$62.33	Medicare
C, P	Focused follow-up (used after treatment of abnormality found on H&P or laboratory tests)	$38.36	Medicare
C, P	MRI		Medicare
	Without contrast	$608.12	
	With and without contrast	$1,294.17	
C	Neuropsychologic testing	$84.33	Medicare
C, P	Laboratory tests		Medicare
	CBC	$4.76	
	ESR	$3.73	
	T_4	$8.95	
	TSH	$23.21	
	Basic metabolic panel	$11.70	
	Hepatic panel	$11.29	
	Folate (RBC, serum)	$44.25	
	Vitamin B_{12} level	$20.83	
	Syphilis serology	$11.40	
P	Brain PET	$1,661	Medicare × private insurance ratio, brain to whole body
C, P	Extra care needed for AD patient who progresses past early stage while going untreated because of false-negative diagnosis	$30,000	$40,000/y of care (*51*) × 0.75-y (minimum) average delay of progression with therapy (*16,19,26,28–31*)
C, P	1-y supply of cholinesterase inhibitor unnecessarily prescribed to Non-AD patient because of false-positive diagnosis	$1,500	Median cost for donepezil and rivastigmine (most common inhibitors in current use) based on survey of local pharmacies

H&P = history and physical examination; CBC = complete blood count; ESR = erythrocyte sedimentation rate; T_4 = thyroxine (L-3,5,3′,5′-tetraiodothyronine); TSH = thyroid-stimulating hormone; RBC = red blood cell; Ref. = reference; Non-AD = no AD identified on neuropathologic examination.

Costs were based on Medicare outpatient reimbursement rates whenever possible. Costs include professional and technical components, where applicable, as listed in the 2001 Medicare Fee Schedule booklet.

Finally, because the values of some branch probabilities and costs vary across clinical settings, range-of-variable analyses were performed on the most potentially variable and critical values (i.e., cost, sensitivity, and specificity of PET studies and cost of AD care). Specifically, this involved evaluating, over a specified range of each variable, the associated range of expected cost savings. A commercially available software product, Data 3.0 for PowerMac (TreeAge Software, Inc., Williamstown, MA), was used to construct the decision tree and to assist in the calculations underlying the analyses. Except as explicitly explained above, the methods used in this investigation were in compliance with the methodologic principles of economic analysis that we outlined previously (*47*).

Sensitivity and Specificity of PET

Hundreds of patients with clinically diagnosed, and in some cases histopathologically confirmed, AD from many independent laboratories have been studied using PET measures of cerebral blood flow, glucose metabolism, or oxygen utilization. The resulting findings have been the subject of several recent reviews (*39,65–67*), and the principal findings that have emerged from that experience are as follows. A consistent pattern of focally decreased cerebral metabolism occurring in AD patients has been identified with PET; the hypometabolism involves neocortical association areas (especially parietotemporal cortex), but largely spares basal ganglia, thalamus, cerebellum, brain stem, and the cortical regions mediating primary sensory and motor functions. The extent of hypometabolism is correlated with the severity of cognitive impairment (*65*) and often shows right–left hemispheric asymmetry (*68*), particularly in the earlier stages of disease. Right-handed patients with primarily visuospatial symptoms show predominantly right-sided hypometabolism, whereas those with language deficits are more likely to show left-sided hypometabolism, with both kinds of cases becoming more symmetric as disease progresses.

Studies comparing neuropathologic examination with PET imaging are the most informative in assessing diagnostic value (Table 2). In a pooled analysis (*39*) of 3 previously published studies (*58–60*), histopathologically confirmed sensitivity and specificity of PET for detecting the presence of AD were 92% and 71%, respectively. In the largest single-institution series, Hoffman et al.

(*61*) found sensitivity and specificity of PET for AD to fall in the ranges of 88%–93% and 63%–67%, respectively. A multicenter study, FDG-PET International Nexus for Diagnosis of Alzheimer's and Other Dementias (FIND-AD), was recently organized to compare dementia diagnosis using FDG PET with neuropathologic diagnosis (*43*). The investigators collected data from an international consortium of clinical facilities that had acquired brain FDG PET and histopathologic data for patients undergoing evaluation for dementia. The PET results identified patients with AD with sensitivity and specificity of 94% and 73%, respectively. Because this latter study included >3 times as many patients as the 4 previous studies combined, the present base-case analysis used the AD sensitivity and specificity values determined for PET in the latter study. These values also accorded with the ranges reported in a broader review of the PET literature (*62*) that included studies lacking neuropathologic confirmation of diagnoses and that reported sensitivities ranging from 90% to 96% and specificities ranging from 67% to 97%. Our investigation included range-of-variable analyses exploring the full ranges of sensitivity and specificity values identified across all of these studies.

Sensitivity and Specificity of Clinical Evaluation

In the recent report of the Quality Standards Subcommittee of the AAN (*38*), an organization that has been the source of arguably the most comprehensive and authoritative guidelines and standards for the clinical evaluation of dementia in the last several years, 3 class I studies (*10,63,64*) were identified in which the diagnostic value of conventional clinical assessment could be meaningfully measured (Table 3). (Class I indicates "a well designed prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, and enabling the assessment of appropriate tests of diagnostic accuracy.") Only 1 of those studies (*10*) focused on evaluating dementia at a relatively early stage. To be included in that study, patients were required to have had onset of dementia symptoms within 1 y of entry. All of the 134 patients evaluated underwent a complete standardized diagnostic work-up comprised of a comprehensive medical history and physical examination, neurologic examination, neuropsychologic testing, laboratory tests, and structural neuroimaging, and an average of 3 additional years of clinical follow-up. Sensitivity of this assessment for AD was 83%–85%, whereas specificity was 50%–55%. It should be emphasized that this was not the diagnostic accuracy of initial clinical evaluation but of an entire series of evaluations repeated over a period of years (in contrast to the accuracies estimated for PET, based on testing performed once and at an early stage of disease). Nevertheless, a conservative bias (i.e., in favor of the conventional algorithm) was permitted in the present analysis, by exercising the assumption that these levels of accuracy (with sensitivity and specificity taken at their mean values of 84% and 52.5%, respectively) could be achieved in only 6 mo of total evaluation time, to allow a match with the maximal length of time required for diagnoses to be reached using the proposed algorithm.

RESULTS

The base-case analysis quantitatively compared the conventional and proposed algorithms, using values for all modeled variables and costs as discussed in the Materials and Methods and listed in Tables 1–4. In the first comparison, initial structural neuroimaging was assumed to consist of MRI without contrast, and only for patients with specific indications (in line with the previous, and best studied, AAN practice parameters (*50,56*)), in the proposed and conventional pathways. Under these circumstances, the financial liability accruing to each algorithm for evaluation and (mis)management of patients was similar ($3,433 and $3,564 per patient; Table 5) when calculated on the basis of costs per all patients evaluated. In other words, in terms of total dollars expended, the cost of obtaining brain PET in those patients for whom it was indicated (Fig. 2) in the proposed algorithm was comparable to the combined cost in the conventional algorithm of more needed care for patients with advancing dementia who could have benefited from earlier accurate diagnosis and treatment and of the medication prescribed to those for whom it was not indicated. Calculation of the cost-to-benefit ratios, which took account of the higher overall accuracy of the proposed algorithm (85%) compared with the conventional algorithm (69%), revealed a cost-per-benefit savings of $1,138 with the proposed algorithm ($4,047 vs. $5,185 per accurate diagnosis). Inversely, this can be viewed in terms of the number of correct diagnoses that could be made for a fixed total expenditure—for example, $100,000, for which the proposed and conventional algorithms would yield 25 and 19 accurate diagnoses, respectively. Thus, with approximately the same number of dollars spent for evaluating a given number of patients, the proposed algorithm provides more value in terms of leading more patients to appropriate management—which in turn decreases morbidity associated with the disease process and the adverse consequences (most commonly nausea and vomiting) of unnecessary medication.

As mentioned previously, the Medicare reimbursement rate for dedicated brain PET, in contrast to all other diagnostic tests included in the algorithms, had not yet been

TABLE 5
Costs and Accuracy Rates of Conventional and Proposed Algorithms in Base-Case Analysis

Algorithm	False-positive rate (%)	False-negative rate (%)	Mean costs per patient for evaluation and management	Overall accuracy (%)	Costs per accurate diagnosis
Conventional	23.01	8.25	$3,564	68.74	$5,185
Proposed	12.04	3.14	$3,433	84.82	$4,047
Cost savings			$131		$1,138

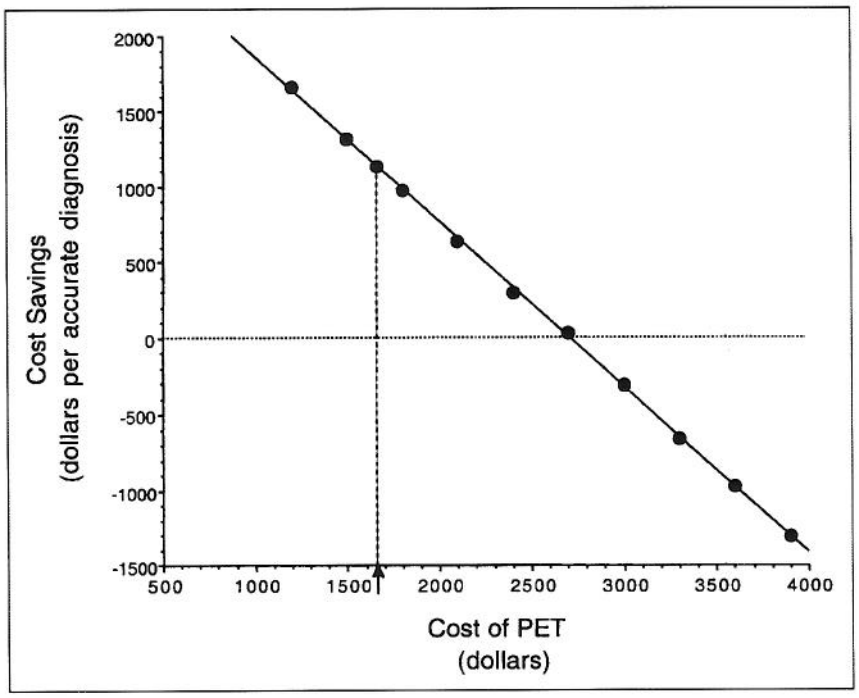

FIGURE 3. Effect of cost of PET on cost savings achieved with proposed algorithm. Arrow indicates PET cost ($1,661) for base case.

established at the time of this investigation. Of course, the magnitude of cost savings generated from following the proposed algorithm is directly related to the cost of PET (Fig. 3). For example, if the cost of PET were reduced from $1,661 to $1,500, cost savings would increase from $1,138 to $1,321 per accurate diagnosis; conversely, if the cost of PET went up to $1,800, cost savings would decrease to $978 per accurate diagnosis. The choice of algorithms becomes cost neutral (i.e., cost savings = $0) when the cost of PET is set at $2,728, an amount that is 64% higher than that in the base case. In other words, given the current levels of other dementia evaluation and management costs conventionally incurred, the cost for each additional correct diagnosis that will be gained through incorporation of PET into the diagnostic process will be lower than the cost that is presently incurred per correct diagnosis made, as long as the cost of a brain PET scan remains under $2,700.

We also examined the influence on cost savings of the recent update of AAN practice parameters (*38*), which made 2 essential modifications from the earlier AAN practice parameters (*56*), concerning concrete guidelines for diagnostic evaluation: (a) Structural imaging is now recommended for initial evaluation, regardless of whether specific findings are present on history and physical examination suggestive of a structural brain lesion, and (b) syphilis serology testing is no longer recommended as part of the routine blood laboratory panel. To examine the effects of those changes on our model, we ran the base-case analysis again, but with the changes introduced into both algorithms that (a) MRI without contrast was obtained for 100% of patients evaluated, and (b) the price of syphilis serology testing ($11.40) was not included in the cost for the laboratory panel. These changes increased somewhat the cost-to-benefit ratios of the proposed and conventional algorithms ($4,334 and $5,659 per accurate diagnosis, respectively) without greatly changing the relative relationship between them. Similarly, changing the original base-case analysis by obtaining MRI with and without contrast, on all patients for whom structural neuroimaging was specifically indicated, increased the cost-to-benefit ratios of the proposed and conventional algorithms by comparable amounts (to $4,553 and $5,809 per accurate diagnosis, respectively). Because this third analysis yields a cost savings for the proposed algorithm that falls intermediate to the first and second analyses ($1,256 vs. $1,138 and $1,325 per accurate diagnosis), it served as the central case around which the range-of-variable analyses were conducted.

As described in the Materials and Methods, range-of-variable analyses were performed to explore the impact of changes in the most potentially variable and critical parameters. Clearly, the accuracy achievable with PET is of critical importance to the value of the proposed algorithm. The base-case analysis used what appears to be the best estimate of that accuracy on the basis of the FIND-AD multicenter investigation (*43*). However, we also examined the effect on cost savings when sensitivity (Fig. 4, top) or specificity (Fig. 4, bottom) was varied across the entire range of estimates reported in other studies (Table 2). Even with PET operating at the lowest estimates of sensitivity, the proposed algorithm maintained a cost-to-benefit ratio comparable to that of the conventional algorithm (while still providing more total correct diagnoses than would be achieved without the use of PET). The cost savings are even more stable with respect to varying specificity: The proposed algorithm was

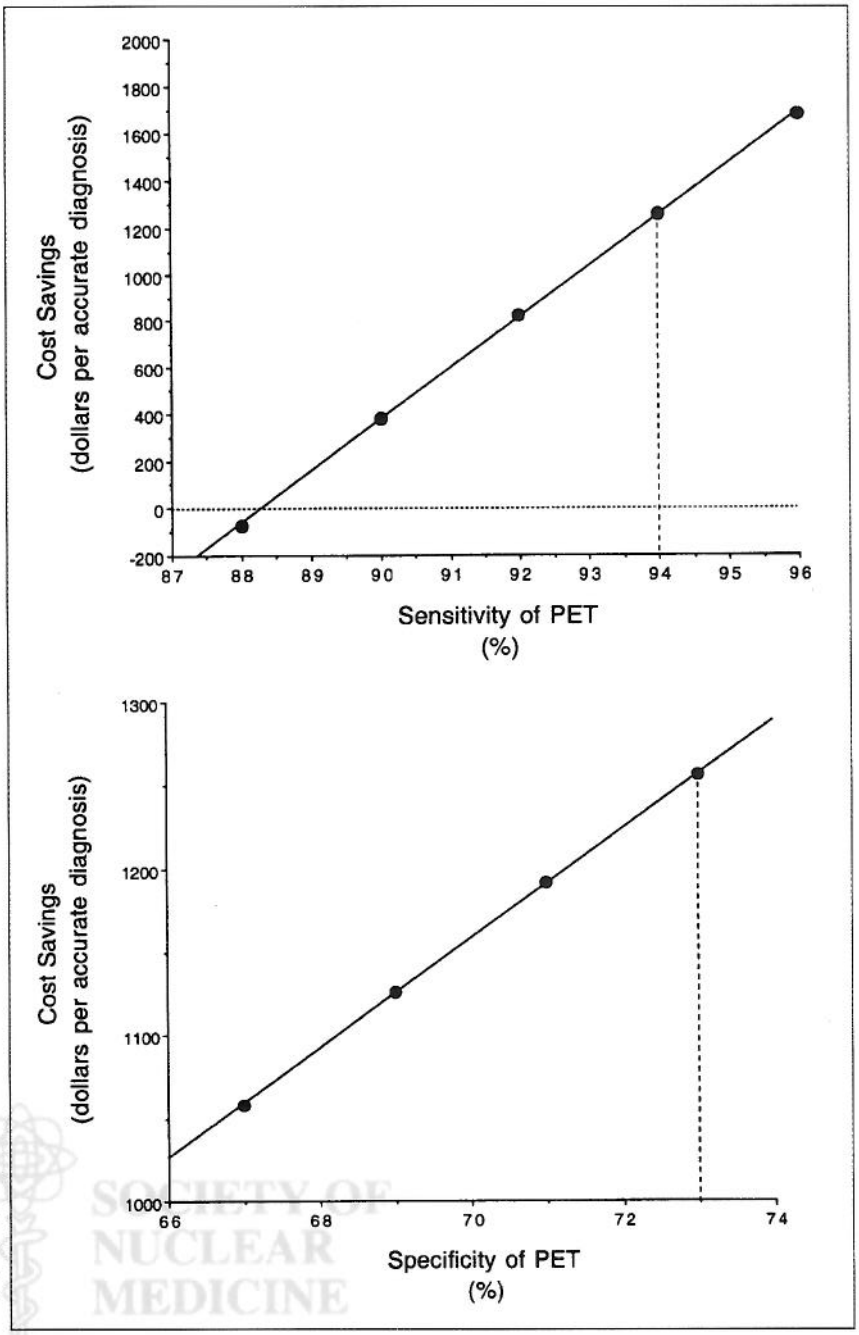

FIGURE 4. Effects of varying sensitivity (top) and specificity (bottom) of PET on cost savings achieved with proposed algorithm. Vertical dashed lines indicate sensitivity and specificity values.

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associated with a cost savings of approximately $1,000 per accurate diagnosis at the lowest literature estimates of specificity for PET. Positive cost savings would in fact be maintained with the specificity of PET ranging as low as 35%. When we simultaneously penalized all 3 of the above variables in the proposed algorithm—decreasing the sensitivity to the floor literature value of 88%, dropping the specificity to the floor value of 67%, and increasing the PET base cost by 15%, to $1,910 per scan—cost savings fell to −$631 per accurate diagnosis. Under those same cost and specificity conditions, cost savings = $0 when PET sensitivity for AD was set at 90.7%.

Finally, we had used for our base case the AAN's own reported estimate of annual costs of caring for a patient with AD along with the most conservative end of the range of 9- to 18-mo delay in disease-related cognitive decline and need for institution of long-term care reported in the literature. Because this expense generates the single largest cost for an individual patient that will accrue to either algorithm, we examined the effect of varying its magnitude by allowing the estimated delay time to vary from 6 to 12 mo (or equivalently, to vary the estimated annual cost of care for an AD patient from 33% below to 33% above the AAN's estimate). As can be seen (Fig. 5), even when the estimate

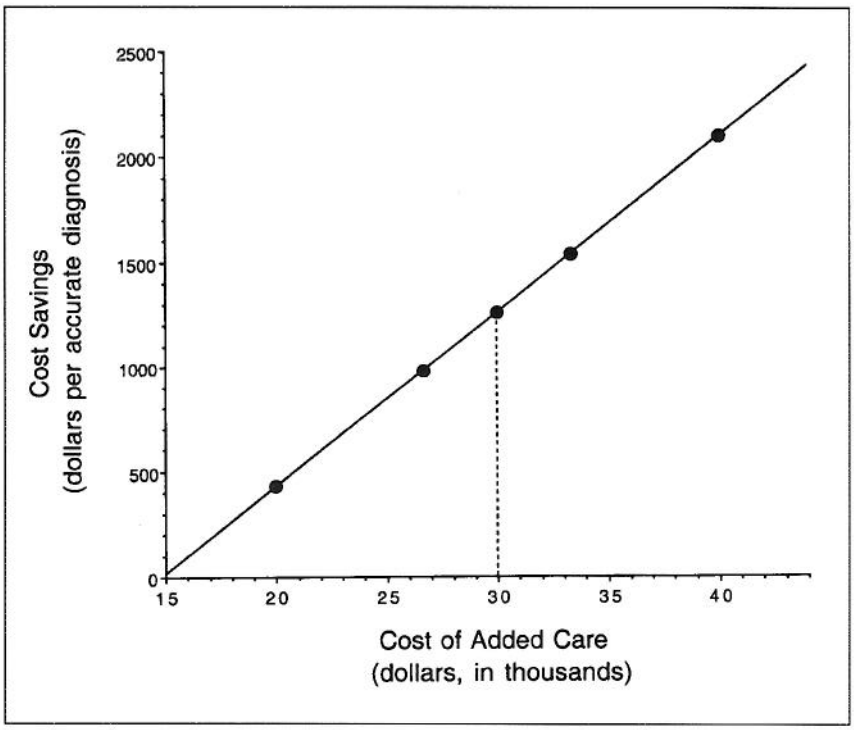

FIGURE 5. Effect of cost of added AD-related care on cost savings achieved with proposed algorithm. Vertical dashed line indicates cost of added AD care established for base-case analysis.

of added care is decreased to 6 mo (or $20,000), a cost savings of >$400 is maintained, and the proposed algorithm would provide positive cost savings with added care estimates extending from 9 mo down to less than half that time. Conversely, with an estimate of 12 mo of added care accruing, cost savings provided by the proposed algorithm exceed $2,000 per accurately diagnosed patient (and would linearly rise to still substantially higher values at the outside end of the literature reports of 18 mo of added care being needed).

DISCUSSION

As suggested by the relevant scientific literature, diagnostic work-ups that do not include assessments of cerebral metabolism tend to be substantially less sensitive in the diagnosis of AD. If one accepts the recently affirmed recommendation of the AAN (*38*) that the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria for "probable AD (rather than the more inclusive "possible AD") should be routinely used," then clinical sensitivity appears to range in the interval of 66% ± 17% and the sensitivity using PET ranges in the interval of 91% ± 3% (Tables 2 and 3). The sensitivity of clinical evaluation can be increased to 90.5% ± 5.5% (comparable to that using PET) by expanding the diagnosis of AD to include patients who meet NINCDS–ADRDA criteria for possible AD, and including moderately and severely advanced dementia cases in the analysis, but at the expense of specificity (55.5% ± 5.5% in the class I studies). In contrast, at that level of sensitivity, the specificity using PET is 70% ± 3%.

The AAN Quality Standards Subcommittee also reviewed 9 studies that addressed the clinical diagnostic accuracy of AD but that were classified as having lower "quality of evidence" than those described in Table 3. Across all of these studies, they found an average clinical specificity of 70% (as occurs with PET), whereas average sensitivity in that analysis was 81% (compared with the 91% ± 3% reported for PET). In the 2 largest class II studies that uniformly used NINCDS–ADRDA diagnostic criteria (*69,70*), at a sensitivity of 90% ± 1% (achieved by including possible AD patients and moderately advanced dementia cases), specificity fell to 29% ± 8%.

With a preponderance of evidence pointing to improving diagnostic accuracy by incorporating FDG PET into the algorithm for evaluation of dementia, the focus then turns to the question of exactly when the PET study should be obtained. Beyond the specific advantages conferred by more accurate diagnoses leading to more appropriate management (Introduction), other ramifications of having the added information provided by PET bear on this issue. For example, if accurate positive diagnoses are achieved early on, patients and their families can be spared the repeated batteries of diagnostic tests often performed over extended periods of time, and they and their physicians would less often experience the frustrations of ambiguous diagnostic conclusions. The information would also help families to plan for issues important to future patient care—particularly so, in light of recent data indicating that the degree of

hypometabolism identified by PET in certain affected brain regions predicts the rate of future cognitive decline, as assessed by standardized measures of memory in the years subsequent to PET examination (*71*).

These and other considerations support the notion that the best time to obtain the PET study is early in the course of the clinical work-up, as soon as it has been determined that the patient is an appropriate candidate for evaluation of cerebrocortical dysfunction. The guiding principle for that determination is simply as follows: A patient who presents with an adverse change in cognition or behavior, which has not been fully explained and fully reversed following prompt and standard diagnostic and treatment approaches, should undergo PET imaging (Fig. 2).

How much will following such an algorithm cost us and, more to the point, how does that compare with the costs incurred when we do not have available the additional information provided by PET? The cost associated with performance of a dedicated brain PET scan amounts to less than the typical costs of 1 y of pharmacotherapy for unnecessary treatment of a patient misdiagnosed with AD or 1 mo of lost productivity and independence of a patient for whom we fail to provide timely diagnosis and treatment. In the present decision analysis, it was found that the added diagnostic accuracy obtained by incorporation of FDG PET into the routine clinical evaluation of patients presenting with early symptoms of dementia could be achieved in an economically practical manner. This was true for the base-case situation, despite that analysis being conservatively biased in 2 important ways: (a) by assuming that reported diagnostic accuracy, based on using conventional means and observing patients over an average of 3 y, could be achieved with equal accuracy after only 6 mo of conventional evaluation; and (b) by assuming that only 9 mo of delay in disease progression would occur from failure to diagnose and treat AD, in the face of the literature reporting a range of 9–18 mo for this. Furthermore, the economic viability of the proposed algorithm was maintained when values were varied widely beyond those of the base-case analysis, affecting the manner in which structural imaging was used as well as the cost, sensitivity, and specificity of PET and the cost of added care for AD patients.

A recent cost-effectiveness study by McMahon et al. (*72*) modeled the role of SPECT and specialized MRI in the management of AD. The authors concluded that the addition of functional neuroimaging to the usual diagnostic regimen for evaluating AD was not cost-effective. Their study differed in several important ways from our analysis. First, it did not focus on early diagnosis but assumed a patient population in which 40% of the AD patients had already advanced to a moderate stage of disease. Second, patients who were thought to be clinically unlikely to have AD were not offered SPECT in their model, thereby forfeiting in advance the opportunity for nuclear imaging to detect unsuspected cases. Third, costs were not compared on the basis of diagnostic accuracy achieved, as in this analysis, but rather on the basis of quality-adjusted life years that were estimated to "accrue to hypothetical cohorts of patients." Other differences included the assumption in the McMahon et al. study of a base-case diagnostic specificity for conventional work-up of 90% (much higher than in this analysis or than that estimated by the AAN (*38*)) and, of course, no explicit incorporation of PET into any of its algorithms.

It may be observed that the conventional algorithm depicted here, derived especially from AAN recommendations, appears (understandably) to be formulated with an orientation pointed primarily toward neurologists approaching dementia patients, whereas we formulated the proposed algorithm with an orientation pointed primarily toward primary care physicians. With respect to effect on the analysis, however, this was more a matter of style than substance, and we expect that neurologists and primary care physicians will be able to navigate through the evaluation process guided by either algorithm and that similar costs should accrue to a given algorithm when appropriately skilled physicians of any specialty are doing that navigating. A major motivating factor for the orientation we have taken, however, is that regardless of the potential benefits of 1 diagnostic algorithm versus another, the more fundamental problem at this time is the failure of physicians to attempt to identify or diagnose dementia at all (*73–75*). Although several professional organizations and consensus groups, as well as the U.S. Public Health Service, have recommended formal dementia screening for elderly primary care patients (*76–79*), most clinicians lack training in the use of cognitive screening tests (*80–84*), and fewer than 1 in 8 physicians actually administers such tests (*83*).

The problem is further confounded by some physicians' fears of the psychologic effects of diagnosing a patient with early dementia. However, the published evidence indicates that such concerns of physicians are often out of step with the desires and needs of their patients. Many families consider their doctors to be reticent in making the diagnosis of dementia and feel that physicians may minimize the associated problems (*84*). One survey of 156 community-dwelling older persons revealed that 80% of them preferred to be informed if they had dementia (*85*). In another study, >90% of 224 consecutive patients in an ambulatory practice said that if their physician thought they had AD, they would want to be told (*86*). Nor are such paternalistic concerns unique to health care providers: In a survey in which 71% of respondents indicated that they would want to be informed of the diagnosis should they develop AD, only 17% of these same individuals stated they would want their family members with that diagnosis to be informed of it (*87*). In light of the accumulated evidence that patients benefit significantly by accurate diagnosis followed by institution of appropriate management in the early stages of disease, it may not be long before failure to diagnose AD in a patient presenting with suggestive signs and symptoms of cognitive decline may come to be viewed similarly to the way that failure to

diagnose malignancy in the face of suggestive evidence that is discovered (or should have been discovered) on history or examination is currently viewed. Once the importance of making an accurate diagnosis in patients with dementia becomes more widely appreciated, application of the most sensitive and accurate tools available for that task will likely become more common.

CONCLUSION

As AD is increasingly recognized as a pharmacologically treatable dementia, it is becoming less tenable to take a watchful waiting approach to making this diagnosis; because more advanced AD may be less amenable to therapy, even a 1-y delay in reaching a therapeutic decision may compromise care. The availability of PET for imaging brain metabolic activity, allowing sensitive detection of neurodegeneration at a very early stage, raises the prospect that patients can be steered toward more appropriate management earlier in the course of their disease. This prospect particularly deserves consideration now that recent developments in instrumentation and radiopharmaceutical distribution have made obtaining scans of cerebral metabolism achievable in routine clinical settings—and for less than the cost of a single month of the 9–18 mo of extra care that typically is needed for a patient who is not diagnosed (and thus not treated) in a timely manner. Analysis of the models of evaluation and management presented in this article predict that improved care can be economically achieved through appropriate incorporation of PET into the diagnostic work-up.

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Brain ^{18}F-FDG PET in the Diagnosis of Neurodegenerative Dementias: Comparison with Perfusion SPECT and with Clinical Evaluations Lacking Nuclear Imaging*

Daniel H.S. Silverman, MD, PhD

Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, California

The clinical identification and differential diagnosis of dementias is especially challenging in the early stages, but the need for early, accurate diagnosis has become more important, now that several medications for the treatment of mild to moderate Alzheimer's disease (AD) are available. Many neurodegenerative diseases produce significant brain-function alterations detectable with PET or SPECT even when structural images with CT or MRI reveal no specific abnormalities. ^{18}F-FDG PET images of AD demonstrate focally decreased cerebral metabolism involving especially the posterior cingulate and neocortical association cortices, while largely sparing the basal ganglia, thalamus, cerebellum, and cortex mediating primary sensory and motor functions. Assessment of the precise diagnostic accuracy of PET had until recently been hindered by the paucity of data on diagnoses made using PET and confirmed by definitive histopathologic examination. In the past few years, however, studies comparing neuropathologic examination with PET have established reliable and consistent accuracy for diagnostic evaluations using PET—accuracies substantially exceeding those of comparable studies of the diagnostic value of SPECT or of both modalities assessed side by side, or of clinical evaluations done without nuclear imaging. Similar data are emerging concerning the prognostic value of ^{18}F-FDG PET. Improvements in the ability of PET to identify very early changes associated with AD and other neurodegenerative dementias are currently outpacing improvements in therapeutic options, but with advances in potential preventive and disease-modifying treatments appearing imminent, early detection and diagnosis will play an increasing role in the management of dementing illness.

Key Words: Alzheimer's disease; brain; dementia; PET; SPECT

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Alzheimer's disease (AD) is the leading neurodegenerative disorder and accounts for approximately two thirds of cases of dementia. AD currently affects 4 million people in the United States and is estimated to eventually affect 14 million as the aging of the baby boomers expands our geriatric population (*1–3*).

Advances in therapeutic agents for the treatment of AD have progressed substantially in the past decade. Cholinesterase inhibitors have successfully been used for a decade to delay cognitive decline associated with mild to moderate disease, and memantine was approved by the U.S. Food and Drug Administration last year for treating patients with more advanced AD. Similarly, neuroimaging techniques, including SPECT and PET, used in the evaluation and early detection of the disease have improved considerably.

AD can be diagnosed definitively only by histopathologic examination of brain tissue (*4*). The identification and differential diagnosis of AD is especially challenging in its early stages, partly because of the difficulty in distinguishing it from the mild decline in memory that can occur with normal aging and from mild cognitive manifestations of other neuropsychiatric conditions, such as depression, as well as other causes of dementia. Physicians frequently err both by failing to make the diagnosis of AD when the disease is present and by diagnosing early AD when it is absent (*5–8*). Moreover, clinical assessment frequently involves multiple examinations and laboratory tests over months or years.

The need for early, accurate diagnosis has become more important, now that several medications for the treatment of mild to moderate AD are available. Patients with neurodegenerative disease have the most to gain from therapy that intervenes as early as possible in the course of inexorably progressive, irreversible damage to brain tissue, and controlled clinical trials have demonstrated that cholinesterase inhibitors can improve, or delay decline in, memory and other cognitive functions in mild or moderately affected AD

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For correspondence or reprints contact: Daniel H.S. Silverman, MD, PhD, Ahmanson Biological Imaging Division, UCLA Medical Center, CHS AR-144, MC694215, Los Angeles, CA 90095-6942.

E-mail: dsilver@ucla.edu

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patients (*9–15*). These treatments can cut by more than half the proportion of patients requiring nursing home placement over a given time (*16,17*). Cholinergic (and other (*18*)) agents also are beneficial through reducing behavioral problems, improving patients' functional abilities, and decreasing caregiver burden (*13,19–22*). Studies examining long-term effects of cholinesterase inhibitors indicate that drug treatment delays cognitive decline in AD patients by 9–12 mo on average and delays the need for institutionalization by 18 mo on average (*19,23–25*). Moreover, delaying the implementation of therapy by as little as 6 mo—besides carrying the inherent adverse consequence of depriving the patient of the short-term advantages of potentially enhanced cognitive and functional abilities during that time—may have long-term consequences as well (*13,19,26*). In a randomized, placebo-controlled trial of the cholinesterase inhibitor galantamine in patients with mild to moderate AD, Raskind et al. (*13*) found that the drug significantly improved cognitive function relative to placebo after 6 mo of treatment; during an ensuing 6-mo open-label treatment period, the patients who were originally in the placebo group were also given galantamine. At 1 y, better cognitive performance was seen in patients who began drug treatment at the beginning of the trial than in those whose treatment had been delayed for 6 mo. Similar benefits have also resulted from earlier institution of therapy with either rivastigmine (*11*) or donepezil (*26*). If functional neuroimaging is indicated for a particular patient, performing it within 6 mo of identifying progressive cognitive decline that could represent incipient AD would be prudent.

LIMITATIONS OF CONVENTIONAL CLINICAL EVALUATION

Few studies have specifically addressed the question of clinical detection of very mild disease, particularly in comparison with the standard criterion of histopathologic diagnosis. In an investigation aimed at doing so, patients who initially appeared healthy or minimally affected were followed up with repeated examinations for an average of 4 y (*27*). Even by the end of this longitudinal follow-up period, a neurologist detected AD in only 70% of the patients who were histologically positive for AD. In the recent report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN) (*28*), the source of the most comprehensive guidelines and standards for the clinical evaluation of dementia in the last several years, 3 class I studies (*7,29,30*) were identified in which the diagnostic value of clinical assessment could meaningfully be measured. Class I indicates "a well designed prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, and enabling the assessment of appropriate tests of diagnostic accuracy." Only one of them (*7*) focused on evaluating dementia at a relatively early stage. To be included in that investigation, patients were required to have had an onset of dementia symptoms within 1 y of entry. All 134 patients evaluated underwent a complete standardized diagnostic work-up comprising comprehensive medical history, physical examination, neurologic examination, neuropsychologic testing, laboratory testing, and structural neuroimaging and an average of 3 additional years of clinical follow-up with repeated testing. Sensitivity of this assessment for AD was 83%–85%, whereas specificity was 50%–55%, yielding an overall accuracy of 69%. In these studies, and in most similar studies, the reported sensitivities and specificities represent not the diagnostic accuracy of an initial clinical evaluation but the diagnostic accuracy of an entire series of evaluations repeated over a period of years.

When neuroimaging is performed in the evaluation of dementia, patients are usually referred for a structural imaging examination—that is, MRI or CT. Conventional MRI or CT of patients with symptoms of dementia may be useful for identifying unsuspected clinically significant lesions, present in approximately 5% of patients (*28*). However, in patients with AD (which is much more common), such scans are typically read as showing normal findings, as demonstrating the nonspecific finding of cortical atrophy, or as revealing ischemic changes that are (mis)interpreted as

TABLE 1
Imaging Findings Pertaining to Differential Diagnosis of Dementias

Etiology of dementia	Regional deficits identified by neuronuclear imaging
AD	Parietal, temporal, and posterior cingulate cortices are affected early, with relative sparing of primary sensorimotor and primary visual cortices and sparing of striatum, thalamus, and cerebellum. In early stages, deficits often appear asymmetric, but degeneration eventually is evident bilaterally.
Vascular dementia	Hypometabolism and hypoperfusion affect cortical, subcortical, and cerebellar areas.
Frontotemporal dementia (e.g., Picks disease)	Frontal cortex and anterior temporal and mesiotemporal areas are affected earlier or with greater initial severity than are parietal and lateral temporal cortices, with relative sparing of primary sensorimotor and visual cortices.
Huntington's disease	Caudate and lentiform nuclei are affected early, with gradual development of diffuse cortical involvement.
Parkinson's dementia	Deficits are similar to those of AD, but with more sparing of mesiotemporal area and less sparing of visual cortex.
Dementia with Lewy bodies	Deficits are similar to those of AD, but with less sparing of occipital cortex and possibly cerebellum.

TABLE 2
Use of PET for Differential Diagnosis of AD

Radiopharmaceutical	Diagnostic standard	Subjects	Major findings	Comments	Reference
^{18}F-FDG	C	69 AD 48 Non-AD	Sens = 93%, Spec = 58%, Accu = 79% (Spec = 80% when patients with Parkinson's dementia are excluded). Severity-stratified analysis shows for mild AD (av. MMSE = 26) Sens = 87.5%; for mod./severe AD (av. MMSE = 10) Sens = 96%.	AD av. age = 66, av. duration = 2.5 y. Groups well matched for level of severity (AD av. CDR = 2.1, Non-AD av. CDR = 2.1, by visual analysis).	(*47*)
^{18}F-FDG	P	13 AD 7 Non-AD	Sens = 92%, Spec = 71%, Accu = 85%.	Pooled analysis (*44*) across 3 studies providing small groups of pathologically confirmed cases.	(*46*) (*47*) (*48*)
^{18}F-FDG ^{99m}Tc-HMPAO	C	20 AD 12 Non-AD 13 NI	PET Accu = 90%, SPECT Accu = 67%. A Stratified analysis to look at early AD shows that for subjects with MMSE > 20, PET Accu = 87%, SPECT Accu = 63%.	Receiver-operating characteristic area-under-curve analysis was performed for both SPECT and PET on same 45 patients to determine accuracy of each method	(*43*)
^{18}F-FDG	L	66 AD 23 MI 22 NI	Group analysis shows significant differences for very early AD (av. MMSE = 25) vs. NI (av. MMSE = 28) Posterior cingulate significantly fell (by 21%–22%, P = 0.0007), as did parietal and temporal areas.	To obtain very early AD cases, minimally impaired patients were scanned and then followed longitudinally to determine whether NINCDS criteria for probable AD developed.	(*53*)
^{18}F-FDG	C	9 AD 9 Non-AD	Group analysis by statistical mapping demonstrates significant PET differences between AD and Parkinson's dementia (Table 1).	Groups well matched for (fairly mild) level of severity (AD av. CDR = 1.2, Non-AD av. CDR = 1.3).	(*73*)
^{18}F-FDG	C	19 AD 19 Non-AD	Group analysis by statistical mapping demonstrates significant PET differences between AD and dementia with Lewy bodies (Table 1).	Groups well matched for level of severity and duration (AD av. MMSE = 18, 24 mo, Non-AD av. MMSE = 18, 24 mo)	(*74*)
^{18}F-FDG	C	21 AD 21 Non-AD 21 NI	Group analysis by region-of-interest method demonstrates significant differences between AD and frontotemporal dementia (Table 1).	Groups well matched for (fairly mild) level of severity (AD av. MMSE = 20, Non-AD av. MMSE = 19). All subjects had normal MRI findings	(*75*)
^{18}F-FDG	P	16 AD 6 NI	AD identified in 13/14 (Sens = 93% of AD-only and 1/2 AD+ cases (overall Sens = 88%). Absence of AD confirmed in 4/6 cases (Spec = 67%).	14 patients had AD as the only pathologic diagnosis, 1 had AD + Lewy bodies, 1 had AD + PSP.	(*49*)
^{18}F-FDG	P	97 AD 41 Non-AD	AD identified in 85/89 (Sens = 96% of AD-only and 6/8 AD+ cases (overall Sens = 94%). Absence of AD confirmed in 30/41 cases (Spec = 73%), including 23 cases with other neurodegenerative dementias. Absence of neurodegenerative disease confirmed in 14/18 cases (Spec = 78%).	Relatively early dementia group, with 70% having mild or questionable dementia; 89 patients had AD as the only pathologic diagnosis; 5 had AD + Lewy bodies; 1 each had AD + PSP, + Parkinson's disease, or + cerebrovascular disease.	(*50*)
$H_2{}^{15}O$ $C^{15}O$	C	16 AD 10 NI	Scans with $H_2{}^{15}O$ show decreased perfusion for AD in parietal and lateral temporal regions. Scans with $C^{15}O$ reveal no cerebral blood volume differences between AD and NI groups.	Relatively mild AD group, having av. MMSE = 21.	(*76*)

C = diagnosis based on clinical evaluation near time of scan; P = diagnosis based on histopathology; L = diagnosis based on longitudinal clinical follow-up of at least 2 y; AD = cognitively impaired secondary to AD; Non-AD = cognitively impaired but not secondary to AD; MI = isolated memory impairment; NI = cognitively normal; Sens = sensitivity with respect to correctly identifying presence of AD; Spec = specificity with respect to correctly specifying that AD is absent; Accu = overall accuracy; av. = average; mod. = moderate; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating.

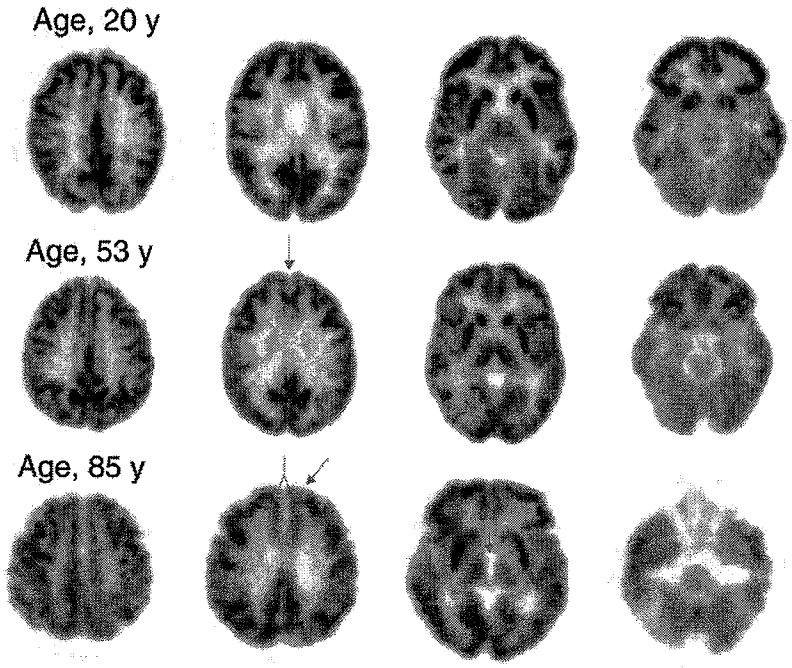

FIGURE 1. Normal adult pattern of cerebral glucose metabolism measured with ^{18}F-FDG. Images are shown from the most superior (far left column) to most inferior (far right column) planes of the brain. In this and later figures, images are cross-sectional and are displayed with the anterior brain at the top of each image and the left side of the brain on the right of each image. Normal aging is associated with some increased generalized cortical atrophy, as evidenced by moderate widening (arrow) of the interthalamic distances in the 85-y-old patient (middle right). Additional arrows highlight the progression of mild metabolic decline, also attributable to normal aging, in the medial prefrontal cortex bilaterally (middle left, ages 53 and 85 y) and in the left anterior prefrontal cortex (middle left, age 85 y). Otherwise, in healthy adults, the pattern of regional cerebral metabolism changes little throughout adulthood.

pointing to cerebrovascular disease as the primary or sole cause of the patient's cognitive decline. The result could be failure to institute appropriate, timely pharmacotherapy (e.g., donepezil, rivastigmine, or galantamine, which are approved for the indication of "mild to moderate dementia of the Alzheimer's type"). It is unfortunately not rare for that type of misinterpretation to occur, even among expert clinicians. In a multicenter study involving 7 university-affiliated AD Diagnostic and Treatment Centers, among patients in whom "vascular dementia" was diagnosed after clinical and structural neuroimaging evaluations and in whom other dementia diagnoses were specifically thought to be absent, fewer than 30% actually had isolated cerebrovascular disease, and the majority (55%) had AD on pathologic diagnosis (*31*).

NEURONUCLEAR IMAGING IN DEMENTIA ASSESSMENT

Over the last 2 decades, clinicians and researchers have obtained substantial experience in using the 3-dimensional imaging capabilities of PET and SPECT for the identification and differential diagnosis of dementia (*32–34*). Thousands of patients with clinically diagnosed and, in some cases, histopathologically confirmed AD from many independent laboratories have been studied using measures of cerebral blood flow, glucose metabolism, or oxygen use obtained through these tomographic neuronuclear imaging modalities. The principal findings from that experience briefly are as follows: A consistent pattern of focally decreased cerebral metabolism and perfusion has been identified, involving especially the posterior cingulate and neo-

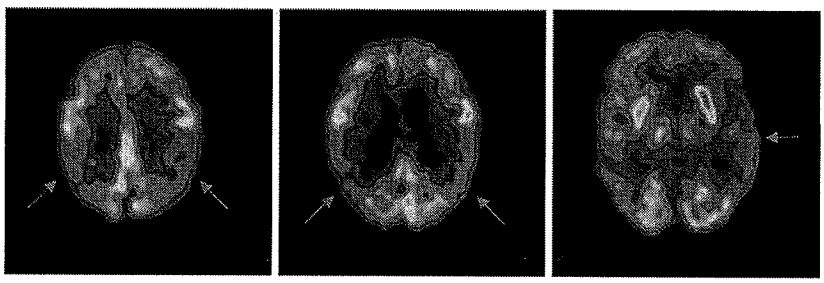

FIGURE 2. ^{18}F-FDG PET images of early AD. Early Alzheimer's typically affects the parietal, temporal, and posterior cingulate cortices. Brain images of this 80-y-old woman demonstrate hypometabolism of the parietal cortex, bilaterally (left and middle), with relative sparing of the primary visual cortex, sensorimotor cortex, thalamus, and basal ganglia. In the early stages of AD, deficits often appear asymmetrically, as evidenced here by mild hypometabolism of the left temporal cortex (right). In later stages of the disease, degeneration will be apparent bilaterally.

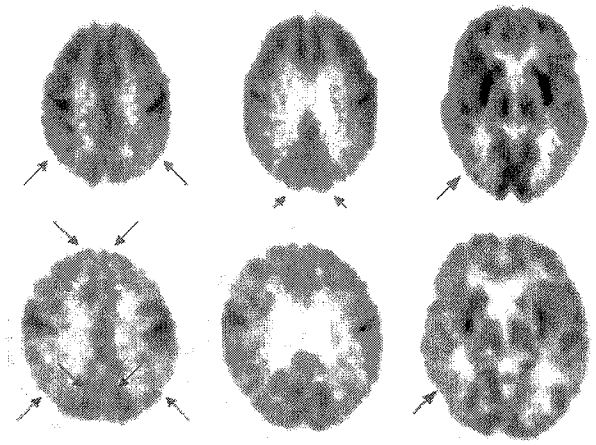

FIGURE 3. ^{18}F-FDG PET images of early- and late-stage dementia with Lewy bodies. Typical cerebral metabolic patterns for patients with dementia with Lewy body disease are similar to AD patterns, but with less sparing of the occipital cortex. A patient with early-stage disease (top row; 63-y-old woman) was clinically followed up for 28 mo, during which her MMSE score dropped from 23 to 14, of 30 possible points. The arrows on her scan highlight bilateral hypometabolism of the parietal (left) and occipital (middle) cortices, as well as hypometabolism of the posterior temporal cortex (right). A patient in a later stage of the disease (bottom row; 71-y-old man) has moderate to severe bilateral hypometabolism in the parietal cortex (left) and in the temporooccipital cortex (right), as similarly seen in the early-stage patient. Additional arrows in the left image refer to progression of hypometabolism in the occipital and prefrontal cortices, bilaterally.

cortical association cortices but largely sparing the basal ganglia, thalamus, cerebellum, and cortex mediating primary sensory and motor functions. Most studies also reported greater sensitivity to disease severity for the parietal lobe deficit than for the temporal lobe deficit. Frontal lobe hypoperfusion was also often reported, but not in the absence of temporoparietal abnormalities. A pattern of focal cortical inhomogeneities, all accounted for by areas of infarction on MRI, implies dementia secondary to cerebrovascular disease, which also often affects cerebellum and subcortical structures. A pattern of focal cortical inhomogeneities unmatched by MRI findings is consistent with a primary neurodegenerative disorder (e.g., AD, Pick's disease, other frontotemporal dementia, dementia with Lewy bodies, dementia of Parkinson's disease, Huntington's disease, or progressive subcortical gliosis.) As a rule, the pattern of bilateral temporoparietal hypoperfusion or hypometabolism well discriminates AD patients not only from age-matched healthy controls but also from patients with vascular dementia or frontal lobe dementia. However, more overlap of that pattern has been observed in patients with Lewy body dementia, Creutzfeldt–Jakob disease, and Parkinson's disease with dementia (Table 1). Neuronuclear imaging abnormalities correlate not only with dementia severity and specific patterns of cognitive failure in AD patients but also with regional densities of neurofibrillary tangles (*35*).

RECENT STUDIES ON PET ACCURACY IN DEMENTIA EVALUATION

Diagnosis

Clinical applications of neuronuclear imaging in dementia patients stem from numerous studies that have found many neurodegenerative diseases to produce significant alterations in brain function detectable with SPECT or PET even when structural images with CT or MRI reveal no abnormality. The utility of PET in this regard has been under study since the early 1980s (*36–39*) and has been extensively reviewed more recently (*40–45*).

Thousands of patients with clinically diagnosed—and, in some cases, histopathologically confirmed—causes of dementia from many independent laboratories have been studied using PET measures of cerebral blood flow, glucose metabolism, or oxygen use. The best-studied application of this type is the use of ^{18}F-FDG PET to evaluate AD. Table 2 presents published studies that assessed the diagnostic value of PET in the evaluation of dementia. The typically high sensitivity of ^{18}F-FDG PET, even in patients with mild impairment, suggests that by the time a patient presents with symptoms of a neurodegenerative dementia, substantial alteration of cortical metabolic function generally has occurred. The associated decreases in glucose metabolism in certain brain areas are readily detectable on ^{18}F-FDG images. Some visually evident differences between scans of patients with different dementing illnesses are seen in Figures 1–7.

Assessment of the diagnostic accuracy of PET had until recently been hindered by the paucity of studies involving patients who were followed up long term or for whom subsequent pathologic diagnosis was available; most previous clinical series compared PET findings with clinical assessments performed near the time of PET. The ability of

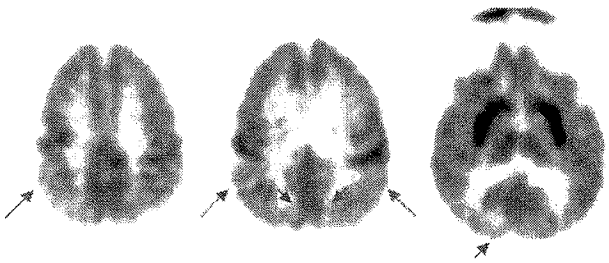

FIGURE 4. ^{18}F-FDG PET images of Parkinson's disease dementia. Typical patterns of regional cerebral metabolism are similar in Parkinson's dementia and AD, with less sparing of the occipital cortex and more sparing of the mesiotemporal area. The diagnosis of Parkinson's disease in this patient (72-y-old woman) was subsequently confirmed by autopsy. The arrows on her scan indicate parietal (left and middle images) and occipital (middle and right images) hypometabolism, whereas the ^{18}F-FDG uptake in basal ganglia is undiminished at this stage of her disease.

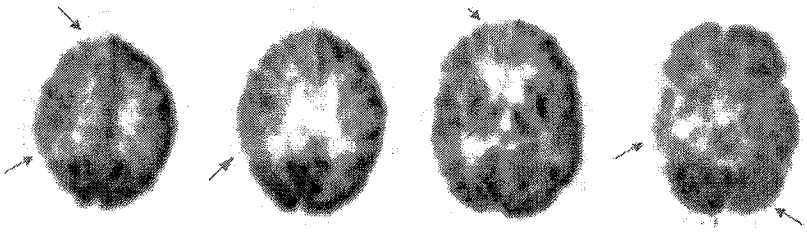

FIGURE 5. ^{18}F-FDG PET images of vascular dementia. Hypometabolism affecting cortical, subcortical, and cerebellar areas is often seen in vascular dementia. This patient (65-y-old woman) was followed for 10 mo, and vascular dementia was diagnosed both clinically and by structural imaging. Arrows indicate hypometabolism of the right frontal cortex (far left, middle right), right parietal cortex (far left, middle left), right basal ganglia and thalamus (middle right), and right temporal cortex (far right). The hypometabolism of the left cerebellum (far right) is characteristic of cross-cerebellar diaschisis, caused by diminished afferent input from the contralateral cortex.

the latter approach to assess diagnostic accuracy is unfortunately limited by the potential inaccuracy of clinical diagnosis, particularly for patients presenting in the earliest stages of disease—a time when the opportunity for effective therapy, and for meaningful planning, is greatest.

Studies comparing neuropathologic examination with imaging are thus most informative in assessing the diagnostic value of PET. In a pooled analysis (*44*) of 3 previously published studies (*46–48*), the histopathologically confirmed sensitivity and specificity of PET for detecting the presence of AD were 92% and 71%, respectively. In the largest single-institution series, Hoffman et al. (*49*) found the sensitivity and specificity of PET for AD to fall in the range of 88%–93% and 63%–67%, respectively. A subsequent multicenter study collected data from an international consortium of clinical facilities that had acquired both ^{18}F-FDG PET and histopathologic brain data for patients undergoing evaluation for dementia (*50*). The PET results identified AD patients with a sensitivity and specificity of 94% and 73%, respectively. This last study, which had more than 3 times as many patients as did the 4 previous studies combined, included a stratified examination of the subset of patients with documented early or mild disease. The performance of PET with respect to sensitivity (95%), specificity (71%), and overall accuracy (89%) was unaltered. These values agree with the ranges found in a broader literature review of PET studies, including those lacking neuropathologic confirmation of diagnoses (*51*). That review found reported sensitivities ranging from 90% to 96% and specificities ranging from 67% to 97%. The values also agree with a recent review of the PET literature reported by the AAN (*28*), which concluded that "PET scanning appears to have promise for use as an adjunct to clinical diagnosis [of AD]," based on its review of published studies that demonstrated diagnostic accuracies of 86%–100% for PET.

Regional cerebral metabolic changes associated with early AD can be detected with PET even before the symptomatic manifestations of the disease become evident (*50,52,53*). How accurate can ^{18}F-FDG PET be in the evaluation of nondemented patients, who are in the earliest stages of cognitive impairment? Table 3 reviews the most recent ^{18}F-FDG PET neuroimaging studies involving patients classified as cognitively impaired nondemented or having mild cognitive impairment. The studies were conducted or published between 2001 and 2003 and were found by searching PubMed in July 2003 (keywords: PET, cognitively impaired not demented, mild cognitive impairment) and by systematically checking the bibliographies of relevant articles so identified. The major criterion for inclusion was the use of ^{18}F-FDG PET to evaluate cognitively impaired nondemented patients or patients with mild cognitive impairment as a specific subject subset in the study; investigations that did not involve ^{18}F-FDG PET were excluded. Overall accuracies achieved with ^{18}F-FDG PET have been nearly as high in very mildly affected patients as in demented patients, generally exceeding 80% and ranging from

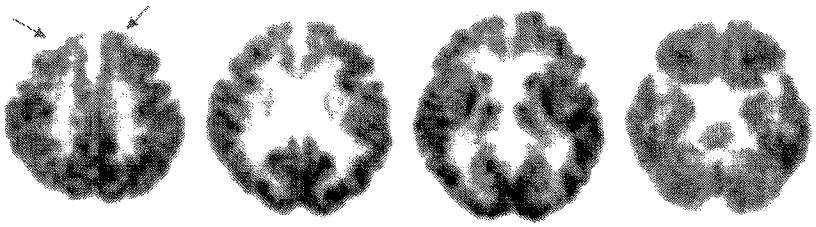

FIGURE 6. ^{18}F-FDG PET images of early frontotemporal dementia. This patient (66-y-old man) was diagnosed both clinically and by PET as having frontotemporal disease. The patient's MMSE score at the time of PET was 27 of a possible 30 points. Arrows indicate bilateral hypometabolism of the frontal cortex (far left), at a time that the remainder of the cerebral activity is not appreciably affected (middle left, middle right, and far right).

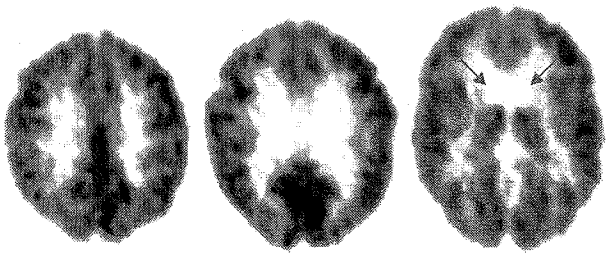

FIGURE 7. ^{18}F-FDG PET images of Huntington's disease. This patient (43-y-old man) has an 8-y history of progressive Huntington's disease. Arrows highlight the typical metabolic pattern of hypometabolism severely affecting the basal ganglia (right) at a time that cortical metabolism is still relatively intact (left and middle). As the disease progresses, diffuse cortical involvement gradually develops.

75% to 100%, in these recent studies. PET may be especially valuable in this clinical setting, considering the difficulty of distinguishing these patients from those with mild memory loss attributed to normal aging.

Prognosis

^{18}F-FDG PET may also serve explicitly as a prognostic tool, to determine likelihood of deterioration of mental status during the time after scanning. Relative hypometabolism of associative cortex can accurately predict whether cognitive decline will occur more quickly than would be expected for normal aging during the first several years after a PET evaluation (*52,54*). Moreover, the magnitude of decline during 2 y, for some standardized measures of memory, correlates with the initial degree of hypometabolism of inferior parietal, superior temporal, and posterior cingulate cortical regions (*55*). As cognitive impairment caused by neurodegenerative disease progresses, associated progression of regions of hypometabolism also occurs.

In a longitudinal evaluation of 170 patients who underwent brain PET, analyses were stratified according to presence of the most common comorbidities affecting cognitive function (other than primary neurodegenerative disease)—depression and thyroid disease—and according to scanner type (*56*). At the time of PET, more than one third (65/170, or 38%) of all patients were documented to have had a history of depression; 18%, a history of thyroid disease; and 6%, a history of both. PET findings accurately predicted, with a sensitivity of 91% (99/109), which patients would have a subsequent progressive course. Patients having a subsequent nonprogressive course were identified with a specificity of 80% (49/61). Of the patients without a history of depression or thyroid disease, the specificity of PET was nearly as high as its sensitivity (89%, with a 95% confidence interval [CI] of 77%–100%), but the specificity tended to be lower for patients with a history of depression or thyroid disease (74%, with a 95% CI of 59%–88%) than in those without either condition. In contrast, sensitivity was unaffected by the presence of those conditions (90%, with a 95% CI of 82%–98%, vs. 92%, with a 95% CI of 84%–100%). Although the prognosis of most subjects was correctly predicted by visual analysis of PET scans regardless of the presence of depression or thyroid disease, specificity tended to be lower for patients with a history of those conditions, and the overall false-positive rate of PET used in the prediction of a clinically progressive course of dementia was 3 times higher (3.5% [3/86] vs. 10.7% [9/84]) in patients with a history of depression or thyroid disease. It is thus suggested that physicians interpret positive brain scan findings with added caution when determining the prognosis for dementia in cognitively impaired patients with depression or thyroid disease, because of the potentially confounding effects of those conditions on regional brain metabolism (Figs. 8 and 9). What is also of clinical pertinence is that, because data were collected for almost a decade, scanner types changed during that time (e.g., brain PET conducted on the older generation of scanners contained only 15 planes, whereas scans obtained on the newer generation of scanners contained either 47 or 63 planes), and specificity tended to be higher for scans obtained on the newer generation of scanners (87%, with a 95% CI of 73%–100%, vs. 76%, with a 95% CI of 63%–90%).

It is interesting to consider the mechanistic basis that may underlie at least some of the false-positive associations. Bench et al. (*57*) reported that metabolism of certain cerebral regions correlates negatively with mood symptoms and severity of psychomotor slowing in depression; these regions included the inferior parietal and superior temporal cortex, areas also affected in AD. Effects of hypothyroidism on regional cerebral metabolism have also recently been described (*58,59*), involving relative reduction in parietal and temporal metabolism. These effects may further help explain the compromise in PET specificity associated with such conditions, particularly with older scanners lacking the resolution to distinguish characteristic patterns of regional involvement from similar but distinct regions.

With respect to the incremental value of PET beyond conventional clinical assessment, it was recently found that among patients having clinical working diagnoses presuming nonprogressive etiologies for their cognitive complaints, those whose PET patterns nevertheless indicated progressive dementia were more than 18 times more likely to experience progressive decline than were those with nonprogressive PET patterns (*54*). Neurologists who diagnosed progressive dementia in their patients were correct 84% of the time. Adding a positive diagnosis from a PET scan boosted the accuracy of that prediction to 94%, and negative PET findings made it 12 times more likely that the patient would remain cognitively stable.

COMPARISONS BETWEEN SPECT AND PET

SPECT has historically been the most widely available modality for functional imaging of the brain and thus became the one most commonly used in the clinical evaluation of dementia (*60*). Most of the clinical and research SPECT

TABLE 3
^{18}F-FDG PET in the Evaluation of Nondemented Subjects (Cognitively Unimpaired or Mildly Impaired)

Gold standard	Subjects	Major findings	Comments	Reference
C	11 NI 15 MCI 12 AD	Anterior parahippocampal gyrus best distinguished MCI patients from healthy controls. Middle/inferior temporal gyri best distinguished MCI patients from AD patients.	The ability of ^{18}F-FDG PET and MRI volume measures to differentiate between patients with clinical diagnoses of MCI, AD, and no cognitive impairment was tested.	(*77*)
C	24 NI 50 AAMI 10 CIND 9 D	Group analysis showed that presence of posterior cingulate hypometabolism increased risk of dementia by more than 2-fold for each 1 SD decline in metabolism.	This study evaluated a population-based cohort of Mexican Americans with varying degrees of cognitive impairment.	(*78*)
L	48 NI	Metabolism of entorhinal cortex in progressive group was decreased by 18%, compared with nonprogressive group. Sens. for progressive = 83%; Spec. for nonprogressive = 85%.	Patients had MMSE scores > 28 and scored a 1 or 2 on Global Dementia Scale.	(*79*)
L	17 MCI	Progressive vs. nonprogressive classification accuracy for right temporoparietal cortex was 100%. Classification accuracy for posterior cingulate cortex was 94%.	Patients had memory complaints but lacked any neurologic, medical, or psychiatric disorders. Memory performances were >1.5 SD below age-matched normal mean in Rey Figure delayed recall or 1 subscore of Grober–Buschke test.	(*80*)
L	22 MCI	Group analysis revealed significantly lower metabolism of bilateral posterior cingulate cortex and right precuneus in progressive group than in nonprogressive group.	Patients had subjective complaints of memory impairment, a performance of at least 1.5 SDs below the age normal on the CERAD delayed verbal recall, a CDR of 0.5, and preserved basic activities of daily living.	(*81*)
L	20 MCI	The most effective predictor for progressive cognitive decline was the combination of cerebral metabolic rate assessment and psychometric measures. rCMRGlu accuracy = 75%; neuropsychiatric accuracy = 75%; rCMRGlu + neuropsychiatric accuracy = 95%.	Patients were initially investigated for suspected dementia. All demonstrated symptoms for stage 3 of GDS but lacked symptoms to fulfill DSM-IV criteria.	(*82*)
L	58 Progressive 44 Nonprogressive	^{18}F-FDG PET data provided more accurate prognosis of cognitive decline. Clinical diagnosis: Sens. for progressive disease = 77%; Spec. for nonprogressive disease = 76%. ^{18}F-FDG PET: Sens. for progressive disease = 95%; Spec. for nonprogressive disease = 79%.	The mean ± SD for MMSE scores was 24.0 ± 6.4.	(*54*)

C = clinical evaluation; L = longitudinal follow-up; NI = cognitively normal; MCI = mild cognitive impairment; AAMI = age-associated memory impairment; CIND = cognitively impaired nondemented; D = dementia; rCMRGlu = regional cerebral metabolic rate of glucose; Sens = sensitivity with respect to correctly identifying presence of Alzheimer's or other progressive disease; Spec = specificity with respect to correctly specifying that progressive disease is absent; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CDR = Clinical Dementia Rating; GDS = Global Dementia Scale; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.*

studies for this application have been perfusion based. Although the specific radiopharmaceuticals and instrumentation used in SPECT differ from those used in PET, the principles of interpretation, as well as the neurobiologic processes underlying the use of the 2 modalities, are similar. The primary practical differences in application are, first, the typically poorer spatial resolution of SPECT images relative to that of PET images and, second, the occasional loss of the generally parallel relationship between cortical metabolism (usually measured with PET) and perfusion in the presence of certain cerebrovascular disorders. In general, the magnitude of hypometabolism seen with ^{18}F-FDG

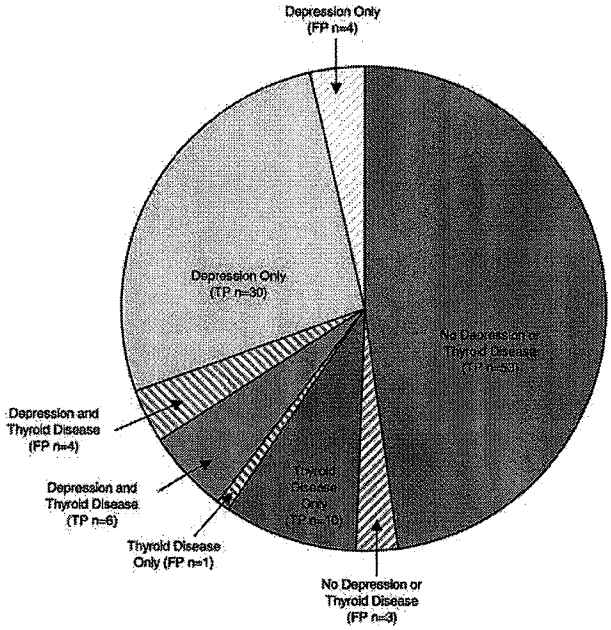

FIGURE 8. Distribution of 111 scan-positive cases among 170 patients undergoing PET for cognitive evaluation. TP = true positives; FP = false positives.

PET is generally greater than the amplitude of hypoperfusion seen with SPECT (*61–63*).

As might be expected, studies of AD using SPECT have yielded results similar to those using PET but typically with less sensitivity and decreased overall accuracy. Optima (Oxford Project to Investigate Memory in Aging) was a relatively large study that compared functional brain imaging data (SPECT regional cerebral blood flow) against clinical diagnosis and, in the dementia subset, autopsy diagnosis. The study included 70 dementia patients (all of whom had autopsy data) and 85 nondemented subjects (only 14 of whom had autopsy data) (*64*). Clinical diagnosis of probable AD was reported to have a 59% sensitivity and a 95% specificity for patients with an autopsy-confirmed diagnosis, and these values increased to 93% and 88%, respectively, for the combination of possible or probable AD. SPECT alone was reported to have a 63% sensitivity and a 93% specificity. The combination of SPECT findings positive for temporoparietal hypoperfusion and a clinical diagnosis of possible or probable AD was associated with a 96% sensitivity and an 84% specificity. These data were acquired with a single-head γ-camera with approximately 12-mm spatial resolution and may represent the lower end of sensitivity measurements possible with state-of-the-art equipment. These authors also used logistic regression analysis to compute the degree to which SPECT enhanced clinical diagnosis. Clinical diagnosis of probable AD alone was associated with an 84% chance of AD on death; positive SPECT findings raised the likelihood to 92%, whereas negative SPECT findings reduced the likelihood to 70%. For the diagnosis of possible AD, clinical measures alone had a 67% likelihood, which increased to 84% with positive SPECT findings and decreased to 52% with negative findings. Therefore, a clinical diagnosis of possible AD combined with a SPECT scan positive for temporoparietal hypoperfusion was as likely to be associated with AD at death as was clinical diagnosis of probable AD alone.

Unfortunately, in this study the nondemented controls were not control subjects in a clinically meaningful sense of the term: the mean Mini-Mental State Examination (MMSE) score for the patients was 13 ± 8 points (of a total

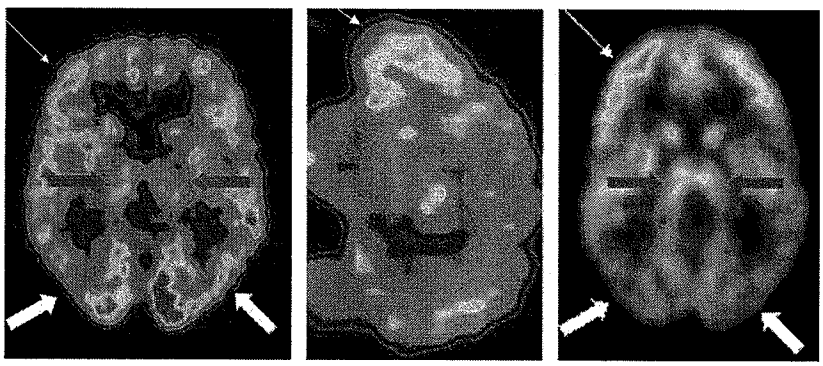

FIGURE 9. ^{18}F-FDG PET scans of a patient with false-positive findings and an AD patient. Shown are representative axial (left) and sagittal (middle) slices through an ^{18}F-FDG PET brain scan of a 79-y-old woman undergoing clinical evaluation for cognitive impairment. The patient had a history of depression and thyroid disease and was receiving thyroid hormone replacement therapy at time of PET. The interpreting nuclear medicine physician had read the scan as consistent with early neurodegenerative changes in an Alzheimer-like pattern, because of the apparent relative decreased activity in the parietal cortex (bold white arrows), relative to the adjacent frontal and temporal cortex (thin white arrows). Longitudinal clinical follow-up for 2.5 y after the scan showed no progressive dementia, so the scan interpretation was classified as false positive. If this scan were being read now, the false-positive interpretation might have been avoided by comparing the thalamic activity (red arrows) to the parietal activity, with which it is approximately isometabolic, and to the (higher) frontal activity—in contrast to the pattern found in AD (right), in which parietal cortex becomes hypometabolic relative to the (preserved and normally isometabolic) thalamus.

of 30 possible points), whereas the mean MMSE of the "controls" was 29 ± 2. Subjects with cognitive performances so discrepant from those of the patient group would easily be distinguishable in clinical practice, even without formal dementia evaluation or functional imaging. Including them in the analysis thus lent a considerable but artificial boost to estimates of specificity and overall accuracy relative to how the test would perform in an actual clinical setting. In addition, the moderately severe degree of mean cognitive impairment of the AD cases may have increased the sensitivity estimates. Moreover, because 71 of the 85 control subjects were not autopsied, for the majority of non-AD cases clinical diagnosis was being compared with a gold standard of clinical diagnosis—a tautology that provided another artificial boost to specificity and overall accuracy. These problems are largely avoided, however, if the analysis is confined to the (autopsy-proven) dementia cases. Among those 70 patients, at a clinical diagnostic sensitivity for AD of 93% (43/46) (achieved by pooling both probable-AD and possible-AD patients), clinical specificity was 46% (11/24). Also among those cases, the sensitivity of SPECT for AD was 63% (29/46) and specificity was 75% (18/24), for an overall accuracy of 67% (47/70).

The higher diagnostic accuracy achievable with PET than with SPECT has been further borne out through side-by-side comparisons of the 2 modalities. These comparisons include studies using high-resolution SPECT scanners (*34,66*) on AD patients with mild symptoms (*65*), with data suggesting an increased accuracy of approximately 15%–20% for PET relative to SPECT. When considering the results of these types of comparative studies, it is worth noting that the utility of both PET and SPECT can be influenced by factors such as the spatial resolution and count sensitivity of detector configurations and by other instrumentation parameters, acquisition and processing techniques, methods and quality of image display, the interpretive criteria used, and the experience of the interpreters with each modality. In a recent study minimizing the impact of at least one (the last) of these factors, Herholz et al. (*67*) compared the ability of PET and SPECT to identify abnormalities in AD subjects, using statistical parametric mapping to assess the number of abnormal voxels relative to a large matched control group for each technique. The [illegible] correspondence was in the temporoparietal and posterior cingulate cortices (r = 0.90). However, tracer uptake reductions were significantly more pronounced with PET than with SPECT. Herholz et al. also measured the correlation between dementia severity and the number of abnormal voxels. That correlation was somewhat better for PET than for SPECT. The higher sensitivity of PET may be especially relevant for identifying disease in its earliest stages to target patients for therapy while neurodegeneration is minimal.

CLINICAL ROLE OF NEURONUCLEAR IMAGING

As previously mentioned, in the recent report of the Quality Standards Subcommittee of the AAN (*28*), 3 studies (*7,29,30*) were identified in which the diagnostic value of conventional clinical assessment could be measured well (Table 4). If one accepts the recently affirmed AAN recommendation (*28*) that the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)–Alzheimers Disease and Related Disorders Association (ADRDA) criteria for "probable AD [rather than the more inclusive 'possible AD'] should be routinely used," then clinical sensitivity appears to range in the interval of 66% ± 17%, whereas PET sensitivity ranges in the interval of 91.5% ± 3.5%, relative to the standard criterion of neuropathologically confirmed diagnosis (Table 5). The sensitivity of clinical evaluation can be increased to 90.5% ± 5.5% (comparable to that using PET), but at the expense of specificity (55.5% ± 5.5% in the class I studies), by ex-

TABLE 4
Sensitivity and Specificity of Conventional Clinical Evaluation, Compared with Neuropathologic Confirmation of Presence or Absence of AD

Subjects	Major findings	Comments	Reference
94 AD 40 Non-AD	Sens = 83%, Spec = 55%, prob AD Sens = 85%, Spec = 50%, prob AD + poss AD	Patients with new onset (<1 y) of symptoms of dementia when first seen, diagnoses based on av. follow-up of 3.0 y	(*7*)
80 AD 24 Non-AD	Sens = 49%, Spec = 100%, prob AD Sens = 96%, Spec = 61%, prob AD + poss AD	40% of patients lived in long-term care facilities. Diagnoses based on annual assessments, from time of referral until death. Followed an av. of 2.3 y, at which time the majority of patients were moderately or severely demented.	(*29*)
68 AD 12 Non-AD	Sens = 50%, Spec = 70%, prob AD	Diagnoses based on annual assessments, from time of referral until death.	(*30*)

AD = cognitively impaired secondary to AD; Non-AD = no AD identified on neuropathologic examination; Sens = sensitivity with respect to correctly identifying presence of AD; Spec = specificity with respect to correctly specifying that AD is absent; Prob AD = diagnosis of probable AD, by NINCDS-ADRDA criteria; Poss AD = diagnosis of possible AD, by NINCDS-ADRDA criteria; av. = average.

TABLE 5
Ranges of Sensitivity and Specificity of Clinical Diagnoses Made With and Without the Use of PET, Compared with Neuropathologic Confirmation of Presence or Absence of AD

Sensitivity	Specificity	Basis of AD diagnosis
66% ± 17%	77% ± 23%	Clinical evaluation, probable AD
90.5% ± 5.5%	55.5% ± 5.5%	Clinical evaluation, probable + possible AD
91.5% ± 3.5%	70% ± 3%	^{18}F-FDG PET, AD pattern

In addition to those discussed in the text, another (class II) study reviewed by the AAN (*83*), which did not uniformly require diagnosis by NINCDS-ADRDA criteria, examined a large series of autopsy-confirmed cases pooled from multiple centers, with and without information about apolipoprotein E genotype. This study required no stratification between possible-AD and probable-AD patients, providing data based only on having pooled together all patients thought most likely to have AD. Nor did the study provide any baseline demographic data, so it was not possible to ascertain the level of severity of dementia in the subjects studied. Similarly to the studies summarized in Table 5, this study found that in achieving a sensitivity comparable to that obtainable with PET (93%), specificity was lower (55%) than that achieved with PET. When presence of apolipoprotein $\varepsilon 4$ allele was used as the diagnostic criterion for AD, sensitivity and specificity were 65% and 68%, respectively. When the data from clinical and genotype evaluations were sequentially combined, sensitivity fell to an unacceptably low 61%, at a specificity of 84% and overall accuracy was 65%.

panding the diagnosis of AD to include patients who meet NINCDS-ADRDA criteria for "possible AD" and including moderately and severely advanced dementia cases in the analysis. In contrast, at that level of sensitivity, the specificity using PET is 70% ± 3%. The AAN Quality Standards Subcommittee also reviewed 9 studies that addressed the clinical diagnostic accuracy of AD but were classified as having lower "quality of evidence." Across all these studies, they found an average clinical specificity of 70% (as occurs with PET), whereas average sensitivity in that analysis was 81% (compared with the 91% ± 3% reported for PET). In the 2 largest class II studies that uniformly used NINCDS–ADRDA diagnostic criteria (*31,68*), at a sensitivity of 90% ± 1% (achieved by including "possible AD" patients and moderately advanced dementia cases), specificity fell to 29% ± 8%.

Thus, when the most reliable published measures of sensitivity and specificity in the diagnosis of AD (*7,28–30*) are applied to a comparison of diagnoses made with PET and diagnoses made without PET, one finds that both false-negative and false-positive diagnoses may substantially be decreased by adding PET to the diagnostic work-up of appropriately selected patients (*69*).

The available evidence supports considering PET for at least 2 groups of patients: patients with mild or moderate cognitive impairment who meet the standard criteria for dementia, the cause of which has not been identified by an appropriate and thorough medical work-up (group A; Table 6), or patients with mild or moderate cognitive impairment who exhibit progressive cognitive dysfunction that has not reversed after a thorough medical work-up including history taking, physical examination, neurologic examination, and indicated standard laboratory and structural neuroimaging tests along with appropriate treatment for any positive findings (group B; Table 7).

For each of these 2 patient groups, the respective tables indicate the impact of the diagnostic accuracy achievable when PET is included as part of the medical work-up, relative to when it is not included. The high sensitivity of PET may be especially useful in identifying progressive dementia among those for whom suspicion of a progressive dementing illness is otherwise low; appropriate therapy to delay decline can then be started earlier. The best time to

TABLE 6
Impact of Diagnostic Accuracy Achievable with Use of PET, for Patients in Group A (Mild or Moderate Dementia of Unclear Etiology)

Diagnostic approach	True negatives	False negatives	True positives	False positives
Without including PET in medical work-up	25.4%	8.3%	43.3%	23.0%
Including PET in medical work-up	36.5%	3.1%	48.5%	11.9%
False diagnoses prevented through inclusion of PET, per 100 patients tested	5.2		11.1	
Proportion of misdiagnoses prevented through inclusion of PET	62.7%		48.3%	

Based on 51.6% prevalence of AD in tested population, best estimates of sensitivity and specificity for AD documented by histopathologic examination, as assessed by the American Academy of Neurology, were 84% and 52.5%, respectively, without PET and 94% and 73%, respectively, with PET. Full details of this analysis can be found in Silverman et al. (*69*).

TABLE 7
Impact of Diagnostic Accuracy Achievable with Use of PET, for Patients in Group B (Progressive Cognitive Decline That All Attempted Treatments Have Failed to Reverse)

Diagnostic approach	True negatives	False negatives	True positives	False positives
Without including PET in medical work-up	32.4%	25.8%	25.8%	16.0%
Including PET in medical work-up	34.4%	2.6%	49.0%	14.0%
False diagnoses prevented through inclusion of PET, per 100 patients tested	23.2		2.0	
Proportion of misdiagnoses prevented through inclusion of PET	89.9%		12.5%	

Based on 51.6% prevalence of AD in tested population, best estimates of sensitivity and specificity for incipient AD documented by neuropathologic examination were 50% and 67%, respectively, without PET, per data compiled by Morris et al. (*84*, Table 2 [p. 403]), and 95% and 71%, respectively, with PET, per Silverman et al. (*50*).

perform functional neuroimaging is thus early in the clinical work-up, as soon as the appropriateness of including neuroimaging in the evaluation of cerebrocortical dysfunction has been determined (*69*).

THE FUTURE

Although AD has no cure, symptomatic treatment has proven effective, especially in earlier stages of the disease, and therapies targeting etiology-based treatments are in development. Possible etiology-targeting cures in the future would be most effective during the milder phases of the disease, making an early clinical diagnosis of AD, when treatment can alter the progression of symptoms, especially important. Progress in understanding of the etiology of AD will lead to new and more effective methods of treatment.

Studies examining combination treatments are limited. Combining current treatments such as anticholinesterase inhibitors with other interventions may further improve the management of AD. For example, the proven benefits of the psychosocial intervention studied by Mittelman et al. (*70*) may be made more dramatic by combining it with anticholinesterase therapy, and studies of the combination of cholinesterase inhibitors with other agents such as memantine or vitamin E are under way. As more studies examine the combined effects of currently available treatments, a better understanding of multimodal treatment plans will emerge.

Current studies targeting earlier processes in the pathophysiologic changes of AD show potential for new treatment approaches. Rinne et al. (*71*) recently determined that acetylcholinesterase activity in the hippocampus differs significantly between control patients, patients with mild cognitive impairment, and patients with early AD. The ability to detect these differences may allow patients requiring therapeutic intervention to be identified early, before the onset of clinical symptoms. Other studies have focused on the amyloid precursor protein-cleaving enzyme responsible for β-site cleavage of amyloid precursor peptide, leading to formation of the amyloid-β-peptide implicated in the pathogenesis of AD (*72*). Inhibitors of this enzyme may potentially be applied for future therapeutic interventions for AD.

As our understanding of the biology of AD increases, we will be able to target future treatment options toward patients in those disease stages for which treatment is most appropriate and beneficial. Currently, the categorization of patients with memory deficits such as mild cognitive impairment and age-associated memory impairment is not universal. Although categorization is not uniform between different groups, the opportunity is arising to sort out and create categories that are more meaningful with regard to the underlying biology of the disease process, as made possible with diagnostic approaches such as ^{18}F-FDG PET.

The biologic changes that occur with AD take place decades before the onset of clinical symptoms. Use of more powerful diagnostic approaches allows earlier detection of initial changes in a target population, before AD is diagnosed. Currently, tools for identifying the early changes of AD are outpacing available therapeutic options. With advances in potential disease-modifying treatments, the benefits of early detection will be even greater by allowing therapy to begin as early as possible.

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Detection of τ Proteins in Normal and Alzheimer's Disease Cerebrospinal Fluid with a Sensitive Sandwich Enzyme-Linked Immunosorbent Assay

*‡Marc Vandermeeren, *‡Marc Mercken, ‡Eugeen Vanmechelen, *‡Jan Six, ‡André Van de Voorde, †Jean-Jacques Martin, and *Patrick Cras

*Laboratories of *Neurobiology and †Neuropathology, Born-Bunge Foundation, University of Antwerp, Wilrijk, and ‡Innogenetics, Ghent, Belgium*

Abstract: Alzheimer's disease is a progressive degenerative dementia characterized by the abundant presence of neurofibrillary tangles in neurons. This study was designed to test whether the microtubule-associated protein τ, a major component of neurofibrillary tangles, could be detected in CSF. Additionally, we investigated whether CSF τ levels were abnormal in Alzheimer's disease as compared with a large group of control patients. We developed a sensitive sandwich enzyme-linked immunosorbent assay using AT120, a monoclonal antibody directed to human τ, as a capturing antibody. With this technique, the detection limit for τ was less than 5 pg/ml of CSF. Using AT8, which recognizes abnormally phosphorylated serines 199–202 in τ, the detection limit was below 20 pg/ml of CSF. However, with AT8, we found no immunoreactivity in CSF, suggesting that only a small fraction of CSF τ contains the abnormally phosphorylated AT8 epitope. Our results indicate that CSF τ levels are significantly increased in Alzheimer's disease. Also, CSF τ levels in a large group of patients with a diversity of neurological diseases showed overlap with CSF τ levels in Alzheimer's disease. **Key Words:** Abnormally phosphorylated τ—Dementia—Diagnostic marker—Microtubule-associated proteins—Monoclonal antibody—Paired helical filaments—τ protein.
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Alzheimer's disease (AD) is the most common form of dementia in adults and is diagnosed clinically, primarily by exclusion of other forms of dementia. Neuropathologically, the illness is characterized by the presence of senile plaques and neurofibrillary tangles (NFT). NFT are neuronal inclusions that consist of paired helical filaments (PHF), of which the main protein component is a modified form of the microtubule-associated protein τ (Brion et al., 1985). Under normal circumstances, τ promotes microtubule assembly and stability (Weingarten et al., 1975). τ present in PHF, called PHF-τ, is abnormally phosphorylated (Lee et al., 1991). This abnormal phosphorylation causes a conformational change in τ, probably resulting in self-association and formation of PHF. PHF-τ is phosphorylated at several sites. We recently developed a monoclonal antibody (mAb), called AT8, that specifically recognizes phosphoserines 199 and/or 202, found only in PHF-τ (Biernat et al., 1992; Goedert et al., 1992).

Previously, we reported the development of a τ-specific sandwich enzyme-linked immunosorbent assay (ELISA) with a lower detection limit of 1 ng/ml (Mercken et al., 1992*b*). By using this ELISA, based on the selective reaction of AT8 with PHF-τ, we were able to distinguish Alzheimer brain homogenates from control brain homogenates (Mercken et al., 1992*b*). However, the assay using AT8 was not able to detect τ in CSF. Therefore, we developed a more sensitive τ-specific catalyzed reporter deposition (CARD) ELISA with a higher sensitivity, using a new mAb directed to human τ called AT120. CARD involves an analyte-dependent reporter enzyme (horseradish peroxidase), which catalyzes the deposition of additional reporter molecules (biotin-labeled phenols) on the surface in a solid-phase immunoassay. This extremely sensitive assay allows the detection of τ protein in nonconcentrated CSF. We used the

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Address correspondence and reprint requests to Dr. P. Cras at Laboratory of Neurobiology, Born-Bunge Foundation, University of Antwerp, UIA Bldg. T, Universiteitsplein 1, B-2610 Wilrijk, Belgium.

The present address of Dr. M. Mercken is Laboratory for Molecular Neuroscience and Aging Research, Mailman Research Center, McLean Hospital, Harvard Medical School, Belmont, MA 02178, U.S.A.

Abbreviations used: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; CARD, catalyzed reporter deposition; ELISA, enzyme-linked immunosorbent assay; mAb, monoclonal antibody; NFT, neurofibrillary tangles; OND, other neurological diseases; PBS, phosphate-buffered saline; PHF, paired helical filaments.

CARD ELISA assay to investigate whether the microtubule-associated protein τ could be detected in the CSF of AD and control patients.

MATERIALS AND METHODS

CSF samples

CSF samples from 190 patients at the Department of Neurology of the University Hospital of Antwerp were obtained by lumbar puncture performed for routine diagnostic purposes. In addition, CSF samples from seven patients with AD, three patients suffering from amyotrophic lateral sclerosis (ALS), and seven patients suffering from other neurological diseases (OND) were obtained from Athena Neurosciences Inc. (South San Francisco, CA, U.S.A.). All CSF samples were frozen and kept at −75°C in small aliquots until use.

Basically, patients were divided into three different groups: 27 patients diagnosed with probable AD according to McKhann et al. (1984), 41–88 years of age (mean 67); 51 mentally intact control patients, who underwent lumbar puncture for radiculography, 5–80 years of age (mean 44); and 129 patients suffering from OND, 1 month to 85 years of age (mean 48). The OND group included inflammatory (n = 55), vascular (n = 19), and other (n = 31) diseases. The OND group further contained a group of patients with neurodegenerative diseases (n = 24), such as adenoleukodystrophy (n = 1), frontal lobe-type dementia (n = 1), hereditary cerebellar atrophy (n = 2), Pick's disease (n = 2), progressive supranuclear palsy (n = 1), Parkinson's disease (n = 2), olivopontocerebellar atrophy (n = 1), ALS (n = 7), polyneuropathy (n = 1), external ophthalmoplegia (n = 1), bulbar palsy (n = 1), and miscellaneous others. For each patient, age, sex, and diagnosis were noted. Statistical differences in τ measures between patient groups were verified using an unpaired Student's *t* test.

Production and characterization of AT120

Purification of PHF-τ and production of mAb AT120, which is produced by a subclone of AT12, were performed as described previously (Mercken et al., 1992*b*). For characterization, AT120 was tested by western blot on both normal τ and PHF-τ. Reactivity of AT120 with normal τ and PHF-τ was tested in a sandwich ELISA with affinity-purified polyclonal rabbit anti-human τ antiserum as coating antibody, as described by Mercken et al. (1992*b*).

Normal τ and PHF-τ protein standards

The preparations of affinity-purified normal τ and PHF-τ were described elsewhere (Mercken et al., 1992*a,b*). Purity of normal τ and PHF-τ standards was determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Dephosphorylation was performed as described earlier (Mercken et al., 1992*b*). The preparations used contained only τ proteins of molecular mass 43–67 kDa. The samples were also analyzed on a 420 A/H amino acid analyzer (Applied Biosystems B.V., Maarssen, The Netherlands) according to the manufacturer's instructions. Both normal τ and PHF-τ showed the expected amino acid compositions. The exact protein concentrations of both affinity-purified normal τ and PHF-τ were determined using an internal standard peptide. The concentrations found were 7.7 μg/ml and 380 ng/ml for normal τ and PHF-τ, respectively.

AT120 ELISA for τ detection in CSF

AT120, purified from serum-free conditioned medium on a protein G column, was coated overnight at 4°C on high-binding microtiter plates (Nunc, GIBCO, Paisley, U.K.) in coating buffer at 3 μg/ml (10 m*M* Tris, 10 m*M* NaCl, 10 m*M* NaN_3, pH 8.5). After overcoating for 30 min with 150 μl of 10% saturated casein in phosphate-buffered saline (PBS) to reduce nonspecific binding, the plates were incubated with 100 μl of an appropriately diluted τ standard, or with unconcentrated CSF samples, supplemented with 5% Tween 20, for 60 min at 37°C. The plates were washed five times with PBS/0.05% Tween 20 (vol/vol), and 100 μl of affinity-purified rabbit anti-normal τ was added at 2 μg/ml and incubated for 1 h at 37°C. After washing, horseradish peroxidase-conjugated donkey anti-rabbit serum (Amersham, Buckinghamshire, U.K.) was added for 30 min at 37°C. After another washing, the CARD enhancement procedure was done by adding a 100-μl stock dilution of 0.3 *M* biotin-tyramine (Sigma, Poole, Dorset, U.K.) prepared in dimethyl sulfoxide, according to Bobrow et al. (1989), diluted 1:100 in conjugate diluent (50 m*M* Tris-HCl, 0.001% H_2O_2, pH 8), and incubated for 15 min at room temperature. Following washing with PBS/Tween 20, 100 μl of streptavidin-biotinylated horseradish peroxidase complex (Amersham) diluted 1:1,000 was added for 15 min at room temperature. All reagents, except the biotin-tyramine conjugate, were diluted in PBS with 10% casein. After a final washing, 100 μl of 0.42 m*M* 3,5,3′,5′-tetramethylbenzidine, 0.003% (vol/vol) H_2O_2 in 100 m*M* citric acid, 100 m*M* Na_2HPO_4, pH 4.3, were added as peroxidase substrate. The reaction was stopped with 50 μl of a 2 *M* H_2SO_4 solution. Absorbance was read in a Titertek Multiscan (Flow Laboratories, Eflab Oy, Finland) at 450 nm. Optical density values obtained from the CSF samples were compared with standard curves generated from known quantities of affinity-purified normal human τ.

We found that absorbance values of CSF samples were reproducible. However, frequent thawing and freezing of samples decreased τ concentrations found in ELISA.

AT8 ELISA for PHF-τ detection in CSF

AT8 ELISA for PHF-τ detection in CSF of AD patients and control patients was essentially the same as the AT120 assay, except that AT8 instead of AT120 was applied as coating mAb.

RESULTS

AT120 characterization

On immunoblots, the antibody reacted equally well with both normal τ and PHF-τ, as shown in Fig. 1. In contrast, the Tau-1 antibody (Binder et al., 1985) reacted solely with normal τ and the AT8 antibody (Mercken et al., 1992*b*) only with PHF-τ.

AT120, AT8, and Tau-1 mAbs were tested for phosphatase sensitivity of their epitopes by ELISA and by western blot on PHF-τ antigen. The reactivity of the AT120 antibody with PHF-τ was not sensitive to phosphatase treatment either in ELISA (Fig. 2) or on western blots (data not shown). The reactivity of AT8 was completely abolished after alkaline phosphatase treatment of the PHF-τ antigen in ELISA. Dephosphorylation of PHF-τ enhanced Tau-1 immu-

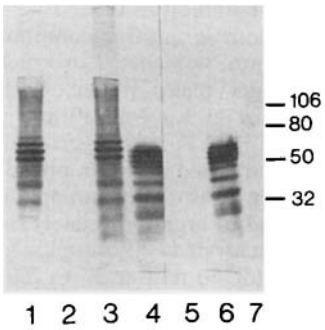

FIG. 1. Western blots of AT8, AT120, and Tau-1 antibodies with equal amounts of PHF-τ and normal τ loaded on a 10% sodium dodecyl sulfate gel. Lanes 1, 3, and 5: PHF-τ; lanes 2, 4, and 6: affinity-purified normal human τ. Lanes 1 and 2 were incubated with AT8, lanes 3 and 4 with AT120, and lanes 5 and 6 with Tau-1. Lane 7 contains prestained molecular mass markers in kDa.

noreactivity, as described before (Papasozomenos and Binder, 1987).

Both τ standards, i.e., normal τ and PHF-τ, spiked in a CSF pool, were run in the amplified AT120 sandwich ELISA and the amplified AT8 sandwich ELISA. We found no significant differences in detection limits between normal τ and PHF-τ detection for AT120 (Fig. 3A). For AT8, no reaction was shown with normal τ (Fig. 3B), as reported earlier (Mercken et al., 1992*b*).

AT120 τ detection in unconcentrated CSF samples

A number of CSF samples were tested in the AT120 CARD assay for τ detection. CSF samples of patients were first divided into three different groups, i.e., AD patients, control patients, and patients suffering from OND (Table 1), and then subdivided according to age group (older or younger than 60 years). Table 1 and Fig. 4 clearly show that CSF τ levels were increased significantly in AD patients. If a cutoff value of 1.11 pg/ml is used (mean of control CSF τ levels + 2 standard deviations), 81% (22/27) of all patients clinically

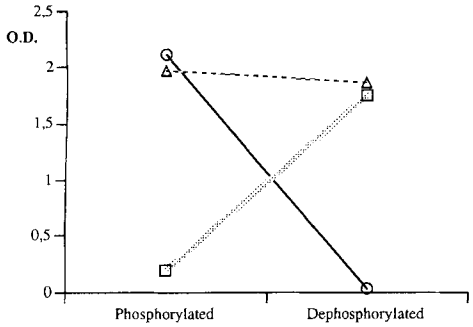

FIG. 2. Reactivity of AT8 (○), AT120 (△), and Tau-1 (□) with untreated (phosphorylated) and dephosphorylated PHF-τ in ELISA. Samples were tested in triplicate and the data presented as optical density (OD) units.

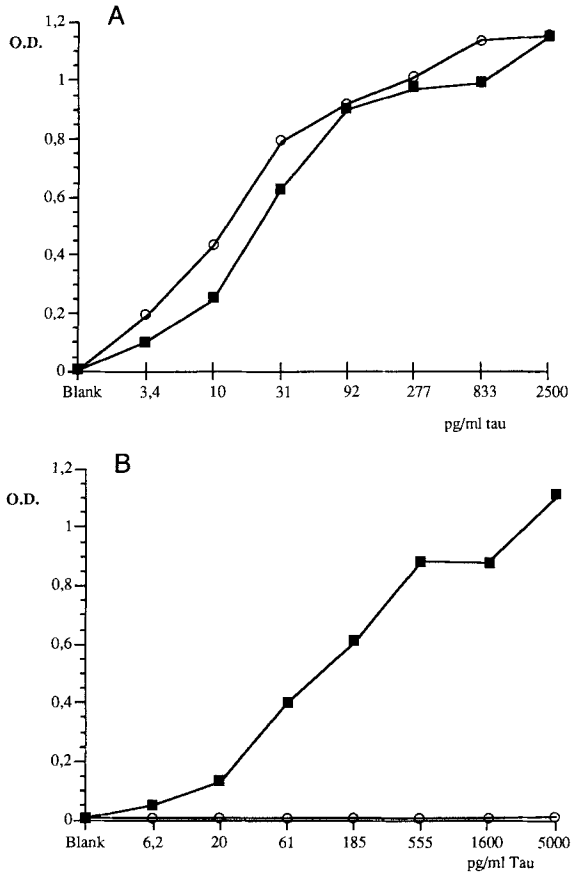

FIG. 3. Titration of normal τ (○) and PHF-τ (■), spiked in a CSF pool in the amplified (CARD) sandwich ELISA with AT120 (**A**) and AT8 (**B**). All dilutions were tested in duplicate and the data presented as optical density (OD) units.

diagnosed as AD showed higher CSF τ levels, compared with 36% (47/129) for the group of patients suffering from OND and 4% (2/51) of the control patients. A significant difference was found between the Alzheimer group in toto and the OND group ($p < 0.001$), as seen in Fig. 4. This difference was also found between the OND and the control groups, and between AD and control groups ($p < 0.001$).

When patient groups were examined in more detail, it was found that two control patients showed slightly positive τ values (Fig. 4). However, as one control patient was 77 years old, we cannot exclude the possibility that he suffered from preclinical AD. Another striking observation is that in patients older than 60, τ in CSF was clearly higher in AD than in OND (Table 1), whereas for younger patients, the difference was much less pronounced and did not reach significance ($p > 0.78$). When the group of OND patients was analyzed in greater detail (Table 1 and Fig. 5), we found no diagnostic groups that consistently showed increased CSF τ. Several patients suffering from neurodegenerative diseases showed a strong increase of CSF τ (hereditary cerebellar atrophy, olivo-

TABLE 1. *CSF levels of τ in AD and OND*

Group (n)	Age (yr)	τ in CSF (pg/ml)		
		All ages	<60 yr	>60 yr
AD (27)	67 ± 13	10.9 ± 4.9	4.7 ± 4.9	14.3 ± 8.5
Controls (51)	44 ± 15	0.1 ± 0.5	0.05 ± 0.3	0.3 ± 0.9
OND (129)	48 ± 18	3.9 ± 7.4	4.5 ± 8.3	2.7 ± 5.1
Degenerative (24)[a]			8.2 ± 8.7	3.6 ± 7.3
Inflammatory (55)[a]			3.8 ± 7	0.7 ± 1.8
Vascular (19)[a]			4.8 ± 9.4	5.3 ± 3.8
Others (31)[a]			4.6 ± 10.5	0.5 ± 1.4

All data are given as means ± SD.
[a] Subpopulations of OND group.

pontocerebellar atrophy, ALS, Parkinson's disease). However, this increase was not consistent, as five of seven ALS patients had CSF τ values within the range of the control group. A similar heterogeneity was observed for inflammatory nervous system diseases: four of 20 multiple sclerosis patients, five of 11 Guillain–Barré patients, two of three herpes simplex encephalitis patients, and one of three Lyme disease patients had increased CSF τ. Patients suffering from cerebrovascular diseases and stroke patients showing multiple old and recent ischemic infarcts had the highest CSF τ values in the OND group. More importantly, three patients suffering from multiple infarct dementia and a patient suffering from vascular dementia and pseudobulbar syndrome had increased CSF τ. Single diagnostic groups were too small to determine whether there was a correlation between the severity of CNS damage and the extent of τ elevation. Two patients with hydrocephalus and an infant with sudden infant death syndrome showed extreme increases in CSF τ, the significance of which remains undetermined.

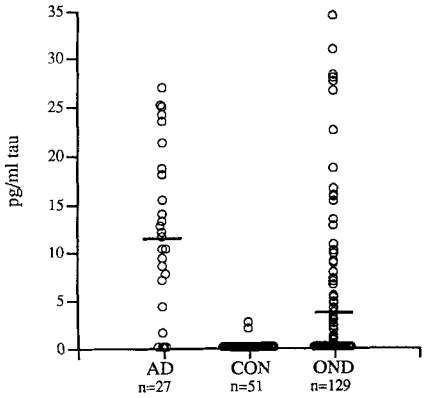

FIG. 4. CSF τ quantification in ELISA (100 μl/assay) of individual CSF samples, using the AT120 assay. The mean value of each group is indicated by horizontal bars. CSF τ concentrations were based on standard curves with affinity-purified normal human τ. Results are shown as pg of τ/ml. CON, controls.

Unconcentrated and concentrated CSF samples analyzed in the AT8 assay

CSF samples of 20 AD patients, 10 control patients, and 10 OND patients were selected for PHF-τ detection using AT8 as a capturing antibody. AD CSF samples having high τ values in the AT120 assay were selected for PHF-τ detection. However, no PHF-τ was found in these unconcentrated CSF samples, indicating that, in our assay, the sensitivity of 30 pg/ml PHF-τ was not sufficient for CSF detection of PHF-τ.

Moreover, when a pool of AD CSF samples was concentrated 12 times, resulting in a hypothetical sensitivity of less than 3 pg/ml PHF-τ, again no signal was found. Thus, if PHF-τ, as detected by the AT8 immunoassay, is present in CSF, its concentration must probably be below 3 pg/ml. Consequently, either τ proteins found in AD CSF samples with the AT120-based assay are not phosphorylated at the

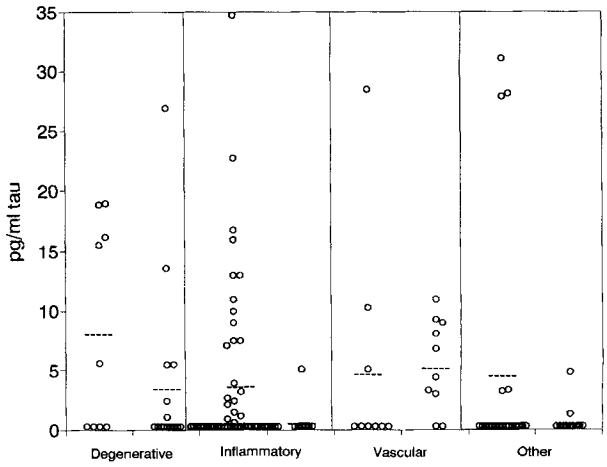

FIG. 5. CSF τ detection in ELISA (100 μl/assay), using the AT120 assay on CSF of OND patient subgroups (see text). Each group is subdivided according to age (left data points: younger than 60; right data points: older than 60). The mean value of each group is represented by a horizontal bar. CSF τ concentrations were based on standard curves with affinity-purified normal human τ. Results are shown as pg of τ/ml.

AT8 site and could be normal τ or dephosphorylated PHF-τ, or the AT8 region is not present or available for immunoreactivity with the AT8 antibody.

DISCUSSION

AD is diagnosed clinically with a variable degree of certainty by excluding other causes of dementia. This diagnosis can only be confirmed histopathologically, by observing a sufficient number of NFT and senile plaques in the neocortex (Khatchaturian, 1985). No protein specific for AD has yet been found. However, PHF and amyloid plaques contain posttranslationally modified normal brain proteins. Because CSF offers the richest potential source of altered proteins in a neurodegenerative disease, we set up a sandwich ELISA that specifically recognized the microtubule-associated protein τ, the principal component of PHF.

Besides τ, other proteins that may play an important role in the pathogenesis of AD, like α_1-antichymotrypsin, ubiquitin, and amyloid precursor protein (APP), can also be detected in CSF.

Recently, α_1-antichymotrypsin, a serine protease inhibitor and an acute phase protein found to be specifically present in senile plaques (Abraham et al., 1988), was analyzed in CSF. Studies concerning α_1-antichymotrypsin CSF levels in AD versus control groups show contradictory results (Matsubara et al., 1990; Delamarche et al., 1991; Vandermeeren, unpublished observations), so it would be premature to argue whether this protease inhibitor represents a discriminative marker for AD.

Other groups investigated the potential usefulness of ubiquitin as an antemortem diagnostic marker for AD. It was found that ubiquitin reactivity of PHF could be measured in CSF (Wang et al., 1991). The authors showed that there was a significant increase in AD ubiquitin CSF levels versus control CSF samples. However, overlaps between the two different patient groups were also reported.

At first, analysis and quantitation of APP in CSF of AD and control patients demonstrated no significant differences (Chong et al., 1990; Henriksson et al., 1991), i.e., only a small decrease in APP CSF levels was found in AD patients as compared with healthy controls. Palmert et al. (1990), using western blot analyses, demonstrated a reduction of soluble APP forms in AD CSF. In addition, their data also suggested an age-dependent reduction in β-APP CSF levels. In a recent report (Van Nostrand et al., 1992), it was shown that β-APP CSF levels were decreased significantly as compared with controls or a group of demented non-AD individuals. One limitation is that this assay does not distinguish between AD and hereditary cerebral hemorrhage with amyloidosis (Dutch type).

PHF contain modified forms of τ as a major protein component (Lee et al., 1991). Therefore, we investigated the presence of this antigen in CSF. CSF τ concentrations are extremely low, so the τ detection assay had to be very sensitive, a problem resolved by applying CARD amplification and a high-affinity mAb, called AT120. Several authors reported the development of a τ-specific assay. One group clearly showed that PHF-τ could be detected in Alzheimer brain homogenates and not in normal brain homogenates (Ghanbari and Miller, 1990; Ghanbari et al., 1990). Their ELISA was based on a combination of a highly specific polyclonal anti-PHF-τ serum and the mAb Alz-50. The latter mAb, the epitope of which has been mapped to the N-terminal region (Ksiezak et al., 1990; Goedert et al., 1991), had already been described as a powerful tool to detect PHF-τ (A68/ADAP) in some concentrated Alzheimer CSF samples with immunoblotting techniques (Wolozin and Davies, 1987). Unfortunately, these early findings have not been confirmed by other groups. Analysis of unconcentrated CSF samples by western blot with highly specific anti-normal τ and anti-PHF-τ polyclonal antibodies showed that a single 55-kDa band was immunostained, quite different from τ profiles that are observed in brain homogenates (Delacourte et al., 1989). Finally, the development of competitive ELISAs for selectively detecting normal, soluble τ and PHF-associated τ protein in brain tissue has been reported (Harrington et al., 1990, 1991). The authors did not discuss normal τ or PHF-τ CSF detection.

In summary, we developed a highly sensitive sandwich ELISA for the detection of τ in unconcentrated CSF samples. The assay detects normal τ and PHF-τ equally well, i.e., applying affinity-purified normal and pathological τ in the AT120 sandwich assay resulted in similar detection limits. The location of the AT120 epitope outside the repeat region (Vanmechelen et al., unpublished observations) indicates that cross-reactivity with other phosphorylated proteins like MAP2, MAP1, and neurofilaments, which share parts of their sequence with τ protein (Nukina et al., 1987; Lewis et al., 1988), can be excluded. In fact, AT120 showed no reactivity in ELISA when the above-mentioned cytoskeletal proteins were applied in the coating phase (data not shown).

Our results with the AT120-based assay indicate that elevated normal τ levels are found not only in AD, but also in different kinds of neurological diseases where neuronal death or damage occurs. Although some of these OND patients can be discriminated clinically from AD patients, our results show substantial overlap between AD and other forms of dementia, reducing the predictive value of elevated CSF τ. However, especially in patients older than 60, CSF τ is a useful marker for AD.

Because of the exquisite specificity of the AT8 antibody, showing no cross-reaction with normal τ, we set up a sandwich ELISA for the selective detection of PHF-τ proteins in AD CSF samples. Unfortunately, we were not able to demonstrate any PHF-τ antigens

in unconcentrated AD CSF samples, nor in a 12-fold concentrated AD CSF pool. It remains unclear why we did not detect any AT8-reactive τ in CSF. Contrary to our own negative results, it was reported that, in some Alzheimer CSF samples, a positive signal with an assay based on the PHF-1 mAb can be found (Ghanbari et al., 1991). This discrepancy may be due to a different sensitivity of both assays. Also it is possible that the AT8 epitope may be eliminated from PHF-τ that would be present in CSF, either by protease or phosphatase activity. In this respect, it may be significant that the AT8 epitope is more sensitive than PHF-1 to phosphatase treatment (unpublished observations). A selective loss of PHF-τ epitopes from CSF could also be explained by the observation that AT8 does not immunostain "ghost tangles" or extracellular NFT in tissue sections. Extracellular NFT are not composed of full-size τ (Tabaton et al., 1991). Possibly some of the N-terminal epitopes outside the repeat region, including the AT8 epitope, are digested by microglia (Cras et al., 1991).

Nevertheless, in brain extracts of AD patients, higher τ concentrations have been described, and it seems that this increase is due mainly to PHF-τ (Ghanbari et al., 1990; Harrington et al., 1991; Bramblett et al., 1992; Khatoon et al., 1992). These findings should stimulate further research on the development of a highly sensitive PHF-τ-specific assay for the study of CSF.

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Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia: a comparative study

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Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia: a comparative study

Lars-Olof Wahlund, Per Julin, Sven-Erik Johansson, Philip Scheltens

Abstract

***Objectives*—It has been shown that atrophy of medial temporal lobe structures such as the hippocampus and entorhinal cortex shown on MRI may distinguish patients with Alzheimer's disease from healthy controls. However, the diagnostic value of visual inspection and volumetry of medial temporal lobe atrophy (MTA) on MRI in a clinical setting is insufficiently known.**

***Methods*—Medial temporal lobe atrophy in 143 patients was visually rated from hard copies, using a 0–4 rating scale and a comparison was made with the volumes (cm^3) of the medial temporal lobe as estimated with volumetry, using a stereological method. All patients were recruited in an unselected way in a clinical setting in the centre for memory impairments at the Huddinge University Hospital. Patients with Alzheimer's disease (n=41), patients with other dementias (vascular dementia, frontotemporal dementia, and unspecified dementia; n=36) as well as non-demented subjects (n=66) were included. Medial temporal atrophy and volumetry were evaluated as a diagnostic tool by performing logistic regression analysis including age, sex, and mini mental state examination (MMSE) score and calculating the sensitivity and specificity and percentage correct classification.**

***Results*—Visual and volumetric analysis yielded statistically significant differences between patients with Alzheimer's disease and non-demented subjects, as well as between those with other dementias and non-demented subjects. Combining MMSE scores and visually rated MTA ratings yielded a sensitivity of 95% for Alzheimer's disease, 85% for other dementias. Non-demented subjects were identified with a specificity of 96%. Volumetry did not have an added value over the MMSE score alone.**

***Conclusions*—Visual rating of MTA is a clinically useful method for differentiating Alzheimer's disease from controls and is both quicker and more accurate than volumetry.**

(*J Neurol Neurosurg Psychiatry* 2000;**69**:630–635)

Keywords: dementia; volumetry; medial temporal lobe; magnetic resonance imaging; Alzheimer's disease

Department of Clinical Neuroscience, Occupational Therapy and Elderly Care Research, Karolinska Institute, Huddinge University Hospital
L-O Wahlund
P Julin
P Scheltens

Department of Statistics, Stockholm University, Stockholm, Sweden
S-E Johansson

Department of Neurology, Academisch Ziekenhuis Vrije Universiteit, Amsterdam, The Netherlands
P Scheltens

Correspondence to:
Professor Philip Scheltens
p.scheltens@azvu.nl

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Magnetic resonance imaging (MRI) has become a complementary diagnostic tool in the evaluation of dementia.[1] Many studies have shown that medial temporal lobe atrophy (MTA) is a sensitive marker for Alzheimer's disease.[2 3] To estimate MTA several techniques are available—namely, volumetric assessment, linear assessment, and visual qualitative rating.[4] Volumetric assessment techniques are mainly used in studies on selected groups of patients and controls. These measurement techniques rely on specifically developed software and are undertaken separately from the clinical examination procedures using postprocessing equipment.

The evaluation of MTA as a tool in the diagnostic procedure of dementia in a clinical routine setting is far from complete. A clinically accessible method for estimation of MTA must be rapid, simple, and reliable, to be used together with the clinical and neuroradiological examinations. Moreover, the method must be able to differentiate between Alzheimer's disease and other dementias as well as between Alzheimer's disease and non-demented subjects. A visual rating scale of MTA, with an acceptable within and between rater reliability, has been developed by Scheltens *et al*.[5 6] In a recent study,[7] this method was found to correlate well with stereological assessments of MTA in a large (n=194) sample of demented and non-demented subjects. Visually rated MTA was shown to have moderate sensitivity and specificity for Alzheimer's disease in small selected (five) and unselected (three) samples. Earlier volumetric work showed that volumetry could distinguish patients with Alzheimer's disease from controls with sensitivity and specificity figures over 80%,[8] but the distinction with other types of dementia yielded lower figures.[9 10]

To investigate further the diagnostic capacity of the visually rated MTA and to compare it with volumetry we used both methods in a large number of consecutive patients screened for dementia. We compared specificity, sensitivity, and percentage correct classification of both methods using the ultimate clinical diagnosis at follow up as the gold standard.

Material and methods

SUBJECTS

The patients enrolled in this study have been described in detail previously.[7] Here we present the results from a subsample of this population. The diagnostic procedure was as follows. All patients referred for dementia investigation at

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the geriatric clinic at Huddinge University Hospital from 1993 to 1995 were enrolled in the study. A validated Swedish version of the mini mental state examination (MMSE)[11] was used as the standard screening instrument. The investigation further included a complete physical, psychiatric, and neurological examination as well as comprehensive psychometric tests. Brain MRI was performed as routine to exclude other brain pathology. In addition, in each patient blood and CSF samples were collected and an EEG and SPECT scan were performed. A cohort consisting of subjects selected as control persons in a study on car driving and dementia[12] and of members of the family with an APP mutation who were not mutation carriers, were subjected to the same procedure (except for SPECT).

After this procedure all subjects were diagnosed using the guidelines in DSM-III-R[13] for assessing dementia, the NINDS-AIREN criteria for vascular dementia,[14] the Lund-Manchester criteria for frontal lobe dementia,[15] the ICD-10 criteria[16] for unspecified dementia, and the NINCDS-ADRDA[17] criteria for probable/possible Alzheimer's disease. If none of these diagnoses was applicable the subject was designated as non-demented. After the diagnostic investigation 10 patients had to be excluded because of a space occupying lesion and another nine were excluded because of poor MRI quality, yielding 143 subjects whose diagnoses were confirmed at follow up examinations 6 months after the initial investigation (table 1).

MAGNETIC RESONANCE IMAGING

All examinations were performed with a Siemens 1.5 Tesla Magnetom. A standard examination was first performed obtaining 24 T2 and proton density weighted, transaxial images through the brain. The volumetric measurements were based on a 3D magnetisation prepared rapid gradient echo sequence (3D MP-RAGE, TR=10 ms, TE=4 ms, flip angle=10°). This sequence yields 64 continuous coronal slices covering the whole brain with a good separation of grey and white matter and between brain tissue and CSF (T1 weighted). The slice thickness was 2.8 mm and the partial volume effect was small. The coronal plane was chosen to be perpendicular to the line intersecting the anterior and posterior commissures in the midsagittal plane (the AC-PC line).

VOLUMETRIC ESTIMATION

A description of the method has been published previously.[7] The volumetric measurements were performed using the method of stereology with a program, CV-Stereo, developed by Context Vision AB, Linköping, Sweden. The point counting stereological method used in this program is based on the Cavalieri theorem of systematic sampling. The computer program generated a grid which was randomly placed on the MRI slices, and the number of intersecting points over the area of interest were counted. The size of the grid depends on the the structure to be measured; as a rule of thumb the total number of test points should be around 100 to give a reasonable accuracy. The volume was estimated with the following formula: (number of measured points)×(area of a square in the grid)×(distance between slices). The requirements for this method is that the structure should be sampled at equal and perpendicular intervals, and the sampling should begin at random. The above described imaging technique meets the basic requirements for the stereological method, as the first slice intersects the brain at random.

Table 1 Demographic data on the study groups

Diagnosis	*n (M/F)*	*Age (SD)*	*MMSE (SD)*
AD	41 (16/25)*	62.6 (8.5)	18.1 (6.0)
OD	35 (21/15)	69.0 (9.2)†	21.6 (5.2)
ND	67 (38/29)	67.5 (11.5)	28.5 (1.6)

AD=Alzheimer's disease; OD=other dementias (see text); ND=non-demented subjects; MMSE=mini mental state examination.
*AD *v* OD and ND ($p<0.01$ for both, χ^2).
†OD *v* AD ($p< 0.02$, ANOVA).

The medial temporal lobe including the amygdala, hippocampus, and parahippocampal gyrus, was measured in 10 slices between the anterior commissure and posterior commissure, using a point distance of 0.5 cm in the test point grid. The intracranial volume (ICV) was defined as the whole volume inside the skull with the lower border defined by the caudal region of the cerebellum, temporal lobes, and orbitofrontal cortex. The brain stem was not included in the ICV. The ICV volume was measured in eight slices with a test point grid of 2 cm. The within rater variation between two measurements on the same image set was 3.5% The within rater variation defined as the mean difference between two measurements done by one operator on two different image sets of six subjects being examined twice in the MRI scanner with a time gap of 2 weeks, was 3.5%. As these variations were identical, the measurements seemed to be relatively independent for image quality and positioning of the patient in the scanner. The between rater variability between two raters on scans of six subjects was 4.5%. The stereological method has also been compared with a method using manual outlining plus thresholding.[18] In 28 patients investigated for suspected dementia bilateral medial temporal lobe volumes were measured with both methods. The stereological method gave systematically lower medial temporal lobe (MTL) volumes with a mean volume in the patient group of 13,3 cm^3 (SD 2.2) compared with 14.9 cm^3 (SD 2.4) with manual outlining plus thresholding. This difference (−1.6 cm^3) was statistically significant ($p< 0,001$, paired *t* test). The correlations between the two methods were high (0.84, $p<0,001$, Pearsson correlation coefficient 0.71, $p<0.001$ within class correlation (Kendall τ)). Sex differences were also detected by the two methods. Men (n=11) had a 2.9 cm^3 larger MTL than women (n=17) using manual outlining+thresholding and a 2.2 cm^3 larger MTL using stereology. Both differences were statistically significant ($p<0.01$, *t* test). These data clearly showed that despite the not surprising systematic difference between the two methods there was a good

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Table 2 Distribution of the rating of MTA in the study groups AD, OD, and ND (left/right)

Score/ diagnosis	0	1	2	3	4	Total
AD	2/2	14/13	12/13	10/8	2/3	40
OD	4/4	8/8	13/13	6/7	3/2	34
ND	23/23	29/29	4/4	0/0	0/0	56
						130

AD=Alzheimer's disease; OD=other dementias (see text); ND=non-demented subjects. χ^2 test: AD *v* ND p<0.0001 (left and right); AD *v* OD p>0.05 (left and right); OD *v* ND p<0.0001 (left and right). Thirteen scans could not be rated for technical reasons.

Table 3 Volumetry in AD, OD, and ND

	Volumetry left MTL/ICV	Volumetry right MTL/ICV
AD (n=41)	0.0037 (0.00053)	0.0038 (0.00047)
OD (n=32)	0.0038 (0.00060)	0.0038 (0.00045)
ND (n=66)	0.0041 (0.00041)	0.0042 (0.00042)

Values are means (SD). AD=Alzheimer's disease; OD=other dementias (see text); ND=non-demented subjects. MTL=medial temporal lobe (see text); ICV=intracranial volume; χ^2: AD *v* ND p<0.0001 (left and right); AD *v* OD p>0.05 (left and right); OD *v* ND p<0.0001 (left and right). Four scans could not be measured for technical reasons.

agreement in ranking the relative relation between volumes within the group. This means that the faster stereology method should be comparable with manual outlining methods for sensitivity.

VISUAL RATING

The MTA was assessed visually by one rater (PS), who was blinded to the subjects' age, diagnosis, and sex. Scores ranged from 0 (no atrophy) to 4 (severe atrophy). The rating scale is based on a visual estimation of both the volume of the medial temporal lobe, including the hippocampus proper, dentate gyrus, subiculum, and parahippocampal gyrus and the volume of the surrounding CSF spaces, in particular the temporal horn of the lateral ventricle and the choroid fissure on both sides, left and right side separately.[5] Rating was performed on T1 weighted coronal slices (hard copies) according to example images published earlier.[6] This visual method of scoring has a reasonably good between and within rater reliability.[6] For this study a modification was made to rate left and right MTA separately.

STATISTICAL METHODS

One way ANOVA and χ^2 were used for group comparisons. Tukey-Kramer HSD was used for pairwise comparisons. The discriminative power of volumetry and visual rating between the pairwise combinations of groups (Alzheimer's disease-non-demented, Alzheimer's disease-other dementias, and other dementias-non-demented) were analyzed by using three logistic regression models (main effect models). The first model included MMSE score only, the second model MMSE score and volumetry and the third MMSE score and visual rating (left and right combined). We wanted to test the discriminative power only of MMSE, volumetry, and visual rating and not of age and sex. For this reason we decided not to include them into the models and found this to be justified by the finding that including age and sex into the models resulted in only marginal changes.

The volumetry variables were continuous and the visual rating variable comprised three categories: 0 (reference), 1, and >1. The cross classification was based on the estimated logistic probabilities from the three models. The chosen cut off point was 0.5. Those with predicted probabilities above 0.5 were classified into one group and those below 0.5 into a second group. The results are shown as sensitivity, specificity, and an overall rate of correct classification (percentage), calculated from the cross classification of observed and predicted group membership. In addition, 95% confidence intervals (95% CIs) were calculated according to the method described by Carrington Reid[19] as follows: sensitivity±1.96 (sensitivity×(1−sensitivity)/n). A p value>0.05 was considered not significant.

Results

The demographic data of the study group is presented in table 1. The results of the visual ratings and volumetry are presented in tables 2 and 3. Both methods yielded statistically significant differences between the diagnostic groups and non-dementias, but not between Alzheimer's disease and other dementias. The patients with Alzheimer's disease showed significantly smaller MTA volumes than those with non-dementias measured both visually and with volumetry. Also the other dementias group had smaller MTA than the non-dementias group.

The first model including the variable for MMSE score was significant in all comparisons. In the second and third models, the variable for MMSE score and volumetry/visual rating were significant (comparing Alzheimer's disease and non-dementias, and other dementias and non-dementias). When comparing Alzheimer's disease and other dementias only the variable for MMSE score was significant. Thus the final diagnostic accuracy was calculated using the scond and third logistic regression models adjusting for MMSE score. In tables 4–6 the specificity, sensitivity, and

Table 4 Diagnostic value for volumetry and visual rating of MTA.

	AD v ND		
		Left/Right MTA	
	MMSE	MMSE+volumetry	MMSE+visual rating
Sensitivity	81 (7)	88 (6)/90 (6)	93 (5)/92 (5)
Specificity	95 (4)	96 (4)/95 (4)	98 (3)/98 (3)
Correct classification	90 (46)	93 (5)/93 (4)	96 (4)/96 (4)

AD=Alzheimer's disease; ND= non-dementias; AD and ND were compared. Sensitivity, specificity, and correct classification are given in % (1.96 SE)

Table 5 Diagnostic value of volumetry and visual rating of MTA

	OD v ND		
		Left/Right MTA	
	MMSE	MMSE+volumetry	MMSE+visual rating
Sensitivity	75 (8)	78 (8)/78 (8)	82 (7)/82 (7)
Specificity	96 (4)	96 (4)/95 (6)	95 (4)/95 (4)
Correct classification	88 (6)	90 (6)/89 (6)	90 (6)/90 (6)

OD=other dementias; ND=non-dementias; OD and ND were compared. Sensitivity, specificity, and correct classification are given in % (1.96 SE).

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Table 6 Diagnostic value of volumetry and visual rating of MTA

	AD v OD		
		Left/Right MTA	
	MMSE	*MMSE+volumetry*	*MMSE+visual rating*
Sensitivity	73 (10)	68 (10)/76 (9)	78 (9)/77 (9)
Specificity	50 (11)	53 (11)/61 (11)	64 (10)/60 (11)
Correct classification	63 (11)	62 (10)/73 (10)	71 (10)/70 (10)

OD=other dementias; AD= Alzheimer's disease; OD and AD were compared. Sensitivity, specificity and correct classification are given in % (1.96 SE).

percentage correct classification, based on the three models, are given. The tables show that visual rating yielded a diagnostic gain for Alzheimer's disease over the MMSE, whereas volumetry did not. In separating the other dementias from non-dementias, visual rating added almost 30% to the sensitivity, but nothing to the specificity, whereas volumetry did not add to the MMSE despite the significant variables. In distinguishing Alzheimer's disease from other dementias both MTA assessments had no further predictive value (non-significant variables) over MMSE score, adjusted for sex and age.

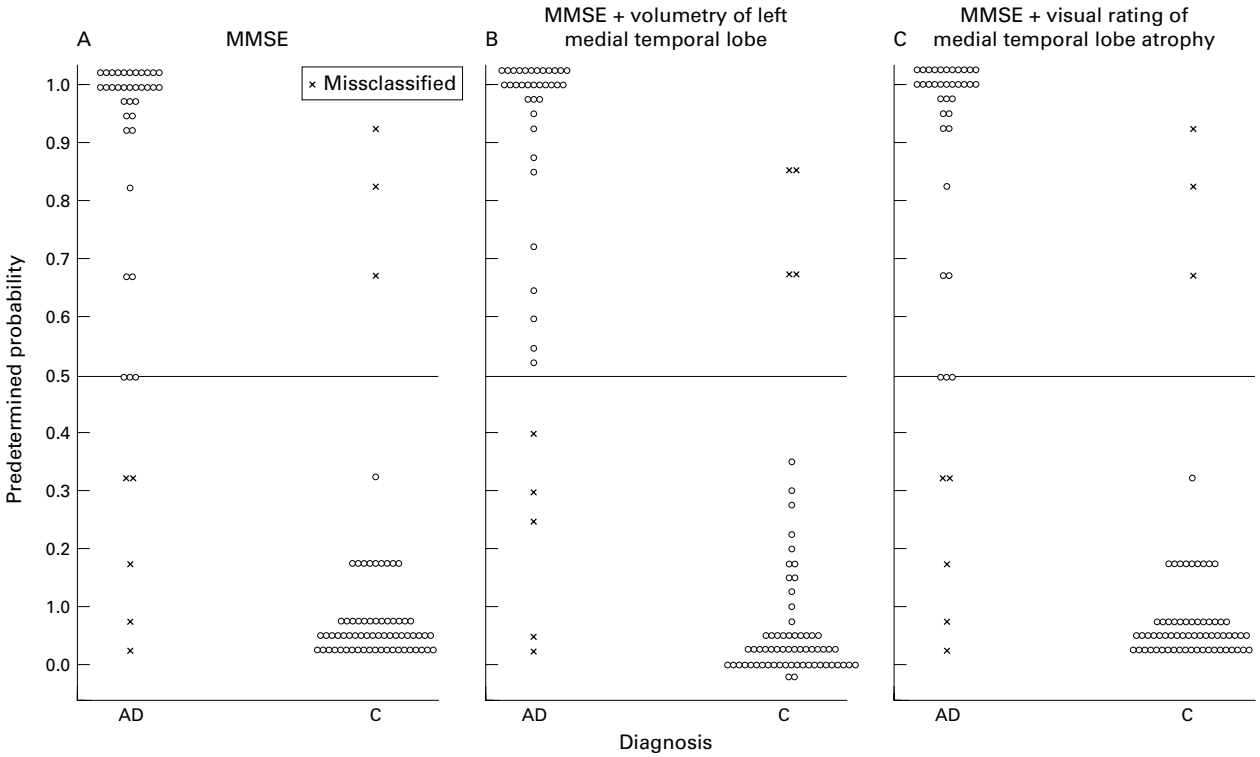
To further clarify the results of the logistic models we plotted the predicted probability for each subject to group membership (only Alzheimer's disease or control) in the figure A–C.

The actual time needed for volumetry (only the point counting of the medial temporal lobes and the volume) was 10–12 minutes/subject and for visual rating 1–2 minutes/subject.

Discussion

In this study we compared two methods for measuring medial temporal lobe atrophy in a large sample of patients evaluated for dementia. We found that both methods yielded significant differences in patients with Alzheimer's disease compared with patients with other dementias and non-dementias. However, in terms of diagnostic gain over the screening MMSE score only, visually rated MTA added to the sensitivity in separating Alzheimer's disease and other dementias from non-dementias. Visually rated MTA also added to the sensitivity in discriminating Alzheimer's disease from other dementias whereas volumetric MTA assessments had a limited value in this.

We investigated patients who were referred to our clinic for evaluation of suspected dementia. The patients were unselectively and consecutively recruited and no exclusions were made except for secondary dementias (n=10) and those patients for whom the MR images were of poor quality (n=9). By doing this we tested the methods in a true clinical setting. Using the clinical diagnosis made by clinicians not involved in this study at follow up and having the MR images evaluated by researchers unaware of the clinical data, we aimed to avoid investigation and review bias.[19] In addition we focused on the clinical usefulness of the methods, defined in this context as a method that is both easy to use and gives satisfactory discriminative power. To this end we used a different way of evaluating the sensitivity and specificity for the methods by including a comparison with the discriminative power of MMSE scores, to reflect more the clinical decision making situation, in which the MMSE is usually done before ancillary studies are ordered. Moreover, a comparison was made



Plots of predicted probability (p values) using three logistic regression models to differentiate patients with Alzheimer's disease (AD) from controls (C). Each circle represents one subject. The cut off level used was 0.5, and the misclassified subjects are marked.

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between patients with Alzheimer's disease and patients with other dementias as well as between these two groups and non-dementias.

We found the diagnostic accuracy to be very high for the combination of MMSE and visual rating of MTA, differentiating Alzheimer's disease from non-demented patients with a sensitivity of 95% (95% CI 88–98%), a specificity of 98% (95% CI 95–100%), and a correct classification of 96% (95%CI 92–100%). Our volumetric method showed a slightly lower degree of correct classification (93% (95% CI 86–98%)) which is in agreement with findings of other groups. For instance, Laakso *et al*[8] reported an overall correct classification of 92% discriminating Alzheimer's disease from controls using volumetry in a slightly larger sample.

Of special interest is the reasonably high sensitivity (82 (CI 75–69%)) of MTA for the diagnosis of other dementias, which included vascular dementia (n=21), frontal lobe dementia (n=4), and unspecified dementia (n=11), but were grouped together as other dementias for statistical reasons versus non-dementias. As could be expected the MMSE had low sensitivity for other dementias, but the added value of MTA suggests medial temporal lobe involvement in some of these non-Alzheimer's disease dementias.[20 21] This also explains the weaker performance of MTA in discriminating Alzheimer's disease from other dementias. Few other studies have considered the problem of discriminating Alzheimer's disease from other dementias using MTA or MRI. Laakso *et al*[9] have compared Alzheimer's disease with Parkinson's disease (with and without dementia) and vascular dementia and found no differences between the groups for medial temporal lobe volumes. Recently, Frisoni *et al*[10] compared volumetry of the hippocampus and entorhinal cortex in patients with Alzheimer's disease and patients with frontotemporal dementia and found equal atrophy in the entorhinal cortex but more severe hippocampal atrophy in Alzheimer's disease. However, in all these studies, including ours, coexistence of Alzheimer's disease and the other dementias could not be ruled out, despite a follow up period of 6 months in our study. In a recent study on patients with histologically confirmed dementia with Lewy bodies and patients with Alzheimer's disease; however, visually rated MTA on MRI was able to differentiate both groups with high accuracy.[22]

Our volumetry focused on the MTL, but visual rating probably also included more lateral parts, which were found to raise the correct classification of Alzheimer's disease from 80% to 91% in a study by De Leon *et al*.[2] This is further supported by findings from Frisoni *et al*[23] in which a sensitivity of 85% and specificity of 95% were found in discriminating patients with Alzheimer's disease from controls, using a combination of the width of temporal horn, width of choroidal fissure, and height of hippocampus.

It is not fully evaluated which substructures of the medial temporal lobes best characterise Alzheimer's disease—the entorhinal cortex,[24] the hippocampus,[8] or both.[25] Juottonen *et al*[25] evaluated the discriminative power of the entorhinal cortex and hippocampus. The sensitivity in detecting Alzheimer's disease was similar for both (80%) but the entorhinal cortex was 3% more specific (94%). Adding sex to the regression analysis increased the sensitivity to 90%, but had no influence on specificity. This illustrates that including other variables into the discriminant models may increase the diagnostic accuracy. We also included, apart from sex and age, MMSE scores into the discriminative model and when adding rating and volumetry this resulted in very high sensitivity and specificity.

It could be argued that the comparison of visual and volumetric analysis is hampered by using a less valid stereological method instead of semiautomated manual tracings and by using a slice thickness of 2.8 mm instead of the 1.5 mm typically seen in studies such as this. The first argument is dealt with in an earlier study[18] in which we compared both methods and found that there was a good agreement in ranking the relative relation between volumes within the group under study. This means that the faster stereology method should be comparable with manual outlining methods for sensitivity. Using a smaller slice thickness would limit the investigation to highly selected research samples as both scan time and image analysis time would be significantly increased. There is also a trade off between high resolution (and longer scan time) and movement artifacts, especially in large clinical samples such as these. The slice thickness we chose may thus be regarded as a compromise. Most importantly, the present paper compared two different methods on the same set of images. Probably both methods could benefit from a smaller slice thickness. However, this was not regarded as a major objective of the present study.

Taking into account that visual rating is rapid (1–2 min/subject) and can be applied to all kind of (coronal) MRI images regardless of type of imager or protocol, the method could be implemented into the standard clinical routines in dementia investigations, provided that the rater has some experience in visual assessment of MTA.

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EFNS TASK FORCE/CME ARTICLE

Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline

G. Waldemar[a], B. Dubois[b], M. Emre[c], J. Georges[d], I. G. McKeith[e], M. Rossor[f], P. Scheltens[g], P. Tariska[h] and B. Winblad[i]

[a]*Memory Disorders Research Group, Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Denmark;* [b]*Department of Neurology and Dementia Research Center, Hopital de la Salpetriere, Paris, France;* [c]*Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey;* [d]*Alzheimer Europe, Luxembourg;* [e]*Institute for Ageing and Health, Newcastle General Hospital, Newcastle upon Tyne, UK;* [f]*Dementia Research Centre, Institute of Neurology, University College London, London, UK;* [g]*Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands;* [h]*Department of Neurology, National Institute of Psychiatry and Neurology, Budapest, Hungary; and* [i]*Department of Geriatric Medicine, Karolinska University Hospital, Huddinge, Sweden*

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The aim of this international guideline on dementia was to present a peer-reviewed evidence-based statement for the guidance of practice for clinical neurologists, geriatricians, psychiatrists, and other specialist physicians responsible for the care of patients with dementia. It covers major aspects of diagnostic evaluation and treatment, with particular emphasis on the type of patient often referred to the specialist physician. The main focus is Alzheimer's disease, but many of the recommendations apply to dementia disorders in general. The task force working group considered and classified evidence from original research reports, meta-analysis, and systematic reviews, published before January 2006. The evidence was classified and consensus recommendations graded according to the EFNS guidance. Where there was a lack of evidence, but clear consensus, good practice points were provided. The recommendations for clinical diagnosis, blood tests, neuroimaging, electroencephalography (EEG), cerebrospinal fluid (CSF) analysis, genetic testing, tissue biopsy, disclosure of diagnosis, treatment of Alzheimer's disease, and counselling and support for caregivers were all revised when compared with the previous EFNS guideline. New recommendations were added for the treatment of vascular dementia, Parkinson's disease dementia, and dementia with Lewy bodies, for monitoring treatment, for treatment of behavioural and psychological symptoms in dementia, and for legal issues. The specialist physician plays an important role together with primary care physicians in the multidisciplinary dementia teams, which have been established throughout Europe. This guideline may contribute to the definition of the role of the specialist physician in providing dementia health care.

Introduction

Dementia afflicts at least 5 million people in Europe [1] and is associated with significant physical, social and psychiatric disability in the patients and with significant burden and distress in family caregivers. Furthermore, Alzheimer's disease (AD) and other dementia disorders rank second in Western Europe when comparing the burden of brain diseases by the loss of disability adjusted life years [2]. The total health care costs in Europe related to dementia amount to at least 55 billion € per year, not including indirect costs and costs in young patients with dementia [1,3], and the majority of the costs are spent on institutional care.

Despite the fact that there is significant evidence for the benefits of early diagnostic evaluation, treatment and social support, the rate of diagnosis and treatment in people with dementia varies considerably in Europe [4]. General practitioners play a major role in the identification, diagnosis and management of patients with dementia. In many places multidisciplinary teams have been established to facilitate the management of the complex needs of patients and caregivers during the course of the dementia disease. The neurologist and other specialist physicians play a major role in these

Correspondence: Gunhild Waldemar, Professor, MD, DMSc; Department of Neurology, Copenhagen University Hospital, Rigshospitalet, section 6702, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark (tel.: +45 35452580; fax: +45 35452446; e-mail: gunhild.waldemar@rh.hosp.dk).

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teams and clinics together with other professionals with special training in dementia.

In 2003, a task force was set up to develop a revision of the EFNS guideline on dementia published in 2000 [5], with the aim to provide peer-reviewed evidence-based guidance for clinical neurologists, geriatricians, old age psychiatrists, and other specialist physicians responsible for the care of patients with dementia. This guideline addresses major issues in the diagnosis and management of AD and other disorders with dementia. Since the previous guideline was published in 2000 significant evidence has accumulated, and new methods have become available for diagnosis and treatment.

The task force panel, appointed by the Scientific Committee of the EFNS, included neurologists, and representatives from geriatrics and old age psychiatry, with clinical and research expertise in dementia, and a representative from the patient organization, Alzheimer Europe. The guideline applies to patients with suspected or diagnosed dementia, and covers aspects of diagnostic evaluation, as well as treatment, with particular emphasis on the type of patient often referred to the specialist. It does not, however, include treatment of mild cognitive impairment (MCI). The main focus of the guideline is AD, but there are many other conditions, although lower in prevalence, which require specific assessment and treatment, and many of the recommendations apply to dementia disorders in general. The guideline represents the minimum desirable standards for the guidance of practice, but does not include an analysis of cost-effectiveness of the recommended diagnostic and treatment interventions.

The evidence for this guideline was collected from Cochrane Library reviews, other published meta-analyses and systematic reviews, other evidence-based management guidelines in dementia, including the practice parameters from the American Academy of Neurology (AAN) [6–8], and original scientific papers published in peer-reviewed journals before January 2006. For each topic, the evidence was sought in MEDLINE according to pre-defined search protocols. The scientific evidence for diagnostic investigations and treatments were evaluated according to pre-specified levels of certainty (class I, II, III, and IV), and the recommendations were graded according to the strength of evidence (grade A, B, or C), using the definitions given in the EFNS guidance [9]. In addressing important clinical questions, for which no evidence was available, the task force group recommended 'good practice points' based on the experience and consensus of the task force group. Consensus was reached by circulating drafts of the manuscript to the task force members and by discussion of the classification of evidence and recommendations at four task force meetings during 2004 and 2005.

This guideline may not be appropriate in all circumstances, and decisions to apply the recommendations must be made in the light of the clinical presentation of the individual patient and of available resources.

Diagnostic evaluation

Clinical diagnosis

With the remarkable exception of autosomal dominant causes of dementia, there is no specific biological marker for degenerative dementias. Therefore, in the absence of neuropathological confirmation, the aetiological diagnosis of a dementia syndrome can only be made in terms of probability. The clinical diagnosis should rely on criteria that have been proposed to increase the reliability and accuracy of the diagnosis. The accuracy of these diagnostic criteria varies as a function of the dementia. For AD, both the *Diagnostic and Statistical Manual*, *3rd edn*, *revised* (DSM-IIIR) [10] and the *National Institute of Neurologic*, *Communicative Disorders and Stroke – Alzheimer' Disease and Related Disorders Association* (NINCDS-ADRDA) [11] criteria achieved a good sensitivity (up to 100%, average 81% across studies), but a low specificity (average across studies 70%) for 'probable' AD, based on class I–II studies with post-mortem confirmation [7]. For dementia with Lewy bodies (DLB), the Consortium for DLB diagnostic criteria from 1996 [12] showed rather low sensitivities in class I and II studies [7]. For fronto-temporal dementia (FTD) [13,14] advances in the understanding of the underlying pathophysiology and genetic mechanisms have indicated that the clinical syndromes are associated with several different neuropathological abnormalities, although generally, specific sets of pathological findings have not been associated with specific clinical syndromes. For vascular dementia (VaD), the *National Institute of Neurologic Disorders and Stroke and the Association Internationale pour la Recherche et l Enseignement en Neuroscience* (NINDS-AIREN) diagnostic criteria [15] achieved a low sensitivity (43%), but a good specificity (95%) in the only published class I study [16]. Mixed pathologies and the prevalent findings of vascular lesions in all patients with dementia add to the complexity of the diagnosis of VaD.

Medical history

The clinical history is a corner stone of medical practice and serves to focus the examination and investigations. The history should include the cognitive domains affected, the mode of onset, the pattern of progression and the impact on activities of daily living (ADL). Past medical history, current co-morbidities, family history and educational history are important. Due both to the

presence of cognitive deficit and to the possibility of anosognosia it is important to obtain a history from an independent informant. Several class I to II studies have confirmed the value of informant based instruments, such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and the Blessed Roth Dementia Scale (BRDS) in the detection of dementia [17–22].

Recommendation: medical history

The clinical history should be supplemented by an independent informant where available *(Level A)*.

Neurological and physical examination

The neurological examination in early AD is unremarkable apart from the cognitive impairment. However, for many of the other dementing disorders, for example DLB and prion diseases, the presence of additional neurological features, such as an extra pyramidal syndrome or myoclonus, is a key component of the diagnostic criteria. Moreover, many of the disorders in which dementia is part of a broader range of neurological dysfunction (the dementia plus syndromes) or in which abnormalities on physical examination such as organomegaly occur, the examination is critical in the diagnostic process. Furthermore, the general physical examination may reveal relevant comorbidities. Whilst no formal studies have addressed the issue of the added value of a neurological and physical examination this is an important part of the differential diagnosis of dementia.

Recommendation: neurological and physical examination

A general neurological and physical examination should be performed on all patients presenting with dementia *(Good Practice Point)*.

Assessment of cognitive functions

Assessment of cognitive function is important for several reasons: (1) the diagnosis of dementia mainly relies on the evidence of cognitive deficits (episodic memory, instrumental and executive functions); (2) most of aetiologies of dementia (e.g. AD, FTD and DLB) can be identified by the nature of their cognitive and behavioural changes; (3) as specialist physicians increasingly see patients at early stages of the disease, it is now important to be able to identify the specific degenerative disorders at a prodromal phase before the symptoms reach the threshold of dementia. Accordingly, an evaluation of cognitive function by a physician and/or by a clinical neuropsychologist is required for the management of patients with a prodromal, mild or moderate stage of dementia, whereas it is less essential for severely demented patients. The battery should investigate the following domains:

Global cognitive functions

The Mini-Mental State Examination (MMSE) of *Folstein et al.* [23] may help for the detection of cognitive impairment (I) and its sensitivity increases, if a decline of the score overtime is taken into account. The 7-min screen and the clinical dementia rating (CDR) (score = 1) demonstrate a specificity of 96% and 94% with sensitivity of 92% for the diagnosis of dementia [24,25] (IV) and can be useful for the detection of dementia. These two tests can be used as screening instruments for assessing general intellectual functioning. The Mattis Dementia Rating Scale [26] takes longer time and tests in addition several areas related to executive functions. It is, therefore, more appropriate for the assessment and follow up of FTD and fronto-subcortical dementias.

Memory function

Memory has to be systematically assessed. Episodic long-term memory impairment is required to fulfil the diagnosis criteria for dementia. Word recall, such as the Rey Auditory Verbal Learning Test (RAVLT), can distinguish between patients with AD and those without dementia (I) [27]. However, an effective encoding of information should be controlled to exclude the influence of depression, anxiety and other emotional states to cognitive problems. Semantic cueing may also help for separating retrieval for storage deficits [28]. For that reason, the Memory Impairment Scale (MIS) (sensitivity of 60% and specificity of 96% for identification of dementia [29]) and the '5 word' test (sensitivity of 91% and specificity of 87% for the identification of AD [30]) are short and simple memory tests that can be useful for a first-line screening tool for medical practitioners. Semantic memory should also be assessed (category fluency test, pictures naming task, word and picture definition), since deficits may be observed in AD and be prominent in Semantic Dementia (SD) [31].

Executive functions

Executive dysfunctions are observed in several dementia conditions. This impairment results in decreased verbal fluency with speech reduction, verbal stereotypies and echolalia; perseverations of mental set; retrieval deficits; attentional disorders; concrete thinking and in some cases disinhibition, impaired

adaptation, and uncontrolled behaviours. These deficits are currently assessed by the Wisconsin card sorting test [32], the Trail Making test [33], the Stroop test [34], the verbal fluency tests [35], and the digit ordering test [36] which trigger the cognitive processes needed for executive functions. In some dementias, executive dysfunction is only an epiphenomenon, part of a more diffuse and global picture. By contrast, it can be a prominent feature and essential for the diagnosis of other dementias, such as FTD [37] and progressive supranuclear palsy (PSP) [28].

Instrumental functions

Language (comprehension and expression), reading and writing, praxis (execution and recognition), visuospatial and visuoconstructive abilities can also be more or less affected according to the type of dementia disorder. These cognitive domains, often referred to as instrumental functions, are particularly impaired in diseases with prominent cortical involvement such as AD and DLB and may be the initial domain of dysfunction in lobar atrophy [progressive aphasia syndromes, progressive apraxia, cortico-basal degeneration (CBD) or posterior cortical atrophy].

Recommendations: assessment of cognitive functions

Cognitive assessment is central to diagnosis and management of dementias and should be performed in all patients *(Level A)*. Quantitative neuropsychological testing, ideally performed by someone trained in neuropsychology, should be considered in patients with questionable, prodromal, mild, or moderate dementia *(Level C)*. The specialist physician should include a global cognitive measure and in addition more detailed testing of the main cognitive domains including memory, executive functions and instrumental functions *(Level C)*.

Assessment of behavioural and psychological symptoms

Various terms including 'behavioural and psychological symptoms of dementia' (BPSD), 'neuropsychiatric features', and 'non-cognitive symptoms' are used to describe a range of symptoms that are common in dementia and which contribute substantially to patient distress and caregiver burden [38]. They are frequently a major factor leading to the prescription of psychotropic medications and to nursing home placement [39] (III). Their presence may contribute to the process of differential diagnosis, e.g. visual hallucinations are a prominent feature of DLB [12] (II), whereas disinhibition and lack of personal concern are characteristic of FTD [40] (II). Their temporal course also varies, e.g. apathy, depression and anxiety tend to occur early in the course of AD with delusions, hallucinations and agitation appearing in the middle to late stages. BPSD may be worsened or caused by somatic co-morbidity. Patients with psychosis experience a more rapid cognitive decline than those without, and neuropsychiatric features may predict an increased rate of conversion to dementia in patients diagnosed with MCI [41] (II).

The accurate identification of BPSD is essential both for diagnosis and management of patients with dementia, but often such symptoms may not be disclosed by patients or caregivers, until they are intolerable or they precipitate a crisis [42]. Earlier detection can be achieved by routine and repeated enquiry. Several rating instruments have been designed for this purpose, enquiring not only about the presence or absence of different symptoms, but also about their frequency, severity and impact upon the caregiver. They usually rely upon the report of an informant who should have regular contact with the patient. Repeated use of such scales can also be useful in monitoring the effects of treatment interventions. Suitable scales include the Neuropsychiatric Inventory (NPI) [43], BEHAVE-AD [44] and the Manchester and Oxford Universities Scale for the Psychopathological Assessment of Dementia (MOUSEPAD) [45].

The most common neuropsychiatric feature of AD is apathy (72%), followed by aggression/agitation (60%), anxiety (48%) and depression (48%) [46] (II).

Apathy and inertia may occur independently of depressed mood and may be particularly frustrating for carers, especially in the early stages. *Agitation and aggression* may be very persistent and frequent causes of requests for institutionalization. *Anxiety* may manifest physically with tension, insomnia, palpitations and shortness of breath and also with excessive worrying and fearfulness particularly if separated from the spouse or carer. *Depressed mood* should be assessed independently of weight loss, appetite changes, sleep disturbances and retardation that may occur as features of the dementia. Core psychological manifestations of depression such as sadness, thoughts of worthlessness and hopelessness, and statements about death and suicide should be enquired about. *Delusions* are common in dementia, usually of theft, intruders or imposters, often rather vaguely expressed and transient. They are typically based in forgetfulness and misinterpretation. Hallucinations, misidentifications and illusions in dementia are usually visual, particularly in DLB, but perceptual disturbances can also be auditory, olfactory or tactile. They are more common in those with impaired vision and hearing. *Purposeless activities* such as pacing and rummaging are characteristic of AD, whilst

compulsions and stereotyped behaviours are more common in FTD as are *disinhibition and euphoria* exhibited as impulsivity, hyperorality, socially inappropriate behaviour and emotional lability. *Sleep disturbances* may be secondary to other psychiatric features, may be associated with daytime drowsiness and are particularly burdensome to carers who are also likely to be kept awake. Rapid eye movement (REM) sleep behaviour disorder is characteristic of DLB [47] (II).

Recommendations: assessment of behavioural and psychological symptoms

Assessment of behavioural and psychological symptoms of dementia is essential for both diagnosis and management, and should be performed in all patients *(Level A)*. Symptoms should be actively enquired about from the patient and a closely involved carer using appropriate rating scales *(Good Practice Point)*. Co-morbidity should always be considered as a possible cause *(Level C)*.

Assessment of activities of daily living

Decline in every day functional abilities is a major component of the dementia syndrome. It has a great influence on the quantity and quality of care and its level is extremely important for the caregiver. Assessment of function in daily life is part of diagnostic process and allows clinicians to evaluate the need for personal and institutional care. Different scales are used to objectively measure these abilities. These are based mainly on the interview with the patient and his/her caregiver. Two classical fields measured are basic, or general (such as eating, dressing, etc.) and instrumental activities (such as the use of devices, shopping). Frequently used scales include the Alzheimer Disease Cooperative Study (ADCS) ADL Scale [48], Functional Activities Questionnaire (FAQ) [49]; the Progressive Deterioration Scale (PDS) [50], and the Disability Assessment for Dementia (DAD) [51].

Recommendations: assessment of activities of daily living

Impairment of activities of daily living due to cognitive impairment is an essential part of the criteria for dementia and should be assessed in the diagnostic evaluation *(Level A)*. A semi-structured interview from the caregiver is the most practical way to obtain relevant information, and a panel of validated scales are available *(Good Practice Point)*.

Assessment of co-morbidity

Co-morbidities are frequent, particularly in elderly patients (IV), and may rapidly worsen the cognitive and functional status of the patient. There is a strong association between medical co-morbidity and cognitive status in AD (IV), and optimal management of medical illnesses may offer potential to improve cognition [52]. Depression, cardiovascular disease, infections, adverse effects of drugs, delirium, falls, incontinence, and anorexia are frequently observed co-morbidities or complications. Some of the co-morbid conditions which were identified in a large postmortem study of patients with dementia would have affected the clinical management of the patient, had they been known antemortem *(IV)* [53].

Recommendation: assessment of co-morbidity

Assessment of co-morbidity is important in the evaluation of the patient with dementia, and should be performed not only at the time of diagnosis, but throughout the course of the disease, with particular attention to episodes of sudden worsening of cognitive or behavioural symptoms *(Good Practice Point)*.

Blood tests

Laboratory screening with blood tests is recognized as an important integral part of the general screening of a patient presenting with cognitive disturbances. The aims of blood tests include (1) to identify co-morbidity and/or complications; (2) to reveal potential risk factors; (3) to explore the background of frequently associated confusional states; and (4) more rarely to identify the primary cause of dementia. Cognitive disturbances may be associated with a wide range of metabolic, infectious, and toxic conditions, which should be identified and treated. For most of these conditions, there is no specific evidence from randomized controlled trials that treatment will reverse cognitive symptoms. Yet, the specialist physician is often dealing with patients with confusional states, rapid progression or atypical presentation, in whom blood tests may be of diagnostic value.

Recommendations: blood tests

The following blood tests are generally proposed as mandatory tests for all patients at first evaluation, both as a potential cause of cognitive impairment or as co-morbidity: blood sedimentation rate, complete blood cell count, electrolytes, calcium, glucose, renal and liver function tests, and thyroid stimulating

hormone. More extensive tests will often be required, e.g. vitamin B12 and serological tests for syphilis, HIV, and Borrelia, in individual cases *(Good Practice Point)*.

Neuroimaging

Traditionally, imaging was considered important solely as a means of excluding treatable causes of dementia. These conditions account for a small proportion of all causes of dementia with far more common causes being AD, VaD, DLB, and FTD [54]. Neuroimaging is now the most important ancillary investigation in the work-up of dementia to aid in differential diagnosis and management decisions.

Computed tomography
Computed tomography (CT) is mostly used to exclude other illnesses that are potentially amenable to (surgical) treatment, e.g. tumours, haematomata, and hydrocephalus. The yield of such a procedure has been debated but probably lies somewhere between 1% and 10% and may even be lower [55,56] (II). Farina *et al.* performed CT in 513 patients referred to a memory clinic of whom 362 were found demented [57] (II). In 26 of them (7.2%) a potential reversible cause of dementia was detected. However, in none of the cases did CT reveal findings that had not been discovered clinically. Foster *et al.* carried out a systematic review on the use of CT scanning in dementia [58]. Comparing costs and outcome they concluded that scanning each patient under 65 years and treating only subdural haematomas would be the most cost-effective approach. Recently, Condefer [59] showed that in a memory clinic setting, routine CT impacted on diagnosis in 12% of cases and on management in 11% (II), mainly because of the identification of vascular changes. Because Gifford *et al.* [60] showed that there is considerable uncertainty in the evidence underlying clinical prediction rules to identify which patients with dementia should undergo neuroimaging and application of these rules may miss patients with potentially reversible causes of dementia, it is generally felt that a structural imaging investigation in the evaluation of a patient suspected of dementia should be performed routinely.

Magnetic resonance imaging
Magnetic resonance imaging (MRI) may be used for the same reason as CT but has the ability to increase specificity to an already quite high sensitivity of the clinical diagnosis.

Hippocampal atrophy in AD. Hippocampal atrophy is an early and specific marker of the AD process [61–65] (II–IV). This structure has been measured using a variety of tracing techniques and anatomical boundaries. Some studies have employed linear or visual measurements [66–71]. Because of their supposedly (but debatable) greater accuracy and reliability, other studies have used volumetric measures of medial temporal lobe structures. Comparative studies have found good correlations between these assessment techniques [72,73]. Several studies used a qualitative method that involves a visual rating scale, usually a four or five point scale ranging from absent to severe atrophy [74]. Frisoni *et al.* used a compound score of linear measurements that included the temporal horn [75]. Pucci *et al.* found the best discriminating parameter to be just the height of the left hippocampus [76]. In a novel approach, Frisoni and co-workers used the radial width of the temporal horn of the lateral ventricle on axial MR scans as measured with a calliper on paper printouts [66].Visual assessment is considerably less time consuming than volumetry and easily applicable in clinical practice [77]. The down-side may be a larger inter-rater variability [68]. The overall sensitivity and specificity figures for detection of mild to moderate AD versus controls were 85% and 88% in a meta-analysis [78], and the accuracy of hippocampal atrophy in mild AD ranged from 67% to 100% in a systematic review [79] (I–II).

Fronto-temporal lobar degeneration. Asymmetric, predominantly left-sided peri-sylvian atrophy characterizes progressive non-fluent aphasia and asymmetric anterior temporal lobe atrophy is diagnostic of SD. In both conditions, with time, atrophy becomes more widespread but usually remains asymmetric. The pattern of atrophy may be more useful than atrophy of single regions in the differential diagnosis of FTD versus AD (II) [80–83].

Vascular dementia. In the most often used NINDS–AIREN international work group criteria for VaD brain imaging is thought to be essential for the diagnosis, and without it VaD will be 'possible' at best [15]. In addition, the criteria specify which vascular territories are 'relevant' for VaD. These include large vessel strokes, such as bilateral infarcts in the anterior or posterior cerebral artery areas, in the association areas, or in the watershed regions. Using operational guidelines on how to classify radiological features as fitting into the NINDS–AIREN criteria, inter-observer reliability of the diagnosis went up significantly from 40% to 60% [84] (II).

Identifying vascular disease in dementia. Like AD, the prevalence of cerebrovascular disease (CVD), both symptomatic and asymptomatic, increases dramatically with age, and pathological studies often find concomitant

cerebral infarction in patients with definite AD [85]. Even small, concurrent infarctions significantly increase the likelihood of expressed dementia, suggesting a synergistic effect. Given that concurrent CVD may be amenable to targeted interventions potentially ameliorating disease progression, brain imaging may prove important to the clinical care of the demented patient with coexisting CVD. Preliminary evidence from anti-hypertensive treatment trials of older individuals supports this notion, although further prospective clinical trials involving brain imaging are necessary.

Miscellaneous. In addition to the above specific imaging signs may include bilateral caudate atrophy in Huntington's disease, hyperintense signal in the putamen in sporadic Creutzfeldt Jakob Disease (CJD) and hyperintense signal change in the pulvinar in new variant CJD [86] (II). Diffusion-weighted MRI shows (the earliest) focal changes in CJD not yet apparent on FLAIR images, and may widely involve the cortex [87] (II). Corticobasal degeneration shows a typical MRI pattern, with striking, asymmetric parietal (peri-Rolandic) and frontal atrophy, sparing medial temporal regions [88] (II). Normal pressure hydrocephalus (NPH) is a questionable disease entity, and it may be difficult to decide whether such a patient would benefit from a shunting procedure. Strict adherence to clinical and MRI criteria is important, with additional information from a positive – but not a negative – cerebrospinal fluid (CSF) tap and the occurrence of B-waves [89] (II). These MRI criteria include widened ventricles with normal sulci and without white matter pathology. In DLB, MRI has been reported to show medial temporal lobe atrophy in a lower frequency than in AD, and therefore the *absence* of medial temporal lobe atrophy may be suggestive of a diagnosis of DLB [90] (II).

Single photon emission computed tomography and positron emission tomography

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are often used as a part of the work-up especially in memory clinics and as a complement to structural imaging in difficult differential diagnostic questions. Here again, the quest should be to increase specificity to augment clinical diagnostic criteria and structural imaging. The most often applied functional imaging studies include regional blood flow measurements performed with SPECT (^{99m}Tc-HMPAO or ^{133}Xe) and measurement of glucose metabolism performed with ^{18}F-FDG-PET. A reduction in blood flow or glucose metabolism in parieto-temporal areas is the most commonly described diagnostic criterion for AD. In a recent meta-analysis, functional imaging studies with SPECT in which AD was contrasted against control subjects yielded pooled weighted sensitivities ranging from 65% to 71%, with specificity of 79% [91]. A very few SPECT studies have adequately addressed the comparison between AD and other dementias. The few that did provided a pooled weighted sensitivity and specificity for AD versus FTD of 71% and 78%, respectively, and for AD versus VaD of 71% and 75%, respectively [91]. In a recent meta-analysis, the summary sensitivity of PET in diagnosing AD versus control subjects was 86%, and the summary specificity was 86% [92]. The majority of SPECT and PET studies were class II, although many did not have blinded evaluation of imaging results (IV). The fact that all positive likelihood ratios were < 5, indicates that cerebral blood flow assessed with SPECT or glucose metabolism assessed with PET moderately improves the diagnostic certainty either when AD is contrasted against controls or against other dementias [93]. Interestingly, there is no difference in diagnostic value between regional cerebral blood flow assessed with SPECT and glucose metabolism assessed with PET. Furthermore, a very few studies addressed the additional value of functional imaging over structural imaging. On the other hand, an international consortium of investigators argued that, although FDG-PET had moderate specificity (73–78%) for the diagnosis of AD both for clinical and pathological diagnosis, due to its high sensitivity, a negative (i.e. normal) PET strongly favours a normal outcome at follow up [94].

There have been studies suggesting that SPECT using the pre-synaptic dopamine transporter ligand ^{123}I-FP-CIT (DAT-SPECT) can distinguish DLB from AD and normal ageing. Low striatal dopamine transporter activity is seen in idiopathic Parkinson's disease (PD), DLB, and PSP, but not in AD (II–III) [95–97]. The positive outcome has led the consensus committee on the diagnosis of DLB to include it in the most recent version of its guidelines [98].

Recommendations: neuroimaging

Structural imaging should be used in the evaluation of every patient suspected of dementia: Non-contrast CT can be used to identify surgically treatable lesions and vascular disease *(Level A)*. To increase specificity, MRI (with a protocol including T1, T2 and FLAIR sequences) should be used *(Level A)*. SPECT and PET may be useful in those cases where diagnostic uncertainty remains after clinical and structural imaging work up, and should not be used as the only imaging measure *(Level B)*.

Electroencephalography

Electroencephalography (EEG) is widely available, non-invasive and suitable for repeated recording.

Generalized slowing of background rhythm is a feature of AD and DLB. The EEG may be entirely normal in advanced frontal lobe degeneration although abnormalities are relatively common in the overall group of FTD [99]. There is an overall relationship between the severity of dementia and abnormalities on the EEG in AD and DLB. There have been many studies demonstrating the ability of the EEG to distinguish clinically diagnosed AD from controls with a sensitivity that is comparable with other techniques such as neuroimaging [100–103]. However, there is a paucity of studies that explore the differential diagnosis of the dementia and which have neuropathological confirmation. Robinson et al. reported a series of neuropathologically confirmed AD (86 patients) and mixed and VaD (17 patients) with blinded assessment of the EEG (II) [104]. Abnormalities on the EEG were frequent in uncomplicated AD with a sensitivity of 87%. Importantly, a normal EEG had a negative predictive value of 82% with respect to a diagnosis of AD. There have been few studies exploring the added value of the EEG over and above a full clinical and neuroimaging assessment. Claus *et al.* investigated the added value of the EEG in a study of 49 control subjects with and without minimal cognitive impairment and 86 probable AD patients (II) [103]. The maximum diagnostic gain of 38% for an abnormal EEG was found when the prior probability was low at 30–40%. If there was a high pre-test probability of 80–90% then the diagnostic gain of an abnormal EEG was much lower, between 7% and 14%.

In some specific dementia conditions, the EEG has a higher diagnostic contribution. Periodic sharp wave complexes are part of the clinical criteria for the diagnosis of CJD, particularly the sporadic variety. Zerr *et al.* reported on 805 patients with neuropathologically confirmed CJD disease in whom the EEG was available (I) [105]. The presence of periodic sharp wave complexes provided 66% sensitivity and 74% specificity, comparable with the smaller series of Steinhoff *et al.* (I) [106]. The appearance of periodic sharp wave complexes is, however, variable and can disappear during the course of the disease making repeated EEG measurements valuable.

Transient epileptic amnesia due to focal temporal lobe seizure activity can masquerade as AD [107,108]. The EEG may be diagnostic in this situation.

Recommendation: EEG

The EEG may be a useful adjunct, and should be included in the diagnostic work up of patients suspected of having Creutzfeldt-Jakob disease or transient epileptic amnesia *(Level B)*.

CSF analysis

Examination of CSF (with routine cell count, protein, glucose and protein electrophoresis) is mandatory when inflammatory disease, vasculitis or demyelination is suspected, and in cases of dementia with early onset, rapid decline, marked fluctuations, or extensive white matter changes on MRI or CT. A vast body of literature has emerged investigating the added value of 'specific' biomarkers in CSF such as amyloid β (1–42) (Aβ42), total tau (tau), phospho-tau and the 14-3-3 protein. Aβ42 is decreased in the CSF of AD patients possibly as a result of the deposition of fibrillar Aβ42 in senile plaques. Tau is increased in CSF of AD patients, as a reflection of the release of tau in CSF with neuronal loss. Phospho-tau derives from tangle deposition. The presence of the 14-3-3 protein in CSF is a measure for (acute) neuronal loss and brain damage and is associated with CJD.

Alzheimer's disease versus controls

Aβ42 is decreased and tau increased in CSF of AD patients compared to non-demented controls, patients with depression, and patients with memory complaints on the basis of alcohol abuse [109–111]. The pooled sensitivity and specificity for Aβ42 in AD versus controls from 13 studies was 86% and 90%. For tau the sensitivity was 81% and the specificity 90%, pooled from 36 studies (II–III) [110]. A recent meta-analysis showed considerable differences in absolute concentrations of Aβ42 and tau between laboratories, even when the same test kit was used [112]. Using the combination of both markers for AD versus controls, a high sensitivity (85–94%) and specificity (83–100%) can be reached (II) [113]. In patients with early onset AD compared with controls, a sensitivity of 81% with specificity of 100% was found (III) [114]. As the reference test, the clinical diagnosis is usually used, sometimes also with a follow-up period in which the diagnosis did not change [114,115]. Only two studies had neuropathological validation of the diagnosis [116,117]. In these studies, the same high sensitivity and specificity for the distinction of AD from controls was found (I). One study investigated and found an association between number of senile plaques and concentration of Aβ42 in CSF [118].

Alzheimer's disease versus other dementias

A decreased CSF-Aβ42 is being found in FTD [114,119], DLB [120], VaD [121,122], and CJD [123] when compared with controls (for AD versus FTD: specificity 59–81% (I) [114–115,119]; for AD versus VaD: specificity 71% (II) [124]). Tau is increased in

many other dementias such as FTD (II) [114,119,125,126] and CJD (I) [127]. In VaD conflicting results have been reported; specificity varied between 14% and 83% (II–III) [124,128,129] compared with AD. In FTD specificity varied from 26% to 75% (II–III) [114,115,119]. In DLB tau is usually normal (II) [120]. The combination of Aβ42 and total tau increases specificity and the negative predictive value (II): AD versus total group other dementias: 58–85% [113]; AD versus FTD: 85% [119]; AD versus DLB and VaD specificity 67% and 48%, respectively, with a negative predictive value of 95% (I) [130].

Alzheimer's disease compared with an age matched FTD group yielded good sensitivity (72%), and high specificity (89%) and a very low negative likelihood ratio ($-LR = 0.03$) [114]. In general, for studies in which phospho tau was added, specificity was even higher (II–III) [110].

Creutzfeldt Jakob Disease

In CJD, very high tau levels have been reported, higher than in AD, yielding a high sensitivity and specificity, 93% and 90–100% (I) [127,131]. Assessment of the 14-3-3 protein in the sporadic form of CJD has a sensitivity of 90–100% and a specificity of 84–96% (I–II) [105,127,132–134]. False positive results are found in cerebral infarcts, encephalitis, tumours and rapidly progressive AD (I–II) [132,133,135]. When the clinical suspicion of CJD is high, the combination of EEG [135] MRI, and 14-3-3 assessment has the maximum accuracy (I–II) [136].

Recommendations: CSF

CSF analysis with routine cell count, protein, glucose and protein electrophoresis is recommended in patients with a clinical suspicion of certain diseases and in patients with atypical clinical presentations *(Good Practice Point)*. CSF total tau, phospo-tau, and Ab42 can be used as an adjunct in cases of diagnostic doubt *(Level B)*. For the identification of CJD in cases with rapidly progressive dementia, assessment of the 14-3-3 protein is recommended *(Level B)*.

Genetic testing

Many degenerative dementias can occur as autosomal dominant disorders with similar phenotypes to sporadic disease apart from an earlier age at onset. The prevalence of autosomal dominant disease varies from $<1\%$ in AD to nearly 50% in some series of FTD. Three causative genes have been identified in familial AD, the amyloid precursor protein (APP) gene and the presenilin 1 and 2 genes. Tau mutations are found in some cases of familial FTD and mutations in the prion protein gene in familial CJD. There is an increasing range of rarer genes, especially in the dementia plus syndromes. The yield of mutation screening in unselected populations is low, for example, no tau mutations were found in a large series of clinically diagnosed non Alzheimer dementias [137]. However, with an appropriate phenotype an autosomal dominant family history gene testing for known mutations can provide a specific diagnosis. This should only be undertaken in specialist centres with appropriate consent and counselling. The identification of a known pathogenic mutation in an affected family member can permit pre-symptomatic testing, and the Huntington's disease protocol for predictive testing and counselling should be followed [138]. Autopsy diagnosis in familial dementias can be valuable for establishing the significance of gene sequence variation in a family for subsequent diagnosis and counselling.

A variety of risk genes have been identified and the most carefully studied has been the Apolipoprotein (Apo) E4 polymorphism. The addition of Apo E testing increased the positive predictive value of a diagnosis of AD from 90% to only 94% in a neuropathologically confirmed series [139]. In those patients with a clinical diagnosis of non-Alzheimer dementia the absence of an Apo E4 ε4 allele increased the negative predictive value from 64% to 72%.

Recommendations: genetic testing

Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. This should only be undertaken in specialist centres with appropriate counselling of the patient and family caregivers, and with consent *(Good Practice Point)*.

Pre-symptomatic testing may be performed in adults where there is a clear family history, and when there is a known mutation in an affected individual to ensure that a negative result is clinically significant. It is recommended that the Huntington's disease protocol is followed *(Good Practice Point)*.

Routine Apo E genotyping is not recommended *(Level B)*.

Other investigations

Additional investigations may provide critical information in the differential diagnosis of dementia, e.g. metabolic studies from fibroblast cultures, white cell enzyme assays, urinary aminoacids, etc. Moreover,

extensive imaging may provide diagnostic information in paraneoplastic syndromes. Biopsies of specific tissues can also be invaluable, for example, liver biopsy in Wilson's disease and skin and muscle biopsies in conditions such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) (100% specificity and 45% sensitivity) [140], Lafora body disease and mitochondrial cytopathies. Tonsillar biopsy can demonstrate the presence of prion protein in variant CJD.

Cerebral biopsy can provide a specific histological diagnosis but should only be undertaken where a treatable disorder is considered, such as cerebral vasculitis. In general, a non-dominant frontal or temporal pole full thickness biopsy to include leptomeninges and white matter should be performed. In many cases, prion disease cannot be excluded from the differential diagnosis and either disposable craniotomy instruments should be used or the instruments should be quarantined until a specific diagnosis has been made.

Recommendation: tissue biopsy

Tissue biopsy can provide a specific diagnosis some rare dementias. This should only be undertaken in specialist centres in carefully selected cases *(Good Practice Point)*.

Disclosure of diagnosis

Of particular interest to specialist physicians are laws pertaining to the disclosure of diagnosis to the person him/herself rather than his/her family. Most European countries have not established the right to a diagnosis into an absolute right without any possible exceptions and most legislations allow doctors to refrain from disclosing a diagnosis, if this is considered to be in the 'best interests' of the person or if such disclosure could cause 'serious harm' to the physical or mental health of the patient [141]. Nevertheless, a growing consensus [142] has emerged in favour of disclosing a diagnosis to the person at a time when the person is capable of understanding this. It has been shown that such disclosure relieves the anxiety of uncertainty and maximises individual autonomy and choice by providing information necessary for decision making and advance planning (IV) [143], including the decision to give informed consent to research projects and autopsy.

Recommendation: disclosure of diagnosis

Disclosure of diagnosis should be done tactfully and should be accompanied by information about the consequences and the progression of the disease, as well as useful contacts such as the local or national Alzheimer's association. In countries where this is possible physicians may also wish to encourage patients to draw up advance directives containing future treatment and care preferences (Good Practice Point).

Management of Alzheimer's disease and other disorders associated with dementia

To address the complex needs of the patient with dementia and the caregiver during the course of a dementia disorder the specialist physicians should collaborate with other health care professionals with special training in dementia. The specialist physician should schedule regular follow-up visits, the purposes of which include: (1) to assess cognitive, emotional, and behavioural symptoms together with the functional status; (2) to evaluate treatment indications and to monitor pharmacological and non-pharmacological treatment effects; (3) to ensure identification and appropriate treatment of concomitant conditions and of complications of the primary dementia disorder; (4) to assess caregiver burden and needs; (5) to assess sources of care and support; (6) to provide continuous advice and guidance to patient and caregiver on health and psychological issues, safety measures, driving, and legal and financial matters; and (7) to administer appropriate patient and caregiver interventions. The primary caregiver, when available, should accompany the patient with dementia at follow-up visits and investigations.

In this guideline, the main emphasis is on recommendations for pharmacological treatment, and many important aspects of the care for patients with dementia, e.g. living arrangements, cognitive rehabilitation, nursing care and end-of-life issues are not covered. For pharmacological treatment, this review is confined dementia (not MCI) and to drugs which have been clinically tested in dementia and which are available on the market, although they may not be registered for dementia worldwide. Negative results were also included, if published, whereas experimental substances were not covered. It must be emphasized that the class of evidence does not necessarily reflect the effect size and the potential clinical relevance thereof, which were taken in consideration in making recommendations.

Treatment of Alzheimer's disease

Cholinesterase inhibitors

Cholinesterase inhibitors (ChEIs) represent the first class of drugs approved for the specific symptomatic treatment of AD. Following the introduction of tacrine, the first ChEI to be approved, donepezil, rivastigmine

and galantamine became available. There are multiple randomized, placebo-controlled, large scale clinical trials with these substances establishing efficacy on cognitive functions, overall evaluation, and ADL in patients with mild to moderate AD, with modest effect sizes [144–149] (I). The ChEIs are generally well tolerated, although gastrointestinal adverse effects such as nausea, diarrhoea, and vomiting are the most common adverse effects, and may lead to discontinuation of treatment in some patients. The use of ChEIs in mild to moderate AD has also been subject to systematic reviews and meta-analyses, and their efficacy was confirmed [150–152]. Likewise, practice parameters such as those provided by AAN, recommend that ChEIs should be considered in patients with mild to moderate AD [8]. Although their appraisal report is currently being revised, the National Institute for Clinical Excellence (NICE) in the UK in their health technology appraisal from 2001 recommended that ChEIs should be considered in mild to moderate AD [153].

With regard to duration of efficacy the longest lasting placebo-controlled studies with continuous treatment were with donepezil, performed over 1 year. These studies revealed that efficacy, in terms of difference from placebo treated patients, was maintained for at least 1 year and there was a 38% reduction in the risk of functional decline compared with placebo [154,155] (I). A recent placebo-controlled study over 3 years, in which multiple withdrawal phases were involved, revealed that cognitive scores and functionality were significantly better with donepezil over 2 years, but the differences were small and did not translate into benefits in primary outcome measures defined as institutionalization or progression of disability over 3 years [156] (II). There have been extensions of placebo-controlled studies with follow-up up to 5 years, where historical data or model-based predictions for non-treatment were used as a control. These studies suggest a slower progression of symptoms in treated patients. Lack of control in these studies and bias due to drop-outs, however, limit their conclusions [157–159] (III).

The initial assessments of efficacy of ChEI were focused on cognitive functions, scales of global change and ADL. Subsequently, small beneficial effects of ChEI on behavioural symptoms of AD were also shown [148,160,161] (I). With regard to disease stage, placebo-controlled randomized trials with donepezil confirmed efficacy in patients with early, mild AD as well as those with moderate to moderately severe AD [160,162] (I). There has been only one large randomized controlled double-blind study with direct comparison of the efficacy of cholinesterase inhibitors: a comparison of rivastigmine with donepezil in a large, randomized controlled trial over 2 years revealed that the efficacy was comparable in the primary outcome measure, some of the secondary efficacy measures favoured rivastigmine, and tolerability was better with donepezil [163] (II). There is some evidence form open-label studies that patients who do not tolerate or do not seem to benefit from one AChE-I may tolerate or draw benefit from the other (III) [164,165]. Several attempts were made to quantify the clinical usefulness of ChEIs, which are not considered to be disease modifying [161,166,167]. A meta-analysis on the cost-effectiveness of ChEIs concluded that on the basis of the current evidence the implications of the use of donepezil, rivastigmine or galantamine to treat patients with AD are unclear [167]. A meta-analysis of 29 controlled studies with ChEIs revealed a modest beneficial impact on neuropsychiatric and functional outcomes, but there seemed to be no difference between the different drugs in this regard [161] (I).

Memantine

Memantine, an non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, represents the second class of drugs approved for the specific symptomatic treatment of AD. The compound blocks the chronic hyper-activation of NMDA receptors that is thought to contribute to the symptomatology and pathogenesis of AD. A number of large-scale, randomized placebo-controlled trials with memantine were reported in patients with dementia.

Two studies were performed in patients with moderate-to-severe AD (I) [168,169], one of them in patients on stable treatment with donepezil [169]. Another randomized placebo-controlled study was performed in a mixed population of severe AD and severe VaD patients [170] (I). To date, no studies in mild AD have been published in peer-reviewed journals.

Recently, the available data were reviewed in a Cochrane meta-analysis, and the authors concluded from the published data that memantine at 6 months caused a clinically noticeable reduction in deterioration in patients with moderate to severe AD (I) [171]. This was supported by less functional and cognitive deterioration (I). Memantine was well tolerated when given alone, and also in the study where it was combined with donepezil (I) [169], and patients taking memantine appeared to be less likely to develop agitation. Whether memantine has any effect in mild to moderate AD is unknown [171].

With the exception of Winblad and Poritis [170], where no performance-based cognitive assessment was performed, all of these studies showed statistically significant superiority in the cognitive performance of memantine treatment of the patients over placebo using

the Severe Impairment Battery (SIB) (I). In the study of Winblad and Poritis, statistically significant effects were demonstrated in functional and global assessments (I). One of the trials in moderate-to-severe AD included a pharmaco-economic questionnaire and demonstrated a reduction in caregiver time and in total societal costs [172]. In the study by Tariot *et al.* [169], memantine showed positive effects on the behavioural disturbances, as assessed by the NPI (I).

Other drugs and interventions

There are several other treatment measures, which have been suggested for the treatment of AD, including gingko biloba, non-steroidal anti-inflammatory drugs (NSAIDs), oestrogens and statins. Three randomized, controlled trials with the gingko biloba extract Egb 761 were reported in AD. All of these studies involved mixed patient populations including those with AD, multi-infarct dementia, and in one study also patients with MCI, and the duration of treatment was up to 1 year. In two studies some parameters measuring cognition and behaviour significantly improved [173,174], although assessment methods in one and analysis of results in the other were not standard (II); in the third study there were no significant differences between gingko biloba and placebo (II) [175]. A meta-analysis of all published data in patients with dementia concluded that although overall there is promising evidence of improvement in cognition and function, the three more modern trials showed inconsistent results, and there is a need for a large trial using modern methodology [176] (I).

Anti-oxidants such as vitamin E have been studied to see if they can delay progression in patients with AD. In a large randomized, placebo-controlled study [177] in patients with moderate AD, vitamin E (given at the dose of 1000 IU, twice a day over 2 years) was found to significantly delay the time to a composite outcome of primary measures, indicative of clinical worsening, and fewer patients receiving vitamin E were institutionalized when compared with those receiving placebo (I). An attempted meta-analysis of randomized, controlled studies with vitamin E, which could find only the above-mentioned study, concluded that there is insufficient evidence for the efficacy of vitamin E in the treatment of AD, but there is sufficient evidence of possible benefit to justify further studies (I) [178]. Furthermore, a large meta-analysis of studies with vitamin E has shown that high-dosage (≤400 IU/day) vitamin E supplements may increase all cause mortality (I) [179].

Chronic exposure to non-steroidal anti-inflammatory drugs was suggested to be protective against AD in a retrospective analysis of epidemiological data [180]. In prospective studies, however, only indomethacin was suggested to stabilize cognition in a 6-month trial with a high drop out rate (I) [181–185]. Similarly, in a recent large, randomized, double-blind, placebo-controlled trial the cyclo-oxygenase-2 inhibitor rofecoxib, administered for 1 year, was not found to be effective in slowing the progression of AD [186] (I).

Statins used for the treatment of hypercholesterolaemia were found to decrease the prevalence of AD in two studies with retrospective or cross-sectional analysis [187,188]. This effect was found to be independent of indication bias (healthier cohort effect), but confined to those below the age of 80 years [189], and appeared to be modified by the presence of certain chronic medical conditions, in that the reduced risk of AD was observed amongst those with diseases such as hypertension and ischaemic heart disease [190]. Pravastatin showed no significant effect on cognitive function or disability [191]; atorvastatin showed significant effect on cognitive function at 6 months, but not at 12 months (III) [192]. A meta-analysis of available data concluded that there is no good evidence to recommend statins for reducing the risk of AD [193] (II).

In retrospective or cross-sectional analyses, post-menopausal use of oestrogens has been suggested to provide symptomatic benefits or reduce the risk of AD. Prospective, randomized, placebo-controlled studies, however, failed to demonstrate symptomatic beneficial effects of oestrogens, given up to 1 year, in women with mild to moderate AD, with or without hysterectomy (III) [194–196]. Although treatment with oestrogen elevated blood oestradiol and oestrone levels, there was no association between hormone levels and cognitive functioning after 1 year treatment [197]. A meta-analysis concluded that oestrogen replacement therapy is not indicated for cognitive improvement or maintenance for women with AD (I) [198]. Likewise, the results of the large, prospective, placebo-controlled 'Women's Health Initiative Memory Study' revealed that the use of oestrogen plus progestin in post-menopausal women, after a mean follow-up time of 4 years, was associated with a significantly increased risk of dementia [199] (I).

Meta-analyses for several other drugs including selegiline [200], nicergoline [201], nimodipine [202], and piracetam [203] concluded that there was not sufficient evidence to recommend their use in AD (II).

Recommendations: treatment of Alzheimer's disease

In patients with AD, treatment with ChEIs (donepezil, galantamine, or rivastigmine) should be considered at the time of diagnosis, taking into account expected therapeutic benefits and potential safety issues *(Level A)*. Realistic expectations for treatment effects and

potential side effects should be discussed with the patient and caregivers *(Good Practice Point)*.

In patients with moderate to severe AD, treatment with memantine can be considered, alone or in combination with a ChEI, taking into account expected therapeutic benefits and potential safety issues *(Level A)*. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers *(Good Practice Point)*.

Currently, there is insufficient evidence to consider the use of gingko biloba, anti-inflammatory drugs, nootropics, selegiline, oestrogens, vitamin E or statins in the treatment or prevention of AD *(Level A–C)*.

Treatment of vascular dementia

Cholinesterase inhibitors

After it became apparent that VaD is also associated with cholinergic deficits, ChEIs were investigated in patients with VaD. Along with patients with dementia due to pure or predominant CVD, vascular pathology can also co-exist with AD pathology, constituting mixed dementia. There have been two large, randomized, placebo-controlled studies with donepezil in patients with possible or probable VaD and one large, randomized, placebo-controlled study with galantamine in patients with VaD or AD combined with CVD. In the two donepezil studies, there was a significant improvement in the two main outcome parameters (cognitive functions and overall scales), ADL was significantly improved in one and showed a trend for improvement in the second study at the end of treatment period [204,205] (I). Results with galantamine were similar: patients on active drug had significant improvement on both primary end-points as well as in ADL and behavioural scales, when compared with placebo (I) [206]. Although the study was not powered to detect changes in the two diagnostic sub-groups (i.e. probable VaD and AD with CVD) the cognitive and overall scales showed significant improvement in AD with CVD group, whereas the differences when compared with placebo were not significant in the probable VaD sub-group [206]. An open label 6-month extension of this study suggested that the benefits may be maintained up to 1 year (III) [207]. A Cochrane meta-analysis concluded that there are some weak indications that galantamine is useful in dementia secondary to vascular damage, but it was associated with higher rates of adverse events and withdrawal (I) [208]. From existing trial data (III–IV), most of which are from open studies or *post-hoc* analyses, there is some evidence of benefit of rivastigmine in vascular cognitive impairment, but larger placebo-controlled double blind RCTs are needed [209]. A meta-analysis of the two studies with donepezil concluded that the evidence indicates that donepezil is well tolerated and can improve cognitive symptoms and functional ability in patients with vascular cognitive impairment [210] (I).

Memantine

Two randomized placebo-controlled 6 month studies are available in patients suffering from mild-to-moderate VaD [211,212], using 20 mg/day memantine. These studies included close to 900 patients and were designed according to modern standards, using the ADAS-Cog and a clinical global rating of change as primary efficacy endpoints. They were summarized by the recent Cochrane meta-analysis [171]: in the two studies memantine improved cognition and behaviour, but this was not supported by clinical global measures (I). Memantine was well tolerated (I). In a subgroup analysis of these studies [213], the cognitive benefit seemed to be more pronounced in the subgroup of patients with small vessel disease, which is more closely linked to AD (III). In addition, a number of short-term studies in less well-defined dementia populations have been published and were also reviewed in the Cochrane database, including studies in patients with VaD, and with dementia of un-specified type. In summary, there were beneficial effects on cognition [214], ADL [214], behaviour and global scales [214,215], and in global impression of change [214,215] (III–IV). The meta-analysis concluded that patients with mild to moderate VaD receiving memantine had less cognitive deterioration at 28 weeks, but the effects were not clinically discernible. The drug was well tolerated in general and the incidence of adverse effects was low [171].

Anti-aggregants and other drugs

There has been one small study with aspirin in patients with VaD. In this study, where the control group was no-treatment, patients treated with aspirin had a better outcome on a cognitive scale by the third year and also a significant improvement in cerebral perfusion in the first 2 years [216] (III). A meta-analysis of available data revealed that, despite its widespread use, there is still no evidence that aspirin is effective in treating patients with a diagnosis of VaD [217]. In a systematic review of clinical studies with pentoxifylline in VaD, four studies were identified fulfilling the criteria (being randomized, double-blind, and placebo-controlled), which revealed a trend toward improved cognitive function, but no statistically significant differences versus placebo [218] (I). When the calcium channel blocker nimodipine was tested in patients with 'multi-infarct dementia' in a large, randomized placebo-controlled

study, there were no significant benefits from nimodipine treatment over placebo in cognitive, functional and global assessments [219] (I). Furthermore, in a recent randomized placebo-controlled trial in patients with subcortical VaD there was no significant effect of nimodipine on the primary outcome measure, a global clinical assessment scale [220]. Studies with gingko biloba are mentioned above.

Recommendations: treatment of vascular dementia

ChEIs (currently evidence exists for donepezil) may be considered in patients fulfilling diagnostic criteria for VaD of mild to moderate severity *(Level B)*. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers *(Good Practice Point)*. In the presence of severe focal neurological deficits, the accuracy of diagnosis and expected therapeutic benefits should be carefully considered based on the presumed contribution of sensory-motor impairment versus cognitive deficits to the overall disability of the patient *(Good Practice Point)*.

There is insufficient evidence to consider the use of memantine in patients with vascular dementia *(Level B)*.

There is insufficient evidence to support the use of aspirin, gingko biloba, calcium antagonists or pentoxifylline in the treatment of VaD *(Level A–C)*.

Optimum management of vascular risk factors, including anti-platelet drugs, should be ensured, not only in vascular dementia, but also in patients with other dementias or co-morbid vascular disease *(Good Practice Point)*.

Treatment of Parkinson disease dementia and dementia with Lewy bodies

There are substantial cholinergic deficits both in Parkinson disease dementia (PD-D) and DLB, and ChEIs have been tested in both of these indications. In total, there have been 14 studies with four compounds (tacrine, donepezil, rivastigmine and galantamine) describing the use of ChEIs in patients with PD-D. All of these studies were small (all including <30 patients), three of them were placebo-controlled, eight were open studies and two case series. Improvement in cognition and neuropsychiatric symptoms, notably hallucinations, were described in the majority of these studies, worsening of parkinsonism was infrequent, and was mostly related to tremor [221,222]. A recent, large, placebo-controlled study with rivastigmine revealed that there was a statistically significant improvement in favour of rivastigmine in both primary endpoints with modest effect sizes [ADAS-cog for cognitive functions and ADCS Clinical Global Impression of Change (CGIC) for overall evaluation] as well as on all secondary measures. Adverse event profile was comparable with that seen in patients with AD, nausea and vomiting being the most frequent adverse events. In the rivastigmine group, 10% of patients reported subjective worsening of tremor, and 1.7% discontinued treatment for this reason. There were, however, no significant differences between rivastigmine and placebo in objectively measured motor scores [223] (I).

There have been eight studies reporting the use of ChEIs in DLB, involving tacrine, donepezil and rivastigmine. One of these studies was placebo-controlled, three were controlled, but not-randomized and others were case series. All studies but one reported improvement in cognitive functions, and half of them reported improvement in neuropsychiatric symptoms, commonly apathy and hallucinations; worsening of parkinsonism was rare [221]. In the large, prospective, randomized, placebo-controlled study, rivastigmine was found to be significantly better than placebo for one of the two main outcome parameters, cognitive speed score. There was also more improvement in the rivastigmine group for the other parameter, neuropsychiatric symptom score, in the last observation carried forward (LOCF) and observed case analyses, but not in the intention to treat (ITT) population. A responder analysis showed significantly greater reductions in NPI score in all three groups. Rivastigmine did not cause worsening of motor symptoms [224] (I).

The efficacy of memantine has not been formally assessed in DLB. The very limited case report literature available suggests that about two-thirds of DLB patients can tolerate memantine, but the symptomatic effects are variable. A significant minority experience worsening of agitation, paranoid delusions, and visual hallucinations when exposed to memantine [225,226] *(IV)*.

Recommendations: treatment of Parkinson disease dementia and dementia with Lewy Bodies

Treatment with ChEIs (currently evidence exists for rivastigmine) can be considered in patients with PD-D or DLB *(Level A)*, taking in account expected therapeutic benefits and potential safety issues. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers *(Good Practice Point)*.

There is insufficient evidence for the use of memantine in PD-D or DLB *(Level C)*.

Monitoring treatment with ChEIs and memantine in patients with dementia disorders

Monitoring treatment with ChEIs and memantine must be guided by the adverse event profiles and the clinical condition of the patient. Monitoring should include regular assessments of compliance, efficacy (cognitive functions, ADL, and behavioural symptoms), and side effects. In patients with known cardiac disease or significant cardoivascular risk factors a baseline ECG may be helpful for future monitoring purposes. There is no evidence from appropriately designed studies, which can guide the clinician in determining when to stop treatment.

Recommendations: monitoring treatment with ChEIs and memantine

Efficacy and side effects should be regularly monitored during treatment *(Good Practice Point)*. In case of rapid worsening or an apparent loss of efficacy discontinuation of treatment may be considered on a trial basis. Such patients should be closely monitored in order to assess withdrawal effects or worsening in which case the treatment should be re-started *(Level C)*.

Treatment of other dementia disorders

There have been no large, randomized, controlled studies in other types of degenerative dementias such as FTD, PSP, or CBD. In a small open and another small randomized, double-blind, placebo-controlled cross-over study, donepezil was not found to be effective in patients with PSP: there were at best modest effects on cognition but deleterious effects on ADL and mobility [227,228] (III). Selective serotonin reuptake inhibitors (SSRIs), particularly paroxetine, were used in two open and one small placebo-controlled cross-over study in patients with FTD. Whilst the open studies suggested some benefits, especially with regard to behaviour, the placebo-controlled study suggested no benefits, rather a deterioration of cognitive functions [229–231] (III).

Recommendations: treatment of other dementia disorders

There are no drugs available for the specific treatment of other degenerative dementias such as FTD, PSP and CBD *(Level C)*. A number of pathological conditions and systemic or central nervous system disorders can be associated with dementia. Their specific treatment must be based on the underlying etiology *(Good Practice Point)*.

Treatment of behavioural and psychological symptoms in dementia

It is the BPSD that contribute most to patient distress and carer burden and which frequently need treatment, sometimes urgently [38]. The sudden onset or worsening of symptoms such as hallucinations, insomnia, anxiety, agitation or aggression may be indicative of a superadded delirium, as may apathy or apparent depression. A physical re-evaluation should therefore always be the first stage of managing BPSD, paying close attention to recent changes in medications, signs of infection or systemic toxicity and evidence for parallel decline in cognitive function [42] (II). Drugs with potential to worsen confusion and psychosis, e.g. anticholinergics, are contra-indicated and should be avoided. Pre-intervention measures of behavioural disturbance or psychiatric symptoms should ideally be established using an appropriate rating scale to help assess treatment effects. Psychosocial interventions may be classified into cognition-orientated, behaviour-orientated, emotion-orientated and stimulation-orientated. There is limited randomized controlled trial evidence about their specific effects upon BPSD, and they tend to be applied in an individualized way or to group settings such as care homes. Education, information and support groups for patients and carers are helpful and should be offered by a skilled multidisciplinary team. Environmental manipulations can be important. A non-confrontational approach to dealing with delusions, wandering, agitation and aggression may be difficult for lone carers to maintain at home and there may be considerable value in providing day and respite care. Locked doors may reduce concerns about wandering although may increase patients attempts to escape from their surroundings. Specific behaviourial interventions may help reduce incontinence [8] (I), and good sleep hygiene may reduce insomnia.

The pharmacological management of BPSD is particularly problematic since very few placebo-controlled randomized controlled trials have been conducted [38]. A target symptom approach, e.g. a focus upon the reduction of agitation or psychosis, is preferable to attempting to reduce BPSD generally. Such fine distinctions may not always however be easy to apply in clinical practice.

There has been recent interest in the potential role of ChEIs for managing BPSD, e.g. rivastigmine reduced apathy, anxiety, hallucinations, delusions and irritability in DLB [224] (I) and galantamine reduced the emergence of neuropsychiatric features in mild to moderately impaired AD patients [152] (I). ChEIs are increasingly being used for BPSD in AD and other dementias. Although they may impact on BPSD they

may also need to be used in combination with other agents. The mainstay of pharmacological management of the symptom cluster agitation, delusions, hallucinations and irritability has been with neuroleptic agents such as haloperidol [232] and more recently with atypical antipsychotics, usually prescribed at a third to half the young adult dose. There is little consistent evidence that these drugs significantly modify unwanted behaviours other than aggression [233,234], and there is often a considerable side effect cost with sedation, weight gain, extrapyramidal features and falls. There are recent reports that atypical antipsychotic medication may be associated with an increased risk of cerebrovascular events and mortality in elderly patients with dementia [234–237]. However, a retrospective cohort study suggested that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death amongst elderly persons [238], and more information is required to help clinicians make judgements about risk-benefits in individual patients [38]. In DLB severe neuroleptic sensitivity reactions are associated with a two- to threefold increased mortality, and antipsychotics should only be used with great caution [239] (II). Thus, in all elderly patients with dementia, conventional as well as atypical antipsychotics should be used with caution and only after careful estimation of risk-benefits. Patients and caregivers should be informed about the expected therapeutic benefits and risks, and the treatment must be reviewed at close intervals. Carbamazepine [240] and valproic acid [241] have both been used to treat agitation in dementia, but with inconsistent effects (II).

The principles of treatment of depression in dementia are probably similar to that in non-demented people of the same age, although adequately conducted trials are lacking for most agents [242]. Selective serotonin reuptake inhibitors and other newer antidepressants are less likely to induce confusion and the anti-cholinergic effects typically seen with tricyclics. Emotional lability and compulsive behaviours have been reported to improve with SSRIs in FTD, and they may have similar effects in other dementias [38] (II).

Recommendations: treatment of behavioural and psychological symptoms in dementia

Clinicians treating patients with dementia should be aware of the importance of treating behavioural and psychiatric symptoms and the potential benefits for patient and carer *(Good Practice Point)*. Somatic co-morbidity should be considered as the cause of the symptoms *(Level C)*. Non-pharmacological and then pharmacological interventions for BPSD may both be effective and should be applied in a targeted symptom approach. The short, medium and long term benefits and adverse effects of such interventions should be regularly reviewed *(Level C)*. Antipsychotics, conventional as well as atypical, may be associated with significant side effects and should be used with caution *(Level A)*.

Counselling and support for caregivers

In patients with mild to moderate dementia, the assistance of a caregivers is necessary for many complex ADL, for instance travelling, financial matters, dressing, planning, and communication with family and friends. With the progression of the disease, increasing amounts of time must be spent on supervision. In patients with moderate to severe dementia caregivers often provide full time assistance with basic ADL, dealing with incontinence, bathing, feeding, and transfer or use of a wheelchair or walker. The majority of AD caregivers provide high levels of care, and at the same time they are burdened by the loss of their spouse or good friend. Caregivers are twice as likely to report physical strain and high levels of emotional stress as a direct result of caregiving responsibilities. They are more likely to report family conflicts, to spend less time with other family members, and to give up vacations, hobbies, and other personal activities. Caring for someone with dementia may also cause a high level of financial strain. Interventions developed to offer support for caregivers to patients living at home include counselling, training and education programmes, homecare/health care teams, respite care, information-technology based support. Many small quantitative or qualitative studies on the effectiveness of formal interventions seeking to support carers and alleviate the burden of caring have been published. Two meta-analyses [243,244] and one systematic review [245] on the effect of caregiver intervention have been published. In general, there is evidence from a few class II randomized trials to support the view that carers to patients with moderate to severe dementia benefit from structured support initiatives, which may reduce depressive symptoms [246,247]. There is a lack of appropriately designed randomized controlled studies, particularly in mild dementia [248]. As a dementia diagnosis is often established early in the course of the disease, intervention programs should also include support, counselling, and education activities for the patient, but there are no appropriately designed quantitative studies which have addressed the outcome of supportive interventions directed towards the patient with mild dementia.

Recommendations: counselling and support for caregivers

A dementia diagnosis mandates an inquiry to the community for available public health care support programs *(Good Practice Point)*. Specialist physicians should assess caregiver distress and needs at regular intervals throughout the course of the disease *(Level C)*. Caregivers should be offered support and counselling *(Level B)*. This includes information about patient organizations *(Good Practice Point)*.

Legal issues

Dementia involves a gradual loss of cognitive and physical capacities and thereby affects memory, decision-making and the ability to communicate one's wishes to others. For these reasons, a person with dementia may be unable to consent to treatment, take part in research or be involved in decisions relating to his or her care. In everyday life, problems may arise if the person with dementia wants to continue driving, make a will or carry out financial transactions. In many cases, it may be necessary to appoint a guardian or tutor [141].

In almost all countries specialist physicians play an important role in the assessment of mental capacity or incapacity, as they may be required to make an assessment of capacity prior to medical treatment, provide a medical certificate at a lawyer's request as to a particular capacity unrelated to medical treatment, witness or otherwise certify a legal document signed by someone, or give an opinion as to a particular legal capacity which is relevant to court proceedings [249].

Although assessing a person's capacity does not require a high degree of legal knowledge, the doctor should understand the relevant legal terms in broad terms as the doctor's role is to provide information on which an assessment of the person's capacity can be based [249].

Recommendations: legal issues

Specialist physicians responsible for the care of patients with dementia should be aware of national legislations relating to assessment of capacity, consent to treatment and research, disclosure of diagnosis, and advance directives *(Good Practice Point)*.

A diagnosis of dementia is not synonymous with mental incapacity, as a determination of capacity should always involve a 'functional' analysis: does the person possess the skills and abilities to perform a specific act in its specific context? *(Good Practice Point)*.

Driving

At the time of diagnosis, a patient's driving skills should also be assessed and discussed, since advice about driving is an essential part of the management of dementia [250] and because patients with AD who continue to drive are at an increased risk for crashes [251] (I). In particular, drivers with mild AD (CDR 1) pose a significant traffic safety problem [252]. There is, however, considerable variability across Europe with respect to the national driving regulations for patients suffering from disorders associated with dementia, the role of specialist physicians in the assessment of driving capabilities, and the confidentiality of medical data with regard to third parties, such as national driving licence authorities [253].

Recommendations: driving

Assessment of driving ability should be done after diagnosis and be guided by current cognitive function, and by a history of accidents or errors whilst driving. Particular attention should be paid to visuo-spatial, visuo-perceptual, praxis and frontal lobe functions together with attention. Advice either to allow driving, but to review after an interval, to cease driving, or to refer for retesting should be given *(Level A)*. This decision must accord with the national regulations of which the specialist physician must be aware *(Good Practice Point)*.

Conclusion

The assessment, interpretation, and treatment of symptoms, disability, needs, and caregiver stress during the course of AD and other dementia disorders require the contribution of many different professional skills. Ideally, the appropriate care and management of patients with dementia requires a multidisciplinary and multi-agency approach. Neurologists should be involved together with old age psychiatrists and geriatricians in the development and leadership of multidisciplinary teams responsible for clinical practice and research in dementia. This review contributes to the definition of standards of care in dementia by providing evidence for important aspects of the diagnosis and management of dementia.

Conflicts of interest

Potential conflicts of interest: Gunhild Waldemar, Bruno Dubois, Murat Emre, Ian McKeith, Philip Sheltens, Peter Tariska, and Bengt Winblad have received speaker's and/or consultancy honoraria from

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The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale

Two methods to assess fluctuating confusion in dementia

M. P. WALKER, G. A. AYRE, J. L. CUMMINGS, K. WESNES, I. G. McKEITH, J. T. O'BRIEN and C. G. BALLARD

Background The identification of fluctuating confusion is central to improving the differential diagnosis of the common dementias.

Aims To determine the value of two rating scales to measure fluctuating confusion.

Method The agreement between the clinician-rated scale and the scale completed by a non-clinician was determined. Correlations between the two scales were calculated; variability in attention was calculated on a computerised cognitive assessment and variability in delta rhythm on an electroencephalogram (EEG).

Results The Clinician Assessment of Fluctuation and the computerised cognitive assessment were completed for 155 patients (61 Alzheimer's disease, 37 dementia with Lewy bodies, 22 vascular dementia, 35 elderly controls). A subgroup (n=40) received a further evaluation using the One Day Fluctuation Assessment Scale and an EEG. The two scales correlated significantly with each other, and with the neuropsychological and electrophysiological measures of fluctuation.

Conclusions Both scales are useful instruments for the clinical assessment of fluctuation in dementia.

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Fluctuating confusion, accompanied by disturbances of consciousness, is an important clinical symptom, with a frequency of 80–90% in dementia with Lewy bodies (DLB) (Byrne *et al*, 1989; McKeith *et al*, 1996), 40% in vascular dementia and 20% in Alzheimer's disease (Kolbeinsson & Jonsson, 1993). Accurate assessment has depended upon clinical judgement, with poor levels of interrater reliability (Mega *et al*, 1996; Litvan *et al*, 1998). The electroencephalogram (EEG) has been used as a standard tool for staging alterations in consciousness from pathological (e.g. delirium) and physiological causes, while numerous reports describe flurries of slow-wave activity in DLB patients experiencing episodic confusion (Yamamoto & Imai, 1988). McKeith *et al* (1996) highlight the importance of attentional impairments in fluctuating confusion, while pronounced deficits of attention are evident in DLB sufferers (Ayre *et al*, 2000). This present study investigates the value of two new scales to measure fluctuating confusion, by determining the agreement between a clinician's assessment and a scale completed by a non-clinician; and by evaluating correlations with neuropsychological and electrophysiological markers.

METHOD

Clinician Assessment of Fluctuation (Appendix I)

This is a short scale, designed for use by experienced clinicians. It consists of a series of screening questions, put to an informant, regarding fluctuating confusion and impaired consciousness during the month prior to the assessment. Fluctuating confusion is rated as present if the informant is able to give a clear-cut example. If present, the frequency and duration of episodes of fluctuating confusion are both rated on a scale of 0–4, and these two scores are multiplied together to produce a severity score from 0–12 (0 representing no fluctuating confusion, 12 representing severe fluctuating confusion; a score of 16 would signify a continuous clouded state, which, by definition, would denote no fluctuation). In the current study, extensive discussions took place between the three clinician raters (I.McK., C.B., J.O'B.), focusing upon illustrations from previously assessed cases, in order to achieve consistency in the way that these criteria were applied. This scale has been used previously in Newcastle as part of the diagnostic approach, and has achieved good diagnostic accuracy for DLB (sensitivity 83%, specificity 91%) against post-mortem diagnosis (McKeith *et al*, 2000).

One Day Fluctuation Assessment Scale (Appendix 2)

This consists of seven items of confusional behaviour (falls, fluctuation, drowsiness, attention, disorganised thinking, altered level of consciousness, communication), scores for which are summed to provide a severity score for fluctuating confusion ranging from 0 to 21. It is based on a validated delirium assessment scale (Inouye *et al*, 1990), with additional items selected from the Barthel index (communication question) (Mahoney *et al*, 1965) and the 'fluctuation' component of the DLB clinical diagnostic criteria (McKeith *et al*, 1996). In the current study, the scale was completed by a postgraduate researcher (M.W.), blind to the operationalised clinical diagnosis and the Clinician Fluctuation Assessment score. This scale focuses upon fluctuating confusion over the day before the assessment, and takes approximately 15 minutes to administer.

Subjects and assessment

Patients were recruited from a dementia case register of consecutive referrals to old age psychiatry services in Tyneside (UK), and the spouses of the patients are recruited as healthy elderly volunteers. All patients were assessed by a structured psychiatric history (History and Aetiology Schedule; Dewey *et al*, 1992), the Mini-Mental State Examination (MMSE; Folstein *et al*, 1975), a standardised physical examination which incorporated the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn *et al*,

1987) and a validated instrument to evaluate psychotic symptoms (Columbia University Scale for psychopathology in Alzheimer's disease; Devanand *et al*, 1992), and fluctuating confusion was evaluated by the Clinician Assessment of Fluctuation.

Diagnosis was undertaken separately, several months after the assessments were completed, at a consensus meeting between the three senior clinicians (I.McK., J.O'B., C.B.). Patients with DLB were diagnosed according to the internationally agreed consensus criteria (McKeith *et al*, 1996), patients with Alzheimer's disease were diagnosed according to the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (McKhann *et al*, 1984), an operationalised clinical diagnosis of vascular dementia was made using the criteria of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (Roman *et al*, 1993).

All participants also received a computerised neuropsychological assessment using the COGDRAS-D battery (Simpson *et al*, 1991). The main parameters used in the present study were choice reaction time (each time 'YES' or 'NO' was presented in the centre of the screen the participant was required to press the corresponding 'YES' or 'NO' button as quickly as possible) and digit vigilance reaction time (a digit was displayed constantly on the right-hand side of the screen and 90 digits were serially presented in the middle of the screen; participants were required to press 'YES' every time the central digit matched the right-hand side digit). Within-trial variability (standard deviation) of these measures was assessed in single trials, all lasting approximately 90 seconds. The choice reaction time and vigilance reaction time trials were administered at another visit, separate from the diagnostic assessment, by a different rater (M.W.).

As it was not feasible with the available staff resources to complete a more comprehensive evaluation for all patients, a subgroup of 40 subjects (15 with DLB, 15 with Alzheimer's disease and 10 healthy elderly volunteers) from this sample received a more detailed assessment. This included an additional evaluation of fluctuation with the One Day Fluctuation Assessment Scale and an evaluation of EEG delta-band frequency (0–3.9 Hz) variability over 90 seconds. Seventeen primary channel electrodes were used, placed according to the international 10–20 system, which recorded EEG from Fp_1, Fp_2, F_z, F_3, F_4, C_z, C_3, C_4, P_z, P_3, P_4, T_3, T_4, T_5, T_6, O_1 and O_2 linked to mastoid electrodes. Eye movement compensation was derived from nasion-linked mastoid electrodes. Signals were amplified using a SynAmps and Neuroscan™ acquisition system. The mean spectral frequency was obtained resting with eyes open and resting with eyes closed. The variability (s.d.) in frequency from this mean was used as a measure of fluctuating electrocortical activity. In these patients the attention tasks, the EEG and the One Day Fluctuation Assessment Scale were all assessed on the same day.

The tests were approved by the Joint Ethics Committee of Newcastle and North Tyneside Health Authority and the University of Newcastle upon Tyne. Following full explanation and discussion of the study, the patients and the healthy volunteers gave their consent to the assessment, with additional assent from the next of kin for all patients with cognitive impairments.

Analysis of data

Non-parametric statistical analysis was applied, since the rating scale yielded ordinal data. A Spearman's rank–order correlation was used in the assessment of associations between the two assessment scales for fluctuation. Cronbach's α was used to assess internal consistency of the Fluctuation Assessment Scale. Optimal cut-off values were obtained following a receiver operating characteristics (ROC) analysis according to the method of Altman (1995), and used to calculate the sensitivity and specificity with which the different groups could be distinguished, both in the overall sample and in the subsample with the more detailed evaluation. All analyses were performed using the SPSS package (SPSS, 1992).

RESULTS

Although all diagnoses were clinical, the patients came from a case register in which the specificity of clinical diagnosis had been established against neuropathological examination (McKeith *et al*, 2000).

One hundred and fifty-five people were studied (61 with Alzheimer's disease, 37 with DLB, 22 with vascular dementia, 35 elderly controls). The age, gender and performance on the MMSE schedule for the different diagnostic groups are shown in Table 1.

In the total sample of 155 patients, the Clinician Assessment of Fluctuation score was strongly correlated with the

Table 1 Clinical and experimental variables

	Alzheimer's disease patients	DLB patients	Vascular dementia patients	Elderly controls
Clinical and experimental variables in the overall sample[1]				
Age, years (s.d.)	79.7 (6.5)	77.9 (7.3)	76.6 (6.8)	75.4 (6.8)
MMSE (s.d.)	17.8 (3.5)	17.5 (5.1)	17.8 (4.3)	28.2 (1.8)
% Female	62	54	59	69
Median clinical fluctuating confusion score (IQR)	0 (0–0)	8 (6–9)	3 (0–4)	0 (0–0)
Clinical and experimental variables in the comprehensively assessed subgroup[2]				
Age, years (s.d.)	78.8 (3.9)	78.7 (6.6)		77.5 (4.5)
MMSE (s.d.)	18.0 (0.9)	17.3 (5.0)		29.4 (3.2)
% Female	47	40		60
Median clinical fluctuating confusion score (IQR)	0 (0–3)	9 (6–12)		0 (0–0)

1. Sample total n=155; patients with: Alzheimer's disease, n=61; DLB, n=37; vascular dementia, n=22; elderly controls, n=35.
2. Sample total n=40; patients with: Alzheimer's disease, n=15; DLB, n=15; vascular dementia, n=0; elderly controls, n=10.
IQR, Interquartile range; MMSE, Mini-Mental State Examination; DLB, dementia with Lewy bodies.

neuropsychological measures of fluctuation (choice reaction time variability and Clinician Assessment of Fluctuation $r=0.73$, $P<0.0001$; vigilance reaction time variability and Clinician Assessment of Fluctuation $r=0.50$, $P<0.001$). In the subgroup of 40 patients who received a more detailed evaluation, the Clinician Assessment of Fluctuation correlated significantly with the electrophysiological measures of fluctuations in delta-band frequency on EEG (resting, eyes open, $r=0.52$, $P<0.001$; resting, eyes closed, $r=0.43$, $P<0.006$), and correlated strongly with the independently rated One Day Fluctuation Assessment Scale ($r=0.88$, $P<0.0001$).

In this group of 40 patients, the One Day Fluctuation Assessment Scale also correlated strongly with the neuropsychological and electrophysiological measures of fluctuation (choice reaction time variability and One Day Fluctuation Assessment Scale $r=0.70$, $P<0.0001$; vigilance reaction time variability and One Day Fluctuation Assessment Scale $r=0.52$, $P<0.001$; fluctuation in delta-band frequency and One Day Fluctuation Assessment Scale: resting, eyes open $r=0.60$, $P<0.0001$; resting, eyes closed $r=0.38$, $P<0.01$).

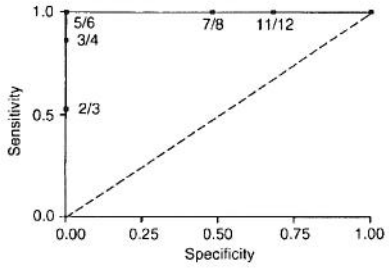

Fig. 1 Receiver operating characteristics analysis for Clinician Assessment of Fluctuation scale score.

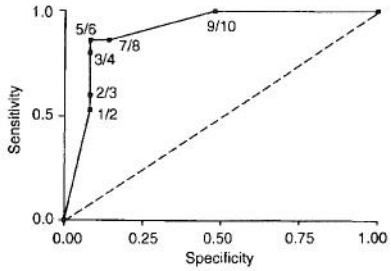

Fig. 2 Receiver operating characteristics analysis for One Day Fluctuation Assessment Scale score.

A reliability coefficient analysis between the seven items of confusional behaviour on the One Day Fluctuation Assessment Scale indicated good internal consistency (Cronbach's $\alpha=0.78$).

Distinguishing diagnostic groups

In the subsample of 40 patients, an ROC analysis identified an optimal cut-off value of $\geqslant 5$ for the Clinician Assessment of Fluctuation (see Fig. 1). Using this threshold, all 15 DLB patients, but none of the controls or Alzheimer's disease sufferers, had significant fluctuation (DLB *v.* Alzheimer's disease, sensitivity 100%). A further analysis, using the same cut-off point in the total sample of 155 patients, indicated that 30 (81%) of the DLB patients, four (18%) of the vascular dementia patients and five (8%) of the Alzheimer's disease patients had significant fluctuation (DLB *v.* Alzheimer's disease, sensitivity 81%, 95% CI 73.2–88.8; specificity 92%, 95% CI 86.6–97.4; DLB *v.* vascular dementia, sensitivity 81%, 95% CI 71–91; specificity 82%, 95% CI 72.2–91.8).

In the subgroup of 40, an ROC was also used to determine the optimal threshold for the One Day Fluctuation Assessment Scale (Fig. 2). A score of $\geqslant 6$ achieved the best discrimination, with 14 of the 15 (93%) DLB patients, but only two (13%) of the Alzheimer's disease sufferers and none of the controls, scoring above this threshold (sensitivity 93%, 95% CI 83.9–100, specificity 87%, 95% CI 75–99).

Direct agreement between scales

A 90% agreement was achieved for the presence of significant fluctuating confusion between the expert clinician-rated scale and the One Day Fluctuation Assessment.

DISCUSSION

Main findings

The current study indicates that structured clinical assessment methods are helpful for the assessment of fluctuating confusion in people with dementia. The two instruments, the Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale, show excellent agreement with each other, have good internal consistency and were significantly associated with neuropsychological and electrophysiological markers of fluctuation. Although there is no clear 'gold standard' against which to evaluate a new instrument, the strong correlation between the scale completed by the non-clinician and the semi-standardised expert clinician's rating, as well as the significant correlation between both scales and the neuropsychological and electrophysiological markers suggest that these scales are capturing the essence of fluctuating confusion.

Two clinical assessment instruments

The two scales are brief and easy to administer, and complement each other well. The Clinician Assessment of Fluctuation evaluates fluctuating confusion over the month prior to the interview, on the basis of an interview with an informant, and needs to be completed by an experienced clinician. It provides a method for standardising the clinical decision-making process. The One Day Fluctuation Assessment Scale evaluates fluctuating confusion over the 24 hours prior to the assessment, again on the basis of an interview with an informant. It can be completed by a variety of mental health professionals or research staff, and hence is well suited to research studies. The scoring system gives it good face validity for measuring change during intervention trials.

Future studies

Interrater reliability has not yet been determined for either scale, although the structured nature of the instrument should have advantages over expert clinical judgement alone. Within the current study, extensive discussion took place between the three raters, working through previously assessed cases in order to achieve consistent scores. The same procedure is recommended for groups of clinicians intending to use the Clinician Assessment of Fluctuation, as an aid to clinical evaluation.

Potential value for differential diagnosis

A preliminary evaluation was also undertaken to assess the potential value of the two scales in distinguishing between the different dementia groups. Just on the basis of fluctuation assessments, both scales were able to achieve a sensitivity and specificity in excess of 80%. Although there is a potential tautology for the Clinician Assessment of Fluctuation, as this information was used as part of the diagnostic procedure, the One Day Fluctuation Assessment Scale was completed independently of, and blind to, the diagnostic process, by a separate rater. It is therefore suggested that using this method to standardise the evaluation of fluctuating confusion, within the framework of the consensus clinical criteria for DLB, could have a significant impact upon diagnostic accuracy. This is potentially important, as poor sensitivity for the diagnosis of DLB has been a problem in some studies (Mega *et al*, 1996; Litvan *et al*, 1998), with the accurate identification of fluctuating confusion highlighted as a major difficulty. This is also highly relevant to everyday clinical practice, as good case identification is essential to optimise clinical management and to avoid neuroleptic sensitivity reactions.

APPENDIX 1. CLINICIAN ASSESSMENT OF FLUCTUATION

'Fluctuating confusion' or 'impaired consciousness' are identified by a positive answer to either one or both of the following questions.

(a) Does the patient ever have spontaneous impaired alertness and concentration, i.e. appear drowsy but awake, look dazed, not be aware of what is going on around? (Clear examples demonstrating impaired consciousness with variations in performance/cognition are required to receive a positive rating.) Have these episodes occurred within the last month?

(0=no; 1=yes; 9=not known)

(b) Has the level of confusion experienced by the patient tended to vary a lot recently from day to day or week to week? Has it become worse then improved for a while, i.e. been up and down? (Significant fluctuation is regarded as present if distinct examples of differences in performance/cognition can be given on at least two occasions over the past month.)

(0=no; 1=yes; 9=not known)

If a positive rating of fluctuating confusion is present, a severity rating should be made.
Frequency of fluctuating confusion:Total score index

Frequency of fluctuating confusion

1=1 per month
2=monthly–weekly
3=weekly–daily
4=≥daily

Duration of fluctuating confusion

0=seconds
1=≤5 minutes
2=5 minutes–1 hour
3=≥1 hour
4=≥1 day

Summary scores

Severity from Scale 1 ____
Severity from Scale 2 ____

APPENDIX 2. ONE DAY FLUCTUATION ASSESSMENT SCALE

1. Falls

Has the patient fallen today?

Yes ____ **(1)** No ____ **(0)**

If yes, how many times? ____

Has the patient had any 'near falls' today? (a near fall is when the patient almost fell but was saved by somebody else or objects such as furniture or a walking aid)

Yes ____ **(1)** No ____ **(0)**

If yes, how many times? ____

2. Fluctuation

(a) Has the patient had a period or periods today when he/she seemed to be confused and muddled and then a period or periods when he/she seemed to be improved and functioning better?

Yes ____ **(1)** No ____ **(0)**

If yes, how much of the day was he/she confused?

(i) 25% (¼) of the day or less ____ **(1)**

(ii) 25–75% (¼–¾) of the day ____ **(2)**

(iii) 75% (¾) or more of the day ____ **(3)**

(b) How great was the difference today between the worst period of function and the best period of function?

(i) a slight degree of variation ____ **(0)**

(ii) a moderate degree of variation which had a clear effect on his/her ability to function at the same level throughout the day ____ **(1)**

(iii) a marked degree of variation which had a large effect on his/her ability to function at the same level throughout the day ____ **(2)**

Give examples of worst period and best period of functioning:

Worst:
Best:

3. Drowsiness

Has the patient been excessively drowsy today?

Yes ____ **(1)** No ____ **(0)**

If yes, for how much of the day was he/she sleeping?

(i) 25% (¼) of today or less ____ **(1)**

(ii) 25–75% (¼–¾) of today ____ **(2)**

(iii) 75% (¾) or more of today ____ **(3)**

Were there any periods when he/she was unarousable (blackouts) today?

Yes ____ **(1)** No ____ **(0)**

4. Attention

Did the patient have difficulty focusing attention (for example, was he/she easily distractible, or did he/she have difficulty keeping track of what was being said) throughout the day?

Yes ____ **(1)** No ____ **(0)**

5. Disorganised thinking

Was the patient's thinking disorganised or incoherent (for example, with rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject) throughout the day?

Yes ____ **(1)** No ____ **(0)**

6. Altered level of consciousness

Overall, how would you rate this patient's level of consciousness today?

(i) Alert (normal) ____ **(0)**

(ii) Lethargic (drowsy, easily aroused) ____ **(1)**

(iii) Stuporous (difficult to arouse) ____ **(2)**

7. Communication

(a) How well does the patient understand what you communicate to him/her (you may use speaking, writing or gesturing)?

(i) Understands almost everything you communicate ____ **(0)**

(ii) Understands some of what you communicate ____ **(1)**

(iii) Understands almost nothing of what you communicate ____ **(2)**

(b) How well does the patient communicate (by speaking, writing or gesturing)?

(i) Well enough to make him/herself easily understood at all times throughout the day ____ **(0)**

(ii) Can be understood sometimes or with some difficulty ____ **(1)**

(iii) Can rarely or never be understood for whatever reason ____ **(2)**

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CLINICAL IMPLICATIONS

- Brief standardised clinical scales are useful for identifying fluctuating confusion in patients with dementia.
- Standardised fluctuation scales may improve the accuracy of differential diagnosis between dementia with Lewy bodies and Alzheimer's disease.
- An electroencephalogram examination also contributes important information to the assessment of fluctuating confusion.

LIMITATIONS

- Not all diagnoses have been neuropathologically confirmed.
- No interrater reliability data were collected.
- Data from the One Day Fluctuation Assessment Scale were only collected for the subgroup of 40 patients who had a more detailed evaluation.

M. P. WALKER, BSc, C. G. BALLARD, MRCPsych, Medical Research Council, Neurochemical Pathology Unit, Newcastle upon Tyne; G. A. AYRE, PhD, K. WESNES, PhD, Human Cognitive Neuroscience Department, University of Northumbria; J. L. CUMMINGS, MD, Professor of Neurology, University of California; I. G. McKEITH, FRCPsych, J. T. O'BRIEN, MRCPsych, Department of Old Age Psychiatry, University of Newcastle upon Tyne

Correspondence: C. G. Ballard, Medical Research Council, Neurochemical Pathology Unit, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, UK. Tel: 0191 273 5251; fax: 0191 272 5291; e-mail: c.g.ballard@ncl.ac.uk

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chapter 10

Progression of cognitive impairment and duration of illness

Zuzana Walker

Progression of cognitive impairment

Although the illness fluctuates markedly in the short term, patients with dementia with Lewy bodies (DLB) experience a progressive cognitive and functional decline in the long term, which leads to severe dementia and death. Compared with the other aspects of DLB, relatively few studies have specifically focused on the longitudinal course of the illness. One of the first to do so showed that patients with severe DLB had a greater annual rate of decline in verbal fluency than patients with Alzheimer's disease (AD) or patients with vascular dementia (VaD) (Ballard et al, 1996). In addition, the annual mean reduction in Cambridge Cognitive Examination (CAMCOG) score was greater in the DLB group (−27.0 points vs −13.2 points in AD), but this did not reach statistical significance, most probably due to the small numbers of DLB patients (n=7). In a much larger autopsy cohort of moderately demented patients (40 DLB patients and 148 AD patients at baseline assessment), the annual decline in Mini-Mental State Examination (MMSE) score was significantly greater for DLB patients (5.8 points per year) than AD patients (4.1 points per year) (Olichney et al, 1998). However significant differences in rate of decline on MMSE score were observed only at 1- and 2-year follow-up but not at 3-year follow-up. The difference became significant again at 4-year follow-up, but by then there were only four patients in the DLB group.

In contrast, more recent studies (Gomez-Isla et al, 1999; Lopez et al, 2000; Ballard et al, 2001; Helmes et al, 2003) did not find significant differences in

rate of cognitive decline between DLB and AD. The first of these studi (Gomez-Isla et al, 1999) measured the annual rate of change of the Blesse Dementia Scale and of the Activities of Daily Living (ADL) scale in 53 A patients and in 8 'mixed' (AD plus Lewy bodies) and 4 'pure' (no or minim concomitant AD pathology at autopsy) DLB cases. No significant differen was observed between the three groups in the annual rate of decline on tl Blessed Dementia Scale, DLB cases had significantly higher rates of decline c the ADL scale than AD cases, but clearly the number of DLB cases was ve small. The second study (Lopez et al, 2000) compared the cognitive and fun tional decline (expressed as the percentage of patients scoring less than 9/ on an MMSE and more than 12 points on the Blessed Dementia Score for Al of a large autopsy-confirmed cohort of moderately demented patients wi AD+LB ('mixed' DLB) and AD. No significant difference in either function or cognitive decline was found but patients with 'mixed' DLB had a short time to institutionalization. Likewise, the Newcastle group (Ballard et 2001), in a study that was much larger than their first study, found no sign icant difference in the annual rate of decline between DLB and AD patien on MMSE or CAMCOG scores (MMSE: −4.3 vs −4.9; CAMCOG: −11.9 −15.0). The most recent study (Helmes et al, 2003) compared the rates deterioration on the Extended Scale for Dementia (ESD; an extension of tl Mattis Dementia Rating Scale with possible scores from 0 to 250) of 15 cas of AD, 7 cases of DLB ('pure' DLB) and 8 cases of 'mixed' DLB. All the cas had autopsy-verified diagnoses. The most severe rate of decline in ESD scor over time was in the 'mixed' DLB group, but nevertheless statistically the was no significant difference between the three dementia groups, perha because of the small sample sizes and low statistical power. All groups dete orated at a rate of approximately 2 ESD points per month. A substanti variability was recorded between individuals in all three groups. In a lar Memory Clinic cohort of clinically diagnosed moderately demented patier (mean MMSE score at baseline: DLB 19.2 vs AD 19.0), we observed no sign icant difference between DLB and AD in annual decline of MMSE and CAI COG scores at 1, 2, 3 and 4 years (Walker et al, unpublished). Although Dl patients were more impaired at baseline as measured by the Instrumen Activities of Daily Living (IADL) scale, there was no difference in the rate decline on this scale over the next 4 years.

A small prospective autopsy study (Perry et al, 2003) investigated tl longitudinal course of illness and the levels of butyrylcholinesterase in tl gray matter of Brodman area 20. In this study of 9 DLB patients, there wa

significant association between lower levels of butyrylcholinesterase and a slower rate of cognitive decline as measured by MMSE. Butyrylcholinesterase is one of the two enzymes responsible for the breakdown of acetylcholine in neuronal synapses, and therefore high levels may contribute to the severe cholinergic deficit observed in DLB patients. The study suggested that variation in the butyrylcholinesterase levels might be a factor that influences the rate of progression of illness.

In summary, increasingly the evidence indicates no real difference between DLB and AD in the overall rate of progression of cognitive decline. However, mean values from large studies may conceal disease heterogeneity, and it is recognized for instance that a proportion of DLB patients have a very rapid disease course (Armstrong et al, 1991). Factors that might influence longitudinal course, such as biological markers, symptomatology, gender, age at onset of symptoms and treatment, need to be further investigated.

Age at onset and duration of illness

The position with regard to survival is even less clear than the rate of cognitive decline. The majority of studies are retrospective and based on autopsy series. Consequently, there is the possibility of selection bias. Survival in DLB has been reported to be anything from a few months to 20 years.

In a case series of five 'pure' DLB patients (Lippa et al, 1994), the mean age at onset of illness was 50 years, with a mean duration of illness of 5 years. In another series, 11 cases of diffuse Lewy body disease without neurofibrillary tangles or neuritic senile plaques, the mean age of onset of dementia was 69 years and the duration of illness was 7.7 years (Del Ser et al, 1996). A series of nine 'pure' DLB cases had a mean age at onset of illness of 61.7 years and a mean duration of illness of 8.6 years (Hely et al, 1996). However, a study of 13 'pure' DLB cases with a mean age at onset of 68 years reported a much longer mean duration of illness, namely 10 years (Gomez-Tortosa et al, 1999).

Looking at individual studies of neuropathologically defined cases with mixed pathology (DLB with variable degrees of concomitant AD pathology), the mean age at onset of illness in different cohorts varied between 59 and 79 years and the duration of illness ranged from 1.8 to 9.5 years. The wide ranges of both age at onset and duration of illness highlight the difficulty of drawing conclusions from preselected samples. A meta-analysis (Cercy and Bylsma 1997) of 150 cases reported in the literature derived the same mean survival for 'pure' DLB and 'mixed' DLB (approximately 6 years).

Numerous autopsy studies have compared the duration of illness in DLB and AD, with conflicting results. Some studies (Perry et al, 1990; McKeith et al, 1992, 1994; Olichney et al, 1998; Ballard et al, 1999; Singleton et al, 2002) reported shorter survival in DLB than AD (Table 10.1). However, other studies (Hansen et al, 1990; Klatka et al, 1996; Samuel et al, 1996; Weiner et al, 1996; Papka et al, 1998; Heyman et al, 1999; Del Ser et al, 2001) found no difference in duration of illness between DLB and AD (Table 10.2). In the latest of these studies (Del Ser et al, 2001), the survival was shorter in 'pure' DLB by comparison with 'mixed' DLB (7.7 vs 11 years).

In a study that compared the survival of AD and DLB patients from an unselected cohort of all patients with a clinical diagnosis of dementia referred to a district general hospital over a period of 1 year (Walker et al, 2000) there

Table 10.1 Autopsy studies showing shorter mean duration of illness in DLB than in AD

	DLB		*AD*		*PD*	
Study	*Cases*	*Years*	*Cases*	*Years*	*Cases*	*Years*
Perry et al (1990)	18	3.3	46	5.6	12	7.9
McKeith et al (1992)	21	1.8	37	4.8		
McKeith et al (1994)	20	3.1	21	5.5		
Olichney et al (1998)	40	7.7	148	9.3		
Ballard et al (1999)	40	4.3	40	5.6		
Singleton et al (2002)	76	3.5	194	5.3		

Table 10.2 Autopsy studies showing no difference in mean duration of illness between DLB and AD

	DLB		*AD*	
Study	*Cases*	*Years*	*Cases*	*Years*
Hansen et al (1990)	13	3.0	23	3.5
Klatka et al (1996)	28	9.5	58	9.2
Samuel et al (1996)	14	6.8	12	6.9
Weiner et al (1996)	24	7.5	58	8.5
Papka et al (1998)	18	9.6	21	11.1
Heyman et al (1999)	27	3.8	74	3.6
Del Ser et al (2001)	29	9.7	35	9.6

were no differences between the AD and DLB groups in age of onset (78.1 vs 75.8 years), age at death (84.3 vs 81.7 years) and survival rate. Survival data gathered from a larger cohort of unselected demented patients that have presented to our psychiatric services over a period of 2 years (n=183) again showed no significant difference in the survival rates of AD and DLB patients (Figure 10.1) (Walker, unpublished data).

Only one published study has examined the influence of the apolipoprotein E gene on survival rates in patients with DLB (Singleton et al, 2002). In this study, the survival rates were reduced by the presence of the ε4 allele. DLB patients either heterozygous or homozygous for ε4 had significantly higher mortality rates than patients without the ε4 allele.

The conclusion therefore has to be that at present there is no overall convincing evidence regarding age of onset and duration of illness. Only large, prospective, longitudinal studies will be able to determine whether there is no difference between DLB and AD or whether survival really is worse in DLB than in AD. It is possible that disease heterogeneity in DLB is greater than in AD, with some patients surviving a significantly shorter time, while others fare much as AD patients do.

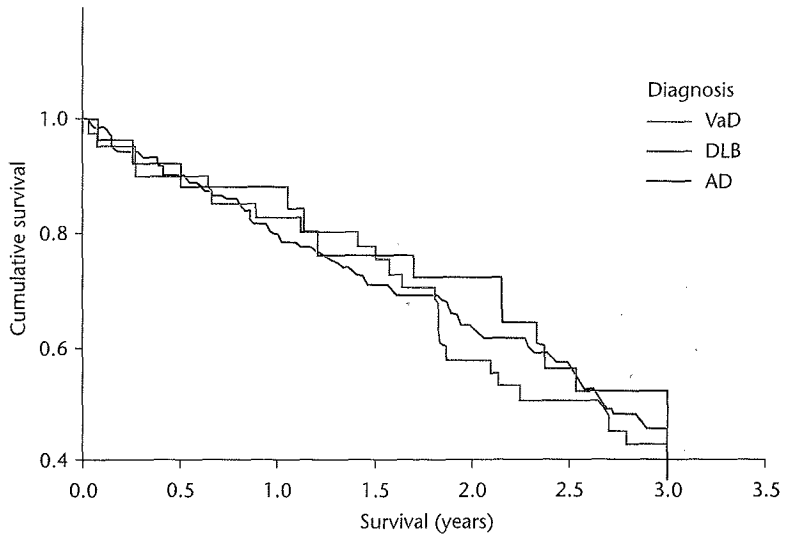

Figure 10.1 *Kaplan–Meier survival curves for AD, DLB and Vascular dementia patients over three years.*

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Genome-Wide Association Studies in Alzheimer Disease

Stephen C. Waring, DVM, PhD; Roger N. Rosenberg, MD

The genetics of Alzheimer disease (AD) to date support an age-dependent dichotomous model whereby earlier age of disease onset (<60 years) is explained by 3 fully penetrant genes (*APP* [NCBI Entrez gene 351], *PSEN1* [NCBI Entrez gene 5663], and *PSEN2* [NCBI Entrez gene 5664]), whereas later age of disease onset (≥65 years) representing most cases of AD has yet to be explained by a purely genetic model. The *APOE* gene (NCBI Entrez gene 348) is the strongest genetic risk factor for later onset, although it is neither sufficient nor necessary to explain all occurrences of disease. Numerous putative genetic risk alleles and genetic variants have been reported. Although all have relevance to biological mechanisms that may be associated with AD pathogenesis, they await replication in large representative populations. Genome-wide association studies have emerged as an increasingly effective tool for identifying genetic contributions to complex diseases and represent the next frontier for furthering our understanding of the underlying etiologic, biological, and pathologic mechanisms associated with chronic complex disorders. There have already been success stories for diseases such as macular degeneration and diabetes mellitus. Whether this will hold true for a genetically complex and heterogeneous disease such as AD is not known, although early reports are encouraging. This review considers recent publications from studies that have successfully applied genome-wide association methods to investigations of AD by taking advantage of the currently available high-throughput arrays, bioinformatics, and software advances. The inherent strengths, limitations, and challenges associated with study design issues in the context of AD are presented herein.

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Alzheimer disease (AD) is the most common cause of dementia and the most prevalent neurodegenerative disorder associated with aging.[1] Alzheimer disease is a heterogeneous disorder with a complex etiology owing to genetic and environmental influences as causal or risk modifiers. The neuropathologic hallmarks of disease are extracellular amyloid plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau protein.[2] Only 10% of AD cases occurring before 60 years of age (early-onset AD) are due to rare, fully penetrant (autosomal dominant) mutations in 3 genes: Aβ precursor protein (*APP*) on chromosome 21,[3] presenilin 1 (*PSEN1*) on chromosome 14,[4] and presenilin 2 (*PSEN2*) on chromosome 1.[5,6] In contrast, most cases of AD are later in onset (≥65 years of age) (late-onset AD), are nonfamilial, and are likely the result of highly prevalent genetic variants with low penetrance.[7] To date, the only genetic risk factor for late-onset AD remains the apolipoprotein E gene (*APOE*), specifically the ε4 allele, which is moderately penetrant, accounting for up to 50% of cases.[8]

For editorial comment see page 307

Author Affiliations: Department of Epidemiology, The University of Texas School of Public Health, The University of Texas Health Science Center at Houston (Dr Waring); Department of Neurology, The University of Texas Southwestern Medical Center at Dallas (Dr Rosenberg); and Texas Alzheimer's Research Consortium (University of Texas Southwestern Medical Center, Dallas; University of North Texas Health Science Center, Fort Worth; Texas Tech University Health Science Center, Lubbock; and Baylor College of Medicine, Houston) (Drs Waring and Rosenberg).

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Table 1. Genetics of AD

Putative Genetic Variants (Selected Individual Source)	Chromosome	Consequences
DAPK1 (Li et al,[12] 2006)	9q34.1	Neuronal apoptosis
UBQLN (Bertram et al,[13] 2005)	9q21.32	Modulates accumulation of presenilin proteins
ABCA1 (Sundar et al,[14] 2007)	9q22-q31	Possible role in lipid regulation
SORL1 (Rogaeva et al,[9] 2007)	11q23	Involved with APP trafficking
GAB2 (Li et al,[11] 2004)	11q14.1	Scaffolding protein possibly affecting tau, amyloid, and other AD-related pathologic mechanism
LRP6 (De Ferrari et al,[15] 2007)	12q13-q14	Altered Wnt/β-catenin signaling

Abbreviations: AD, Alzheimer disease; APP, amyloid percursor protein.

However, a robust literature reports numerous putative genetic risk alleles and promising genetic variants. Recent reports from individual studies reveal significant associations with the sortilin-related receptor (*SORL1* [NCBI Entrez gene 6653])[9,10] and glycine-rich protein 2–associated binding protein 2 (*GAB2* [NCBI Entrez gene 9846])[11] on chromosome 11; death-associated protein kinase 1 (*DAPK1* [NCBI Entrez gene 1612]),[12] ubiquilin 1 (*UBQLN1* [NCBI Entrez gene 299798]),[13] and adenosine triphosphate–binding cassette transporter 1, subfamily A (*ABCA1* [NCBI Entrez gene 19]), on chromosome 9[14]; and low-density lipoprotein receptor–related protein 6 (*LRP6* [NCBI Entrez gene 4040]) on chromosome 12.[15] All of these putative variants still lack replication in large representative populations but have relevance to neuropathologic mechanisms and pathways that may be associated with AD pathogenesis (**Table 1**).

A large meta-analysis from the AlzGene database[16] representing 1055 polymorphisms and 355 genes reported in the literature as of August 2006 revealed the following 13 additional potential AD-susceptibility genes: angiotensin I converting enzyme (*ACE* [NCBI Entrez gene 1636]); cholinergic receptor, nicotinic, beta 2 (*CHRNB2* [NCBI Entrez gene 1141]); cystatin C (*CST3* [NCBI Entrez gene 1471]); estrogen receptor 1 (*ESR1* [NCBI Entrez gene 2099]); glyceraldehyde-3-phosphate dehydrogenase, spermatogenic (*GAPDHS* [NCBI Entrez gene 26330]); insulin-degrading enzyme (*IDE* [NCBI Entrez gene 3416]); 5,10-methylenetetrahydrofolate reductase (*MTHFR* [NCBI Entrez gene 4524]); nicastrin (*NCSTN* [NCBI Entrez gene 23385]); prion protein (*PRNP* [NCBI Entrez gene 5621]); presenilin 1 (*PSEN1*); transferrin (*TF* [NCBI Entrez gene 7018]); mitochondrial transcription factor A (*TFAM* [NCBI Entrez gene 7019]); and tumor necrosis factor (*TNF* [NCBI Entrez gene 7124]).[17] All are associated with relevant biological mechanisms and pathways but await replication to further elucidate their utility as significant markers for AD.

Understanding the role that genetic defects play in the pathogenesis of AD has been a major focus of investigation for several years. These collective efforts have provided valuable insights into the genetic and molecular mechanisms associated with AD. Until recently, most reports have been from linkage analyses and studies that have examined the association of single-nucleotide polymorphisms (SNPs), usually in a single candidate gene.[16] However, the completion of the Human Genome Project,[18] along with the development of public databases to catalog variation between individuals (SNPs) and advances in high-throughput, high-density genotyping technology have led to a sharp increase in the number of studies now examining a large number of SNPs simultaneously in hypothesis-independent designs. Indeed, genome-wide association studies (GWASs) have emerged as an increasingly effective tool for identifying genetic contributions to complex diseases and represent the next frontier for furthering our understanding of the underlying etiologic, biological, and pathologic mechanisms associated with chronic complex disorders. There have been early success stories for diseases such as macular degeneration[19-21] and diabetes mellitus.[22,23] Whether this will hold true for a genetically complex and heterogeneous disease such as AD is not known, although indications from early reports are encouraging.

This review considers recent publications from studies that have successfully applied genome-wide association methods to investigations of AD by taking advantage of the currently available high-throughput arrays, bioinformatics, and software advances. The inherent strengths, limitations, and challenges associated with study design issues are presented herein to help guide future GWASs in AD.

GWASs IN AD

The recent decline in the cost of genotyping coupled with technological advances that now allow simultaneous examination of up to 1 000 000 SNPs in a single high-throughput assay has led to an explosion of GWASs of common chronic diseases, including AD. Initial studies focusing on AD have taken advantage of already amassed robust data from case-control and longitudinal cohorts with reliable information on the phenotype of interest (eg, age at onset, diagnosis, and cognitive profile) and DNA available for genotyping [24-27](**Table 2**).

A GWAS of neuropathologically confirmed AD cases and control subjects from the United States and the Netherlands revealed a significant SNP (rs4420638) in linkage disequilibrium to the *APOE* ε4 variant on chromosome 19, thus providing support for the *APOE* locus as the major susceptibility gene for late-onset AD, with an odds ratio significantly greater than that for any other locus in the human genome.[24] That study also supported the feasibility of using the most recently available ultrahigh-density GWAS (502 627 SNPs) for AD and other heritable phenotypes. A subsequent study on the

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Table 2. High-Density Genome-Wide Association Studies on AD

Source	Population	Total Markers (SNPs) Examined	Significant Markers	Relevance
Coon et al,[24] 2007	Neuropathologically confirmed AD (n=664) or healthy (n=422) from United States and the Netherlands)	502 627 (Affy 500k)[a]	rs4420638 on chromosome 19 in LD to *APOE* ε4 variant	Confirms strength of association of *APOE* and development of AD; would have been missed except for 1 SNP; importance of increased SNP density for more complete coverage
Reiman et al,[25] 2007	Total: 1146 subjects from the United States and the Netherlands Discovery: neuropathologically confirmed cases of AD (n=446) and controls (n=290) Replication: neuropathologic sample of 197 cases of AD and 114 controls; clinical sample of 218 cases of late-onset AD and 146 controls	312 316 (Affy 500K)[a]	rs2373115 (*GAB2*) on chromosome 11q14.1	rs2373115 genotype GG inferred significantly higher risk (OR, 2.36) of AD among *APOE* ε4 carriers compared with genotypes GT or TT but not among *APOE* ε4 noncarriers; *GAB2* modifies risk of AD in *APOE* ε4 carriers
Liu et al,[27] 2007	103 Patients with late-onset AD and 170 first-degree relatives from pedigree of 4645 members in the Netherlands	262 000 (Affy 250 Nsp arrays of Affy 500k)[a]	Chromosomes 1q25 (*RGSL2*, *RALGPS2*, and *C1orf49*), 3q22-24 (*NMNAT3* and *CLSTN2*), and 10Q22-24 (*HTR7*, *MPHOSPH1*, and *CYP2C*)	Confirmatory for previous linkage to 1q21-25 and 10q22-24; with cognitive function as endophenotype, authors conclude that *RGSL2* on chromosome 1 and *NMNAT3* on chromosome 3 likely to be the relevant genes; first to show significant linkage to 3q23 markers
Grupe et al,[26] 2007	5 Case-control sample sets from the United Kingdom and the United States, including cases of late-onset AD (n=1808) and healthy controls (n=2062)	17 343 (Celera cSNP)[b]	3 SNPs on chromosome 19 in LD to *APOE* gene; rs3745833 (*GALP*) on chromosome 19q13.42; rs1554948 (*TNK1*) on chromosome 17p13.1; rs8192708 (*PCK1*) on chromosome 20q13.31	Three most significant SNPs in LD to *APOE* lends to validity of design; galaninelike peptide precursor (*GALP*); nonreceptor tyrosine kinase (*TNK1*) and phosphoenolpyruvate carboxykinase (*PCK1*) show direct or indirect effect on metabolic, trafficking, or signaling pathways that may have relevance to AD

Abbreviations: AD, Alzheimer disease; LD, linkage disequilibrium; OR, odds ratio; SNP, single-nucleotide polymorphism.
[a] Determined using Affymetrix GeneChip Human Mapping 500K Array set (Affymetrix, Inc, Santa Clara, California).
[b] Available from Celera Diagnostics (Alameda, California).

same population enriched with clinical samples divided into *APOE* ε4 carriers and noncarriers for discovery and replication demonstrated a modifying effect on the risk of AD associated with the *GAB2* among *APOE* ε4 carriers but not among noncarriers.[25]

The first GWAS to appear in the literature, and which focused on putative functional variants (SNPs) in AD, examined 17 343 markers in a robust sample of 1808 late-onset cases of AD and 2062 controls from the United States and the United Kingdom. Results revealed 19 significant markers associated with the risk of AD. Three of these were galaninelike peptide precursor (*GALP* [NCBI Entrez gene 85569]) on chromosome 19q13.42, nonreceptor tyrosine kinase (*TNK1* [NCBI Entrez gene 8711]) on chromosome 17p13.1, and phospho*enol*pyruvate carboxykinase (*PCK1* [NCBI Entrez gene 5105]) on chromosome 20q13.31, all with potential relevance to AD.[26] The fact that 3 of the 19 SNPs were in linkage disequilibrium to the *APOE* ε4 locus lends validity to the study design. However, replication in large appropriately designed studies is necessary for confirmation and further elucidation of their relevance in AD pathogenesis.

A GWAS from a genetically isolated population in the Netherlands of 103 patients with late-onset AD and 170 first-degree relatives from a complex pedigree of 4645 members focused on genetic variants associated with cognitive endophenotypes in addition to risk of AD.[27] This was the first study to show significant linkage to 3q23 markers associated with AD. Findings also confirmed previous linkage to 1q25, 10q22-24, and 11q25 associated with AD. Using cognitive function as the endophenotype, the authors[27] concluded that *RGSL2* (NCBI Entrez gene 84227), *RALGPS2* (NCBI Entrez gene 55103), and *C1orf49* (NCBI Entrez gene 84066) on chromosome 1; *HTR7* (NCBI Entrez gene 3363), *MPHOSPH1* (NCBI Entrez gene 9585), and *CYP2C* (NCBI Entrez gene 1559)

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on chromosome 10; and *NMNAT3* (NCBI Entrez gene 349565) and *CLSTN2* (NCBI Entrez gene 64084) on chromosome 3 are likely to be the relevant genes. They failed to confirm *SORL1* on chromosome 11 but reported *OPCMS* (NCBI Entrez gene 4978) and *HNT* (NCBI Entrez gene 50863) to be the relevant genes. Another GWAS of endophenotypes with relevance to AD from the Framingham group focused on changes in brain volumetric measures on magnetic resonance imaging and cognitive performance in 705 individuals free of dementia and stroke.[28] They found significant associations between *SORL1* (rs1131497) and abstract reasoning and between *CDH4* (rs1970546) and total cerebral brain volume. They also reported polymorphisms with 28 of 163 candidate genes for AD, stroke, and memory impairment for the endophenotypes studied. Overall, these results indicate that genetic variants may be detectable with subclinical phenotypes known to increase the risk of developing clinical neurological disease.[28]

Although these studies represent an excellent start, with several new associations already detected within the past year, they constitute only the beginning, as many of these putative associations await validation in sufficiently large and representative populations before their utility as genetic markers for disease is completely understood. An important consideration is that the results thus far show very modest effect sizes in the order of relative risks (or odds ratios) of less than 2.0, and most in the range of 1.1 to 1.5. As expected with most common complex diseases with onset later in life,[29] late-onset AD likely results from genetic variants with modest effect size that, while statistically significant, are neither sufficient nor necessary to explain all occurrences of disease.[30] It is therefore incumbent that the synthesis and interpretation of weak but consistent associations that are biologically plausible afford distinction from spurious associations that may result from bias and inferior study design.

GWAS DESIGN CONSIDERATIONS IN AD

Sample Size and Power

One of the most important and challenging steps in designing large-scale GWASs on currently available high-density genotyping platforms is assembling sufficiently large study populations that will allow robust gene discovery and replication. Sample size and power calculations for GWASs are statistically rigorous and beyond the scope of this review. Interested readers are referred to recent publications on the subject that take into account the density and coverage of newer available genotyping platforms and software.[31,32] These reports and others point to the importance of issues that must be taken into account when planning a study.

Power to detect a causal variant increases with sample size and magnitude of effect (relative risk or odds ratio) and can vary by genotyping platform and the population studied. The effect of stratification on *APOE* and the effect of population stratification need to be taken into account. Owing to the large number of genetic variants (SNPs) examined and the lack of independence with SNPs in linkage disequilibrium to each other, multiple testing and type I error are even greater threats to validity for the modest effect sizes expected. In addition, power calculations should take into account misclassification error, not just of the genotype but of clinical misclassification error associated with the phenotype, particularly when the trait of interest is disease status in the case of AD (as discussed in the "Phenotype" subsection).

To overcome these inherent issues, large sample sizes of well-characterized phenotypes and tiered strategies for discovery and replication have proved to be the most successful strategy for studies appearing in the recent literature. Most studies, such as those funded through the Genetic Association Information Network[33] and the Wellcome Trust Case Control Consortium,[34] have included 2000 to more than 10 000 cases and controls to identify truly significant results. Considering the current cost of genotyping large-scale samples and the availability of large numbers of well-characterized research subjects, some of which have already been included in GWASs, a similar approach is both timely and feasible for AD, albeit not without challenges and limitations.

Phenotype

Although the initial analyses for most GWASs of AD may use disease status as the phenotypic trait of interest, testing for associations with secondary traits such as clinical and cognitive features, biomarkers including neuroimaging, and neuropathological features has considerable merit. Because of established criteria for a diagnosis of AD and the need for standardization across sites for large multicenter studies, considerable effort goes into making a clinical diagnosis of AD. However, establishing an appropriate control continues to be a challenge. The presence of AD neuropathologic changes in brains of nondemented individuals at autopsy is not uncommon, and a number of patients with a clinical diagnosis of probable AD also have cerebrovascular comorbidities that may influence cognition. This has important implications for designing GWASs, because most genetic defects will be associated with neurobiological and biochemical processes that lead directly to clinical AD through neurodegenerative changes (eg, formation of neurofibrillary tangles and amyloid deposition) or indirectly through other mechanisms (eg, cerebrovascular disease). Indeed, the potential for biological heterogeneity among individuals with clinical AD and among nondemented controls presents a challenge in the design of a GWAS and in the interpretation of the findings. Therefore, strategies to minimize the effects of misclassification error associated with the phenotype of interest need to be developed for implementation in future large-scale studies.

Discovery and Replication Samples

Ideally, a GWAS for AD would begin with a discovery sample that is sufficiently large with a wealth of quantitative and qualitative information available for phenotypic structuring. Another large sample with similar phenotypic structure would then be used to further narrow the most significant SNPs resulting from discovery genotyping to identify a much smaller number of significant

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SNPs. Those SNPs would then be examined in a larger sample with similar phenotypic structure for replication (**Figure**). Finally, the most significant SNPs identified would then need to be subjected to further analyses (gene expression, sequencing, fine mapping, and functional studies) for final confirmation of relevant putative causal variants. Guidelines for replication of genotype-phenotype associations and GWASs have been published recently.[35,36]

Although the numbers are arbitrary, because of the number of traits to be examined and the modest effect size expected for most traits, it is clear that multiple large samples for discovery and replication are necessary to ensure a successful GWAS.[37,38] This will require forming consortia that will afford pooling across studies because it is unlikely that a single study will have adequate power to unequivocally identify novel genetic risk factors for AD. To take advantage of available data on a large number of patients with AD and controls, plans to form consortia such as the National Institute on Aging (NIA) Genome-Wide Association Study Consortium are already under way. These collective efforts will attempt to design and complete GWASs in the near future to provide an excellent and timely foundation for numerous studies to follow. These initial efforts will likely include GWASs already completed or in progress such as the Translational Genomics Research Initiative study of AD, the National Institute of Mental Health AD sample, the Framingham Study, and the Texas Alzheimer's Research Consortium among other publicly funded and public-private initiatives in progress or planned. Valuable resources such as the National Cell Repository of AD, the NIA National Alzheimer Coordinating Center, and ongoing studies such as the Adult Changes in Thought, the Washington Heights–Inwood Columbia Aging Project, and the Chicago Healthy Aging Project should also be considered, along with ongoing biomarker and neuroimaging studies such as the Alzheimer Disease Neuroimaging Initiative. All of these resources would be expected to have readily available DNA from a large sample of well-characterized research participants and could provide a robust pooled sample that is immediately available to initiate a large-scale GWAS.

The potential contribution from large family studies such as the NIA Late Onset Alzheimer Disease centers, particularly for discovery, should also be evaluated. Although the "common disease–common variant" hypothesis[39] provided the conceptual framework for the HapMap Project on which the commercially available high-density genotyping platforms are based, multiple rare variants would not be identified by the tagging SNPs. However, their role in susceptibility to common complex diseases may be significant.[40,41]

This discussion focuses on replication-based multistage design analysis. However, some groups recommend joint analysis as an alternative strategy for GWASs, whereby data from both stages are analyzed together. This strategy may be even more efficient and achieve greater power when a large proportion of the study sample is genotyped in stage 1 and a relatively large proportion of markers is selected for stage 2. An excellent review comparing joint analysis with replication-based analysis is provided by Skol et al.[42] The choice of analysis for multistage design is an important study design issue that must be taken into account to minimize genotyping cost and maximize statistical power within the context of the available sample size.

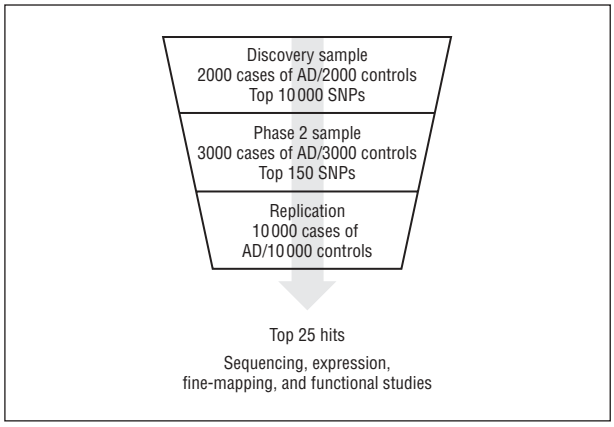

Figure. Hypothetical tiered design strategy for a large-scale genome-wide association study of Alzheimer disease (AD). SNP indicates single-nucleotide polymorphism.

CHALLENGES

Assembling large representative samples for discovery and replication is certainly not without challenges. The extent to which individual institutional review board–approved protocols allow sharing of banked DNA and genetic information must be verified. Logistical and technical issues associated with locating and assembling large DNA sample sets and subsequent genotyping is a large and expensive undertaking. Cataloguing all available data required to support the various endophenotypes to be tested initially and transforming these data into a standardized format for entry into a unified database require considerable planning, technical support, and funding. As evidenced by the success of studies already completed, these initial large-scale studies are expected to produce a number of candidate polymorphisms and haplotypes that will require replication and confirmation in other samples. Expanding current studies now to include comparably collected information on anticipated significant endophenotypes and collection of biospecimens and neuroimaging will require tremendous resources and planning. Research teams populated with subject matter experts representing the entire spectrum of expertise required must be in place to ensure success of such an undertaking over the next 5 years and beyond and therefore becomes a matter of funding and prioritization of research agendas among all respective stakeholders.

CONCLUSIONS

Although there are challenges to assembling a large representative population for discovery and replication studies, the prospect of new insights that will further our understanding of the role of genetic defects in the neuropathogenic mechanisms that lead to AD make the GWAS an attractive and powerful tool worth the effort and investment. However, there is tremendous work yet to be done, not only in designing appropriately large and representative studies that will lead to numerous new gene discoveries but also in translating these discoveries to ad-

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vance clinical practice. Indeed, the time has come to leverage the wealth of advancing methods in genetics, neuroscience, bioinformatics, statistics, and genetic epidemiology that will lead to better treatment outcomes, drug discovery, and prognosis for the millions of individuals already affected by or at risk of developing AD.

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Correspondence: Stephen C. Waring, DVM, PhD, Department of Epidemiology, The University of Texas School of Public Health, 1200 Herman Pressler, RAS-E629, Houston, TX 77030 (stephen.c.waring@uth.tmc.edu)
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Detection of Abnormal Memory Decline in Mild Cases of Alzheimer's Disease Using CERAD Neuropsychological Measures

Kathleen Welsh, PhD; Nelson Butters, PhD; James Hughes, MS; Richard Mohs, PhD; Albert Heyman, MD

• The present study was designed to determine which of the memory tasks included in the CERAD (*C*onsortium to *E*stablish a *R*egistry for *A*lzheimer's *D*isease) neuropsychological battery best differentiate patients with early Alzheimer's disease from cognitively normal elderly control subjects and also best distinguish between the various levels of severity of the dementia process. A sample of CERAD patients with Alzheimer's disease was stratified by disease severity into those with mild, moderate, or severe dementia and matched with control subjects for sex, age, and education. Using multivariate procedures and cutting scores, the efficacy of each memory measure in distinguishing between these groups and control subjects was determined. The test for delayed recall was found to be the best overall discriminatory measure. The other tests of memory, ie, immediate recall, intrusion errors, and recognition memory, had poor overall discriminability. None of the CERAD memory measures were found to be particularly powerful in staging the severity of dementia. These findings suggest that tests for delayed recall may be particularly useful in the early detection of Alzheimer's disease and should be considered in screening batteries for dementia in community surveys.

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From the Department of Psychiatry and Bryan Alzheimer's Disease Research Center (Dr Welsh) and Department of Medicine, Division of Neurology (Dr Heyman), Duke University Medical Center, Durham, NC; Psychology Service, Department of Veterans Affairs, Veterans Administration Medical Center, and Psychiatry Department, University of California, San Diego (Dr Butters); Department of Biostatistics, University of Washington, Seattle (Mr Hughes); and Department of Psychiatry, Mount Sinai School of Medicine, New York, NY (Dr Mohs).

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Reprint requests to Bryan Alzheimer's Disease Research Center, Box 3450, Duke University Medical Center, Durham, NC 27710 (Dr Welsh).

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was organized to develop brief standardized assessments of the clinical and neuropsychological manifestations of Alzheimer's disease (AD).[1] The application of such standardized tests in multicenter studies of AD is expected to reduce the variety of psychometric measures currently used in a number of research laboratories, a problem that often complicates comparison of data.

The measures included in the CERAD neuropsychological battery characterize the primary cognitive manifestations of AD, ie, memory disturbance, language impairment, apraxia, and general intellectual deterioration. The CERAD battery as a whole has been found to have substantial test-retest reliability, cross-center interrater reliability, and longitudinal validity.[2] It also has demonstrated discriminative validity, ie, each of the individual psychometric tests differentiates normal elderly control subjects from patients with mild to moderate dementia. However, there is still need to establish the relative sensitivity and specificity of the individual test measures in distinguishing between patients with very mild dementia and normal elderly individuals. Such information would be important, for example, in determining whether the instrument is effective in detecting early dementia in population surveys.

The present study is an initial analysis of the clinical sensitivity and specificity of the verbal memory test, which is part of the tests included in the CERAD battery. The specific issue addressed in this report is which of the learning and memory measures included in the CERAD neuropsychological battery best differentiate patients with very early AD from normal elderly control subjects. Although it is well known that learning or "acquisition" of new information is severely impaired in early AD, recent work using standardized tests of memory[3-5] and experimental paradigms[6] has emphasized the importance of the rate of forgetting as measured by delayed recall and savings scores. Other studies have shown that intrusion errors[7] and recognition memory performance[8] may also be useful in making such differentiations.

We examined various memory indexes in AD subjects with mild, moderate, and severe cognitive impairment and, also, in normal elderly control subjects whose data had been entered into the CERAD national study.

SUBJECTS AND METHODS

Subjects

To ensure that the groups would be matched on the basis of age and education, subjects were selected for this study from the total number of 549 individuals with AD and 390 control subjects who had been entered into the study from its onset in April 1987 to a cutoff period in July 1989. The data presented in this report are based on 147 patients and 49 control subjects derived from the pool who were recruited from the referral populations of the 19 participating institutions. The control subjects were either informants for the patients or community volunteers. On entry into the study, informed consent was obtained from each subject and/or from a responsible person by procedures approved by the individual center's Institutional Review Board.

The patients included in the study met the diagnostic criteria for probable AD using the criteria adopted (with minor modifications) from the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association Work Group.[9] They were 50 years of age or older, could speak and comprehend English, and had a caregiver/informant who could provide adequate history. The patients with severe cognitive impairment, as deter-

mined by scores greater than 24 on the Orientation-Concentration-Memory test[10] or less than 10 on the Mini-Mental State Examination (MMSE),[11] were excluded. Control subjects met the same inclusion criteria as the patients but were free of cognitive impairment at entry.

The pool of 549 subjects was stratified into three groups based on the severity of overall cognitive impairment, as defined by the MMSE scores. The *mild* group comprised those with MMSE scores of 24 or greater; the *moderate* group had scores between 19 and 24, whereas the *severe* group scored between 10 and 19. This procedure resulted in 84 cases of mild AD, 206 cases of moderate impairment, and 255 cases of severe impairment.

A comparison of demographic variables revealed that the mean age of patients was significantly higher than that of control subjects (71.1 years vs 68.2 years; SD = 6.8 and 7.6, respectively; $P \leq .0001$) and that the average education of the patients was significantly lower than that of the control subjects (13.1 years vs 14.0 years; SD = 3.0 for each group; $P \leq .0001$). Since age and education frequently modify outcome on cognitive testing, it was anticipated that the age and education differences in our groups might bias the findings and disproportionately favor the performance of the control subjects.

To control for these factors, the smallest group (mild AD cases) was computer matched to individuals in each of the other groups on the basis of age (within 2 years), education, and gender. Matching on these three variables resulted in four groups of 49 individuals (25 men, 24 women) each, as seen in Table 1.

Table 1.—Demographic Information and MMSE Scores for Control Subjects and Groups With AD*

Variables	Control Subjects (n = 49)	Groups With AD: Mild (n = 49)	Moderate (n = 49)	Severe (n = 49)
MMSE score				
Mean	28.9	25.0	21.0	13.9
SD	1.0	1.0	1.3	2.9
Sex, No.				
Male	25	25	25	25
Female	24	24	24	24
Age, y				
Mean	71.1	71.2	71.1	71.1
SD	5.7	5.6	5.6	5.7
Education, y				
Mean	14.0	13.8	13.9	13.7
SD	2.9	2.5	3.0	3.0

*MMSE indicates Mini-Mental State Examination; and AD, Alzheimer's disease.

Table 2.—Mean Performance Levels of the Control Subjects and the Groups With AD*

Memory Measures	Control Subjects	Groups With AD: Mild	Moderate	Severe
Learning				
Trial 1	4.8 (1.4)	2.8 (1.4)	2.2 (1.6)	1.0 (1.1)
Trial 2	7.0 (1.5)	4.2 (1.5)	3.4 (1.6)	2.2 (1.3)
Trial 3	7.9 (1.6)	4.7 (1.8)	3.9 (1.7)	2.3 (1.6)
Delay recall	6.8 (1.9)	1.8 (1.8)	0.7 (1.5)	0.5 (1.0)
Savings, %	85.6 (19.3)	35.8 (30.9)	16.7 (32.8)	16.3 (28.2)
Recognition				
Rec-Yes	9.7 (0.6)	8.2 (2.4)	7.7 (2.3)	6.9 (2.6)
Rec-No	9.7 (1.5)	7.7 (2.7)	7.5 (2.6)	6.4 (3.0)
Intrusions				
Trial 1	0.3 (0.5)	0.6 (1.0)	0.6 (1.5)	0.4 (0.8)
Trial 2	0.2 (0.4)	0.4 (0.8)	0.4 (1.2)	0.5 (1.9)
Trial 3	0.1 (0.2)	0.3 (0.7)	0.6 (1.1)	0.7 (1.0)
Delay	0.4 (0.7)	0.9 (0.9)	0.9 (1.4)	0.8 (1.6)

*Values in parentheses are standard deviations. Higher scores on the intrusion measures and low scores on all other memory measures represent poorer performance levels. AD indicates Alzheimer's disease; Rec-Yes, true-positive recognition responses; and Rec-No, true-negative recognition responses.

Neuropsychological Assessment

The CERAD neuropsychological battery[2] includes a measure of category fluency, a modified Boston Naming Procedure; the MMSE; a word-list learning, memory, and recognition procedure; and an assessment of constructional praxis. As mentioned earlier, the tests were chosen to measure the principal cognitive manifestations of AD and to have a range of difficulty sufficient to characterize patients with the different stages of disease.

This study examined the performance on three learning and memory procedures: word-list learning, word-list delayed recall, and word-list delayed recognition. The *word-list learning* task consists of an immediate free recall procedure for a 10-item word list assessed over three separate learning trials. On the first trial, 10 printed words are presented at a rate of one every 2 seconds; the subject is instructed to read each word aloud to ensure adequate attention to the stimuli. Immediately following presentation, the subject is asked to recall as many of the words as possible. Two additional learning trials immediately follow using the same procedure. The items on the list are randomized across the three learning trials in a standardized manner. The number of words recalled correctly on each trial (maximum 10) is scored. In addition, the number of *intrusion* errors, ie, responses of words not on the study list, is also recorded.

The *delayed recall* procedure tests memory for the 10-item word list after a delay of 5 to 8 minutes. To prevent rehearsal of the list, an intervening (constructional praxis) task is administered between the last learning trial and the spontaneous uncued recall of the word list. The number correctly recalled on the delayed recall trial (maximum score of 10) and the number of intrusion errors are recorded. The *delayed word-list recognition* procedure tests the subject's recognition of the 10-item word list (targets) from among 10 distractor items. Words are presented one by one, and the subject must indicate whether each item had or had not been on the previously learned list of 10 words by responding "yes" for targets and "no" if the item (the distractor) was not on the list.

Measures

To assess the relative impairment of learning and memory functions in AD, the performances of the three AD groups and the normal control group were compared on a series of memory measures. Assessment of acquisition was measured by the number of words learned on each of the three learning trials (hereafter abbreviated T1, T2, or T3) and by the number of intrusion errors committed on each of the learning trials.

The memory measures included the number of words recalled correctly on the delay trial (Td) and three measures of recognition memory: total number correct; correct recognition of target items (ie, correct "yes" responses, hereafter abbreviated Rec-Yes), and correct validation of distractors (ie, correct "no" responses, hereafter abbreviated Rec-No). *Savings* scores defined as percent of words correctly recalled on Td when compared with the last learning trial [(Td/T3) × 100 = Savings(%)] were also calculated. Only data from subjects scoring two words or more correct on the last learning trial were included in the savings measures.

Statistical Analyses

The CERAD Data Management Center carried out statistical calculations using the statistical analysis system (SAS, Ver-

Table 3.—The Efficacy of Test Measures in Correctly Classifying Subjects Based on Cutting Scores (+2 SDs From the Control Mean)*

Memory Measures	Control Subjects	Groups With AD, % (No.)		
		Mild	Moderate	Severe
Learning				
Trial 1	96 (47)	41 (20)	67 (33)	92 (45)
Trial 2	94 (46)	49 (24)	74 (36)	96 (47)
Trial 3	98 (48)	41 (20)	59 (29)	90 (44)
Delay recall	94 (46)	86 (42)	96 (47)	96 (47)†
Savings	96 (47)	62 (29)	93 (41)	82 (28)†
Recognition				
Rec-Yes	96 (47)	39 (19)	53 (26)	73 (35)
Rec-No	98 (48)	25 (12)	32 (16)	48 (23)
Intrusions				
Trial 1	96 (47)	14 (7)	16 (8)	14 (7)
Trial 2	78 (38)	33 (16)	27 (13)	33 (16)
Trial 3	94 (46)	20 (10)	35 (17)	39 (19)
Delay	90 (44)	27 (13)	26 (12)	18 (9)

*The percentage and number of subjects correctly classified are indicated for each memory measure. Cutting scores were selected 2 SDs from the control mean and rounded up to nearest whole integer. By deliberately setting the cutoff at this level, classification of controls will be, by definition, approximately 95% correct.

†The best overall measure is the delayed recall measure. Savings scores also differentiated well between groups, but they were not as powerful as the delayed recall measure. The differing capacities of the two measures: delayed recall and savings scores, appear due to restricting the analysis of savings to individuals who successfully learned two words or more by the learning trial.[3] By this procedure, the data from the most severely amnesic individuals are not included in the savings measures and the sizes of the groups with Alzheimer's disease (AD) are reduced from 49 subjects to 47, 45, and 34 subjects for the mild, moderate, and severe groups, respectively.

Table 4.—Efficacy of the Memory Measures in Determining Group Assignment Based on Stepwise Discriminant Function Analysis Results

Comparables	R^2	F	P
Control subjects vs group with mild AD*†			
Delay	.588	132.7	<.001
Rec-No	.026	2.48	<.120
Group with mild AD vs group with moderate AD‡			
Delay	.091	8.86	<.004
Group with moderate AD vs group with severe AD§			
Rec-Yes	.065	5.23	<.025
Intrusions	.052	4.09	<.047

*AD indicates Alzheimer's disease.

†In this comparison, the delay measure was the single best discriminator between the groups. When this score was combined with the true-negative recognition responses (Rec-No), the discriminant formula correctly classified 91% of the subjects, separating 89% of the mildly demented patients from 92% of the control subjects.

‡In this comparison, only the delay recall measure entered into the linear model. This measure correctly classified 65% of the subjects, separating 47% of the mildly demented patients from 84% of the moderately demented patients.

§In this comparison, the true-positive recognition responses (Rec-Yes) and intrusion errors entered into the equation, correctly classifying 66% of the subjects: 73% of the moderate group and 59% of the severe group.

sion 5, SAS Institute, Cary, NC, 1981). The results were analyzed in several ways. To provide an overall view of group differences, mean scores on each memory measure were computed for the normal group and AD groups. Differences between groups were assessed through a one-way ANOVA. When significant differences arose, post hoc comparisons were made with individual *t* tests.

Once the distributions for each of the memory measures were established, cutting scores were then determined, so that impaired performance on each task was defined as scores falling 2 SDs below the control mean (ie, performance levels exceeded by approximately 95% of those of the control subjects). These scores were subsequently used to identify the number of subjects scoring in the adequate or defective range on each memory measure. Sensitivity and specificity were determined through a comparison of performance on the different memory measures.

In addition to the above analyses, the accuracy of the test scores in predicting whether a person was a normal control subject or a patient with mild, moderate, or severe AD was determined by means of stepwise linear discriminant function analysis. This procedure identifies the combination of tests that best discriminates the patients from the control subjects. This method also allows the computation of the percentage of patients (sensitivity) and control subjects (specificity) classified correctly by the discriminant procedure.

RESULTS

Mean scores for each of the learning and memory measures were computed for the control subjects and for the patients with AD (Table 2). Analyses of these data disclosed a highly significant group difference on each test ($P < .001$) with the patients performing more poorly than the matched control subjects.

Evaluation of sensitivity and specificity at a set cutoff score was used to determine the efficacy of each memory measure in differentiating the patients with mild dementia from the control subjects, the mildly demented from those moderately demented, and the moderately demented from the patients with more severe dementia. By analyzing the frequency distribution of scores, the percentage of patients and control subjects correctly classified by a 2-SD cutoff score was determined (Table 3). On the basis of this procedure, it was apparent that not all measures were equally effective in discriminating between the older-aged control subjects and the groups with dementia. The best overall discriminator was found to be delayed recall. This measure correctly classified 96% of the control subjects, 86% of the patients with mild dementia, and 96% of both the moderately and severely demented patients. Although the patients with AD committed more intrusion errors than did the control subjects, the intrusion measures had poor overall discriminability. Recognition memory also proved to be a poor discriminating measure.

The most effective combination of discriminating tests was determined by submitting the data to stepwise linear discriminant function analysis (Table 4). All tests were included in the procedure. This procedure, again, identified the delay recall score as the single best discriminator between the patients with mild dementia and the control subjects. When combined with the correct "no" score (Rec-No) on the recognition task, the discriminant function formula correctly classified 91% of the subjects, separating 89% of the mildly demented patients from 92% of the control subjects.

In the comparison of the mildly and moderately demented patients, the delayed recall measure was the only measure entering into the linear model. This measure correctly classified 65% of the subjects, separating 47% of the mildly impaired patients

from 84% of the moderately impaired individuals.

In the later stages of disease, the moderate and severe comparison, the combination of correct "yes" recognition (Rec-Yes), and intrusion errors appeared to be the best—albeit not very powerful—discriminators between groups. The overall accuracy of the combined measures in discriminating between the groups was 66%, separating 73% of the moderately impaired individuals from 59% of the severely demented patients.

COMMENT

The major finding of this study pertains to the ability of the CERAD verbal memory test to discriminate between patients with very mild AD and normal elderly control subjects. Our results suggest that in patients with subtle cognitive impairment caused by AD, predictive accuracy can be enhanced by focusing on delayed recall measures. Other measures, including learning (immediate recall), recognition memory, and intrusions, are also affected by AD, but they are not as powerful in terms of differentiating the patients with very mild AD from the control subjects. The data suggest that emphasis on these latter measures in the early stages of dementia caused by AD is more likely to lead to false-negative errors than is attention to the delayed recall measure for which sensitivity and specificity are both high. Thus, for detection of the early stages of AD, the delayed recall measure (which is an index of forgetting) appears to be most useful. These findings are consistent with other reports that stressed the importance of rate of forgetting in distinguishing AD from other dementing disorders,[3-5] as well as from normal control cases.[6]

Delayed recall proved useful in detecting early evidence of AD; however, because AD cases "bottom out" so quickly on the measure, it had little practical value in staging this disorder. All memory measures discriminate clearly between patients with moderate dementia and elderly control subjects, and also between the severely demented patients and control subjects. However, none of the measures was particularly powerful in discriminating between the moderately and severely demented cases. The results from the linear discriminant function analyses indicate that, of the various memory measures, recognition memory and intrusion errors have the greatest value in discriminating between the more severely demented groups, although the accuracy of correct group placement is limited (66% accuracy). Despite this limitation, the data suggest that for staging of dementia, attention to the commission of intrusions and to recognition memory is likely to be more informative at the later stages of AD. Other memory measures, including delayed recall that is important at the early stages of dementia, do not differentiate between the later stages of the disease.

It should be cautioned that the current study compared patients who had a diagnosis of AD with normal, high-functioning control subjects. It has not determined the predictive validity of the memory tasks for detecting cognitive changes in an open community population in whom the degree of memory impairment may be very subtle. Nonetheless, our results in patients with very mild AD indicate that the delayed recall measure is a robust discriminator of early impairment and should be considered in screening for dementia in population surveys.

In conclusion, this study of the CERAD verbal memory task suggests that it may be a useful clinical tool for the early detection of AD in this population. However, all memory indexes were not of equal value. Delayed recall proved to be the most sensitive and selective measure. The memory test does not appear to have much practical value in the later staging of the illness, in which there are significant memory impairments. Other cognitive measures from the CERAD battery or an evaluation of global cognitive function based on scores derived from the entire CERAD battery may prove more useful for the staging of such patients.

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An Estimate of the Worldwide Prevalence and Direct Costs of Dementia in 2003

A. Wimo L. Jonsson B. Winblad

Division of Geriatric Epidemiology, Neurotec, Karolinska Institutet, Stockholm, Sweden

Key Words
Worldwide direct costs · Worldwide prevalence · Cost of illness

Abstract
Dementia disorders are today considered to be a major driver of costs in health care and social systems and worrying estimates of future dementia prevalence have been presented. It is of great interest for policy makers to have an estimate of dementia disorders' contribution to global social and health care costs, particularly in light of the demographic prognoses. The worldwide costs of dementia were estimated from prevalence figures for different regions, and cost-of-illness studies from key countries using a model based on the relationship between direct costs of care per demented and the gross domestic product per capita in each country. The worldwide direct costs for dementia in 2003 are estimated at 156 billion USD in the main scenario based on a worldwide prevalence of 27.7 million demented persons (sensitivity analysis: 129–159 billion USD). Ninety-two percent of the costs are found in the advanced economies with 38% of the prevalence. Although there are several sources of uncertainty, it is obvious that the worldwide costs are substantial and the expected increase in elderly people in the developing countries presents a great challenge.

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Introduction

Dementia disorders are today considered to be a major driver of costs in health care and social systems of developed countries. The main reason is the 'greying population', and pessimistic estimates of future dementia prevalence and costs have been presented [1–3]. A new situation for the millennium is the 'greying' of the developing countries, which may present a scenario for dementia care and costs that is even more worrying. However, this view is affected by severe methodological problems. Even if there are controversies regarding how to perform cost-of-illness studies and cost-effectiveness research in the developed countries, we are indeed facing great methodological problems if we intend to include developing countries in the analyses. Methodological challenges from the worldwide perspective include, for example, accuracy of dementia prevalence estimates, different care systems, issues related to the costing of informal care and, last but not least, the incompleteness of data in many developing countries. Nevertheless, we regard it as important to try to estimate the worldwide costs of dementia, since it may be of great interest for policy makers to have a rough estimate of dementia disorders' contribution to global social and health care costs, particularly in light of the demographic statistics showing that the majority of demented persons live in developing countries. Since the prognoses also show that the greatest increase in the num-

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Dr. Anders Wimo
HC Harmånger
Backv 3
SE–820 75 Harmånger (Sweden)
Fax +46 652 71261, E-Mail Anders.Wimo@neurotec.ki.se

ber of demented will occur in these countries [4], an estimate of the costs will have consequences for how these countries will organize and finance the care for demented persons.

Materials and Methods

Two basic sources for the calculations were used: epidemiological data regarding the prevalence of dementia in different parts of the world, and available sources regarding cost of illness of dementia. These sources are combined in a model which estimates the worldwide costs of dementia. The cost-of-illness model used in this paper refers to the methods in a paper by Andlin-Sobocki et al. [5] although the present model is somewhat simplified due to the availability of data. The basic assumption is that there is a relationship between the direct costs and resources for dementia care and the gross domestic product (GDP) per capita [6].

Epidemiology: The Worldwide Occurrence of Dementia

In a previous paper [4], we presented an estimate of the worldwide occurrence of dementia. This estimate was based on the worldwide demographic statistics from the United Nations (UN) and the best available data on age-class-specific dementia prevalence [7]. In the present paper, the prevalence figures are updated to 2003.

The UN presents demographic statistics (5-year age classes) and forecasts for countries, regions and the world [8]. In the forecast we used, the 1997 version, there is a deviation of just 0.3% from the latest prognoses. It is also assumed that the age-specific dementia prevalence is similar worldwide. In the sensitivity analysis, different sources for age-specific dementia prevalence are tested [9, 10].

Cost of Illness

The cost of the illness due to a disease in question is equal to the value of what these resources would have produced if there had been no cases of the illness, i.e. opportunity costs. Two approaches can be used: an incidence approach or a prevalence approach [11]. If the aim is to illustrate the economic consequences of various interventions, the incidence approach is preferable. If the aim is to estimate the economic burden during e.g. a year, the prevalence approach is recommended, as in the present study.

The perspective of a cost of illness assessment informs the reader of whose viewpoint the costs are calculated from. The societal perspective includes all costs, irrespective of the payer, and is recommended by most published guidelines for economic evaluations [12]. In the case of dementia, this means that informal care is assigned a cost. However, due to the great methodological problems in calculating the costs of informal care from a worldwide perspective, this paper focuses on direct costs.

Costs are calculated as the product of the quantities of resources consumed (q) and a price vector (p). As definitions of care resources vary between countries and published cost-of-illness studies rarely disaggregate quantities and prices, this analysis was based on the total cost estimates reported in previous research.

The Worldwide Perspective

The worldwide perspective presents several methodological difficulties. Country-specific cost-of-illness studies are based on demographics of the elderly, dementia occurrence figures and an estimate or knowledge of how demented persons are distributed in the care organization and their use of resources. To these basic figures, a theory of costing must be added. Such a detailed approach is not possible when a worldwide perspective is applied. Even if there are several country-specific cost-of-illness studies published, such studies do not represent all the different regions of the world. The range of costs illustrates not only true differences in the costs of dementia, but also that the differences reflect methodological aspects, such as whether costs of informal care are included or not and how informal care is costed. Other methodological problems are incompleteness of demographic statistics of the elderly and of information on how demented persons are distributed in various kinds of care organizations of the elderly in different parts of the world. Since a great proportion of costs occur outside the formal medical system, such as home services, nursing home care, informal care, it is not sufficient to use medical register data.

Results are here presented as world continent figures but also according to International Monetary Fund/World Economic Outlook's (WEO) terminology as 'advanced economies' and 'other emerging market and developing countries' [13] as well as according to the UN terms 'more developed regions' (MDR) and 'less developed regions' (LDR) [8] and the World Bank's 4-level classification [14].

The Economic Model

Since many countries lack specific cost data on dementia, a method for imputation of such data needs to be used. Imputation is based on a selection of cost data concerning dementia from countries where such data are available. Different imputation algorithms based on international statistical data to reach the most appropriate estimates for countries with no original cost data are used. From macro-economic research it is well known that there is a strong correlation between expenditures on health care per capita and the GDP per capita [15, 16]. A similar relationship can be used to make an estimate of the worldwide costs of dementia, based on two approaches. The first (which is the base option) assumes that the expenditures per demented person as a proportion of GDP per capita for the countries and regions where imputation is necessary is similar to the proportion in the countries where dementia cost data are available. It is accordingly assumed that differences between countries in unit costs, e.g. costs of hospital care, are reflected in differences in the GDP per capita and year. Furthermore, it is also assumed that differences in GDP per capita also reflect differences in care resources (e.g. countries with a high GDP per capita and year have more costly caring resources, such as long-term care, than countries with low GDP per capita).

The second approach (in the sensitivity analysis) is based on the assumption that expenditures of health care per capita reflect dementia costs worldwide.

All costs are expressed as US dollars in 2003 (currency transformations by the use of Purchase Power Parities [17]) and for the time transformation of costs to the year of 2003 the Consumer Price Index for each source country was used [18].

The criteria for inclusion of cost-of-illness studies from the key countries was that transparent and established methods for cost-of-illness calculations were used. It should also be possible to identify

Table 1. The worldwide population and worldwide dementia population

Major areas/regions	Population 2003, n × 1,000	Proportion of population, %	Demented 2003	Proportion of demented, %
Africa	838,462.8	13.4	1,354,033	4.9
Eastern	264,659.6	4.2	359,334	1.3
Middle	103,909.1	1.7	164,034	0.6
Northern	183,217.7	2.9	377,897	1.4
Southern	48,259.8	0.8	87,299	0.3
Western	238,416.6	3.8	365,469	1.3
Latin America	541,294.7	8.6	1,867,134	6.7
Caribbean	38,443.5	0.6	188,767	0.7
Central	142,284.7	2.3	426,847	1.5
South	360,566.4	5.7	1,251,521	4.5
Northern America	316,467.0	5.0	3,282,080	11.8
Asia	3,823,656.4	60.9	13,209,989	47.6
Eastern	1,518,013.8	24.2	7,204,199	26.0
South Central	1,565,087.1	24.9	4,011,709	14.5
South Eastern	540,117.4	8.6	1,449,370	5.2
Western	200,438.0	3.2	544,712	2.0
Europe	727,749.1	11.6	7,787,243	28.1
Eastern	305,056.1	4.9	2,501,209	9.0
Northern	94,422.0	1.5	1,216,518	4.4
Southern	144,017.0	2.3	1,756,113	6.3
Western	184,254.0	2.9	2,313,404	8.3
European Union	451,081.9		5,504,683	
Oceania	31,523.6	0.5	230,078	0.8
Australia and New Zealand	23,382.2	0.4	215,726	0.8
Other	8,141.4	0.1	14,351	0.1
World	6,279,153.6	100	27,730,557	100

included cost categories, and a minimum requirement was that at least direct costs were presented. Some recalculations were made in order to obtain comparable cost figures.

Fourteen eligible studies were used [2, 19–31]. All studies are from the WEO's category for advanced economies. Since the selected studies represented countries with a wide range in the number of demented persons, the average ratio between direct costs of dementia and GDP per person was weighted versus the size of the dementia population in the countries from which studies were selected. The average weighted ratio between direct costs per demented person and GDP per person, which is used in the base option, was 43.6% (unweighted 44.0%, median 41.2%). The estimated worldwide direct cost is the sum of the estimated direct costs of all countries worldwide. The model can be expressed as an equation (for e.g. country A):

$$\text{direct cost}_{(\text{country A})} = \text{direct cost per demented}_{(\text{key countries})} \times [\text{GDP}_{(\text{country A})}/\text{GDP}_{(\text{key countries})}] \times \text{prevalence}_{(\text{country A})}.$$

Results

Direct Costs

In 2003, the estimated number of demented persons worldwide was 27.7 million (tables 1, 2), of which 38% lived in the advanced economies (47% in the MDR part of the world). By far the greatest dementia population lives in China (5.2 million). The worldwide direct costs of dementia in 2003 were estimated to be 156.2 billion USD (tables 3, 4). In contrast to how the prevalence was distributed, 92% of the costs occur in the advanced economies/high-income countries (93% in the MDR). The highest single country direct cost was in the USA, 48.6 billion USD, followed by Japan with 24.7 billion USD, while in the EU-25 region it was 60.5 billion USD. In China, the costs were estimated at 2.5 billion USD.

Sensitivity Analysis

The sensitivity analysis of the direct costs (table 5) showed a variation between 129 and 159 billion USD,

Table 2. The worldwide population and worldwide dementia population in different economic areas

Major areas/regions	Population 2003, n × 1,000	Proportion of population, %	Demented 2003	Proportion of demented, %
World	6,279,153.6	100	27,730,557	100
IMF/WEO classification				
Advanced economies	921,770.2	15	10,540,885	38
Other emerging market and developing countries	5,357,383.4	85	17,189,672	62
UN classification				
MDR	1,194,840.0	19	12,969,903	47
LDR	5,084,313.6	81	14,760,654	53
World Bank classification				
Low income	2,313,445.9	37	5,202,278	19
Lower middle income	2,694,142.8	43	10,371,024	37
Upper middle income	335,048.4	5	1,542,461	6
High Income	936,516.4	15	10,614,793	38
OECD countries	1,140,823.4		11,494,933	

IMF = International Monetary Fund; Advanced economies = China Hong Kong SAR, Japan, Republic of Korea, Singapore, Cyprus, Israel, Denmark, Finland, Iceland, Ireland, Norway, Sweden, UK, Greece, Italy, Portugal, Spain, Austria, Belgium, France, Germany, Luxembourg, The Netherlands, Switzerland, Canada, USA, Australia, New Zealand; LDR = Africa, Latin America and the Caribbean, Asia (excluding Japan), Melanesia, Micronesia and Polynesia; MDR = North America, Japan, Europe, Australia, New Zealand.

where the variation of prevalence resulted in the lowest cost. The alternative, based on expenditures on health, gave almost the same result as with the base option, which is not surprising since GDP per capita and expenditures on health are highly correlated. However, particularly between North America (mainly the USA, 63.7 billion USD in this option) and Europe there was a shift, depending on the high expenditures on health in the USA.

Discussion

It is important to stress the fact that the prevalence and cost figures presented in this paper must be seen as estimates rather than exact calculations of costs. To transform and compare cost results between different countries is difficult, as there are many ways to organize and finance care. Most sources also only cover some parts of the world, mainly the advanced economies. Another great problem is the incompleteness of data, both regarding demographics, care organization and costs. The use of macro-economic data, such as our GDP-based model, is a way to avoid these drawbacks.

The estimated number of demented individuals is also crucial for the estimation of the economic burden. Our prevalence figure, 27.7 million, which is an update of a previous calculation [4], is higher than figures presented in one WHO source (about 10 million [32] or 18 million), while it is lower than in another WHO publication (about 34 million) [33].

The key question in this paper is whether the combination of cost-of-illness data from the key studies and macro-economic data are applicable to other parts of the world. The figures from Europe can be compared with the figures presented in the paper by Andlin-Sobocki et al. [5] where a much more comprehensive battery of sources could be used. Our cost per demented is about 91% of the cost in their paper for the corresponding countries. However, it is hard to say whether it is appropriate to assume that the relationship between GDP data and social and health care resources is also valid from a worldwide perspective, particularly since the key studies are all from advanced economies. The knowledge about formal and informal care for demented persons in the developing countries is limited [34]. Even if it is logical to assume that in low-income countries the number of institutional resources is indeed low (or they are not existing), one can question the assumption that, for instance, an increasing GDP per capita correlates in a rather linear way to more (and costly) institutional care. The assumption that unit costs of dementia care correlate with GDP can also be questioned, although it is difficult from a worldwide per-

Table 3. The estimated worldwide direct costs of dementia in 2003

Major areas/regions	Direct costs, billions US	Percent	Costs, USD	
			per demented person	per person 0+
Africa	0.53	0.3	393	0.6
Eastern	0.06	0.0	163	0.2
Middle	0.04	0.0	225	0.4
Northern	0.25	0.2	650	1.3
Southern	0.12	0.1	1,402	2.5
Western	0.07	0.0	189	0.3
Latin America	3.00	1.9	1,604	5.5
Caribbean	0.47	0.3	2,505	12.3
Central	0.98	0.6	2,298	6.9
South	1.54	1.0	1,232	4.3
Northern America	52.62	33.7	16,032	166.3
Asia	31.96	20.5	2,419	8.4
Eastern	28.87	18.5	4,007	19.0
South Central	1.11	0.7	276	0.7
South Eastern	0.88	0.6	610	1.6
Western	1.10	0.7	2,019	5.5
Europe	65.78	42.1	8,447	90.4
Eastern	3.60	2.3	1,439	11.8
Northern	16.38	10.5	13,462	173.4
Southern	15.65	10.0	8,912	108.7
Western	30.15	19.3	13,035	163.7
European Union	60.47		10,985	134.0
Oceania	2.30	1.5	10,071	73.5
Australia and New Zealand	2.30	1.5	10,671	98.5
Other	0.00	0.0	1,058	1.9
World	156.20	100	5,633	24.9

0+ = total population.

spective to confirm or reject it. An indirect support for this assumption may be the well-known correlation between expenditures on health care and GDP (even if most of the direct costs of dementia care can be regarded as non-medical). Nevertheless, we think that the estimates, with all these drawbacks, represent a rather valid estimate of the worldwide direct costs of dementia.

The dichotomous way of dividing the countries in the world (as 'advanced economies' vs. the 'other emerging market and developing countries' or MDR vs. LDR) is rather rough since there are, indeed, differences between countries in these categories, and many countries are in a transition toward a better economic situation. The World Bank classification offers somewhat more detailed information and can also catch the transitions in a better way.

The 'greying' of populations not only in the advanced economies, but also in the developing countries with an expected increase in the prevalence of dementia [4], will put a stress on the care systems in all countries. However, whether it is good or bad to build up a formal care infrastructure in the developing countries similar to that in the advanced economies (e.g. institutions, home medical care, day care) is hard to say, and the assumption that an economic transition with changing family patterns poses a threat to the elderly has been questioned [35]. On the other hand, in many advanced economies there is a trend of deinstitutionalization, often combined with an economic crisis in the public health and social systems, leading to other kinds of problems. Since dementia disorders are costly and also constitute a great part of the total costs in the welfare system, dementia disorders should be the focus for not only specific care planning on all levels in the society, but also for extensive cost-effectiveness research.

Table 4. The estimated worldwide direct costs of dementia in different economic areas in 2003

Major areas/regions	Direct costs, billions USD	Percent	Costs, USD	
			per demented person	per person 0+
World	156.20	100	5,633	24.9
IMF/WEO classification				
Advanced economies	143.53	92	13,617	155.7
Other emerging market and developing countries	12.67	8	737	2.4
UN classification				
MDR	145.44	93	11,214	121.7
LDR	10.76	7	729	2.1
World Bank classification				
Low income	1.1	1	216	0.5
Lower middle income	7.3	5	705	3
Upper middle income	3.7	2	2,411	11
High income	144.0	92	13,570	154
OECD countries	145.14	93	13,589	136.9

0+ = total population; IMF = International Monetary Fund.

Table 5. Sensitivity analysis of the direct costs

	Base option	Prevalence [10]	Prevalence [9]	GDP-based (outliers excluded)	Health expenditures
Africa	0.53	0.55	0.43	0.51	0.70
Latin America	3.00	3.00	2.46	2.87	4.76
Northern America	52.62	51.41	43.40	50.49	67.79
Asia	31.96	31.84	26.44	30.67	25.76
Europe	65.78	64.78	54.68	63.12	57.30
Oceania	2.32	2.29	1.92	2.22	2.30
World	156.20	153.87	129.33	149.90	158.62

It is not easy to compare worldwide cost-of-illness studies, due to methodological issues (different methods for cost calculations, lack of data from many parts of the world, different care systems etc). The worldwide direct costs of diabetes, another long-lasting chronic disorder, has been estimated at 44.4 billion USD (in 1997) [36], giving a hint of the magnitude of the direct costs of dementia.

In conclusion, due to several sources of uncertainty, the range of cost estimates is relatively wide. The research database is small, particularly in the developing countries, and there is a great need for extensive research in a broad way. It is also necessary to perform cost studies from countries with different ways of financing and organizing care. Incomplete demographic statistics, different ways of financing and organizing dementia care, available resources and the relative importance of informal care are examples of factors that contribute to between-country variability and uncertainty in estimates. Nevertheless, it is obvious that the worldwide costs are substantial and the expected increase in elderly people in the developing countries presents a great challenge for social and health care systems.

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RESEARCH

Survival times in people with dementia: analysis from population based cohort study with 14 year follow-up

Jing Xie, research associate,[1] Carol Brayne, professor,[1] Fiona E Matthews, senior research scientist,[2] and the Medical Research Council Cognitive Function and Ageing Study collaborators

[1]Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge CB2 0SR

[2]MRC Biostatistics Unit, Institute of Public Health, Cambridge

Correspondence to: C Brayne carol.brayne@medschl.cam.ac.uk

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ABSTRACT

Objectives To provide estimates of survival after onset of dementia by age, sex, self reported health, disability, and severity of cognitive impairment.

Design Analysis of participants from prospective population based cohort study in 1991-2003, with follow-up of dementia status in all individuals after two and six years (in one centre) and 10 years and in subsamples additionally at six and eight years and mortality until 2005.

Setting Multicentre population based study in England and Wales: two rural and three urban centres.

Participants 438 participants who developed dementia from a population based study of 13 004 individuals aged 65 years and over drawn from primary care population registers.

Main outcome measures Sociodemographic factors, cognitive function, specific health conditions, and self reported health collected at each interview. Cox's proportional hazards regression models were used to identify predictors of mortality from the selected variables in people who received diagnosis of dementia according the study's criteria.

Results By December 2005, 356 of the 438 (81%) participants who developed dementia during the study had died. Estimated median survival time from onset of dementia to death was 4.1 years (interquartile range 2.5-7.6) for men and 4.6 years (2.9-7.0) for women. There was a difference of nearly seven years in survival between the younger old and the oldest people with dementia: 10.7 (25th centile 5.6) for ages 65-69; 5.4 (interquartile range 3.4-8.3) for ages 70-79; 4.3 (2.8-7.0) for ages 80-89, and 3.8 (2.3-5.2) years for ages ≥90. Significant factors that predicted mortality in the presence of dementia during the follow-up included sex, age of onset, and disability.

Conclusion These analyses give a population based estimated median survival for incident dementia of 4.5 years. Such estimates can be used for prognosis and planning for patients, carers, service providers, and policy makers.

INTRODUCTION

Life expectancy is increasing globally. One consequence is that the number of people affected by dementia is estimated to double every 20 years to 81.1 million by 2040.[1] A Delphi consensus study of global prevalence of dementia estimated that 24.3 million people have dementia, with 4.6 million new cases every year.[1] Dementia is also a major cost to health care and social systems in the developed world. In the United Kingdom in 1998, the institutional cost of people with cognitive impairment (n=224 000) was estimated at 0.6% of the UK gross domestic product (£4.1bn, €5.7bn, $8.2bn).[2] Given its impact on society, improvements in our understanding of causes, course, and consequences of dementia are of key importance.

One frequently raised question in clinical and policy settings is the impact of dementia on life expectancy. People with dementia have markedly decreased survival rates compared with those without dementia[3-5] and are two to four times more likely to die at a given age than those of the same age without dementia.[6 7] Even mild cognitive impairment is associated with the increased relative risk of mortality.[6 8] The median survival time of patients with dementia has been investigated in cohort studies and case series in various settings and ranges from three to nine years.[4 7 9] Characteristics reported to be associated with variation in survival include age, sex, sociodemographic characteristics, initial severity of dementia, type of dementia, other comorbid conditions, and genetic characteristics. The high mortality in people with dementia persists into the older age group.[3 6 10] Sex is less related,[11 12] although most studies report shorter survival in men across all age groups compared with women.[10] The influence of education is also inconsistent, with some reports of increased mortality with lower levels of education[13] while others report no such relation[14] or even the reverse.[15] The more severe the dementia, the higher the risk of mortality over the long term,[10 16] but again, this finding is not consistent.[17]

Variation in survival might also be caused by differences in study design. Some studies are population based,[18 19] others community based,[3 4 10] and some are institution based.[20] Shorter survival is reported in institutional compared with community based settings.[21] Some are control studies, others are case control or case series.[3 4] Different diagnostic criteria for dementia and age at diagnosis might result in differential survival time.[13 22] Most studies are based

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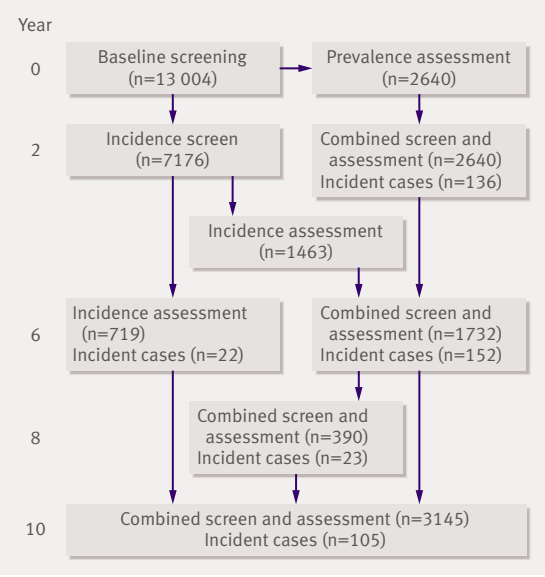

Flowchart of incident dementia cases

on prevalent cases, which could lead to bias because of the exclusion of patients with relatively rapid progressive dementia.[13 23] Analysis that uses incident dementia avoids this bias, but introduces other difficulties such as how to decide the time of onset, which could be based on dates of first symptoms and first consultation, median time between two interviews, or initial clinical diagnosis. Few studies have investigated the difference, but one study reported a median survival of 5.7 years from diagnosis of dementia, but 10.5 years from onset of first reported symptomatic sign.[3]

There is considerable uncertainty about what influencessurvival of people with dementia in the real population. Thisis an important public health issue and provides information for policy makers, practitioners, and families.[24] We have already shown that dementia and severe cognitive impairment can be present at the end of life, increasingly so with increasing age.[25] We looked at overall survival for people with dementia and examined the association between factors that could affect survival in incident dementia over a 14 year follow-up.

METHODS

Study design and population

The Medical Research Council's cognitive function and ageing study (MRC CFAS) is a multicentre, longitudinal, prospective population based epidemiological study of cognitive function and disability in the UK. The fieldwork methods were standardised for Cambridgeshire, Gwynedd, Newcastle, Nottingham, and Oxford, where at least 2500 people aged 65 years and over were interviewed at each centre, divided equally between two age groups: 65-74 and 75 years and over. The sampling included institutions, and the overall response rate (82%) provides good population representation. Details of the study design and a description of the baseline sample are reported elsewhere.[26] Incidence was measured at a two year repeat of these.

Participants were re-interviewed over a 10 year period and followed up for mortality for 14 years. All participants underwent a screening interview for the baseline examination, with 20% being assessed in a more detailed interview after a median of three months. At two years interviews consisted of an incidence screen for those who had not previously been selected for assessment followed by a selection of 20% for assessment and a combined screen and assessment for those who had been assessed previously at baseline. The assessment sample (representing 20% of those screened) at both baseline and two year interviews represented all those with cognitive impairment (using AGECAT algorithm and mini-mental state examination scores) and a random sample above mini-mental state examination score cut points. The combined screen and assessment interview was repeated at six, eight, and 10 years. All interviews contained the mini-mental state examination. The Cambridge centre additionally interviewed the complete sample with a combined screen and assessment interview at six years. At the time of most assessment interviews, and when a diagnosis of dementia was likely from the combined screen and assessment interviews, a participant's relative or carer underwent an informant assessment interview, also known as the history and aetiology schedule. We included in the analysis incident dementia cases in all individuals after two, six (in Cambridge), and 10 years and in subsamples additionally at six and eight years.

Participants were flagged at the Office for National Statistics National Health Service Central Register so we received an automatic notification of death. We collected date of death for all those who died on or before 31 December 2005.

All participants gave informed consent when appropriate and next of kin gave assent on the wishes of the respondent when capacity to make informed decisions was impaired.

Definition of incident dementia

The assessment comprised standardised questions required for the identification of major psychiatric disorders of old age (the geriatric mental state examination). Diagnosis of incident dementia was based on the geriatric mental state examination algorithm at the assessment interview.[27] This is a validated algorithm most similar to *Diagnostic and Statistical Manual of Mental Disorders* (third edition). We classed the time of onset of dementia as the midpoint between the last follow-up without dementia and the first follow-up with dementia.

Cognitive impairment within dementia

Cognitive function was measured with the mini-mental state examination.[28] If a non-physical question was not asked or any item was skipped, a person's score was set to missing. Scores for those unable to complete all items because of physical difficulties such as blindness were

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coded as zero. The score was divided into four groups (≤17, 18-21, 22-25, and 26-30). Lower scores suggest poorer cognitive function. If a score is missing it means that participants could not be tested and are considerably impaired.

Associated factors

In keeping with the findings of other studies we included variables known to have an association with mortality: age, sex, marital status, accommodation type, education level, social class, functional status, self reported health, and area deprivation.[3 4 6 13 22]

Functional impairment (disability)—Functional health status was measured using Blessed dementia scale items. Scores ranged from 0-17. The score was calculated for individuals for whom an informant was interviewed—that is, at prevalence assessment, incidence assessment, and at combined screen and assessments at baseline and two, six, eight, and 10 years. We divided the scores into thirds for analysis.

Self reported health—Self reported health was measured with a four point scale, based on the question: "How would you say your health is these days: Would you say your health is excellent, good, fair, or poor?"

Table 1 | Characteristics of 438 incident dementia cases in the Medical Research Council's cognitive function and ageing study. Figures are numbers (percentages) unless stated otherwise

Variables*	Women (n=311)	Men (n=127)	Total
Median (IQR) age at onset	84 (80-88)	83 (77-87)	84 (79-88)
Median (IQR) age at death	90 (85-93) (n=252)	87 (83-91) (n=104)	89 (84-92) (n=356)
Education in years:			
≤9	217 (71)	91 (73)	308 (71)
10-11	56 (18)	25 (20)	81 (19)
≥12	34 (11)	8 (7)	42 (10)
Social class:			
I/II	83 (27)	32 (25)	115 (26)
III	129 (41)	62 (49)	191 (44)
IV/V	82 (26)	31 (24)	113 (26)
Armed force/unclassified	17 (6)	2 (2)	19 (4)
Accommodation type:			
Community†	188 (61)	90 (71)	278 (64)
Residential and nursing home	122 (39)	37 (29)	159 (36)
Marital status:			
Married/cohabiting	30 (10)	12 (10)	42 (10)
Single	61 (20)	71 (58)	132 (31)
Widowed	213 (70)	39 (32)	252 (59)
Townsend deprivation index:			
Top third	108 (36)	42 (33)	150 (36)
Middle third	105 (35)	40 (32)	145 (34)
Bottom third	84 (29)	44 (35)	128 (30)
Self reported health:			
Excellent	44 (14)	15 (12)	59 (13)
Good	141 (45)	52 (41)	193 (44)
Fair	85 (27)	39 (31)	124 (28)
Poor	26 (12)	15 (12)	41 (9)
Missing	15 (5)	6 (5)	21 (5)
Blessed dementia scale:			
Least impaired third	74 (24)	36 (28)	110 (25)
Middle impaired third	73 (23)	29 (23)	102 (23)
Most impaired third	82 (26)	23 (18)	105 (24)
Missing	82 (26)	39 (31)	121 (28)
Mini-mental state examination:			
26-30	3 (1)	4 (3)	7 (2)
22-25	27 (9)	18 (14)	45 (10)
18-21	63 (20)	33 (26)	96 (22)
0-17	167 (54)	52 (41)	219 (50)
Missing	51 (16)	20 (16)	71 (16)

IQR=interquartile range.
*Missing data for 7, 1, 12, and 15 in education, accommodation type, marital status, and Townsend deprivation index, respectively.
†Community accommodation (own home, granny flat, or warden controlled accommodation).

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Deprivation—The Townsend deprivation score was chosen as a measure of area level deprivation. Based on the 1991 census data, we calculated the score from the respondents' postcodes at baseline screen.

Statistical analyses

We excluded individuals with prevalent dementia at entry into the cohort from these analyses. All participants alive on or after 31 December 2005 were censored in the analysis. Person years of observation were defined as the interval between the date of onset of dementia and death or 31 December 2005. We excluded individuals seen only at baseline, two years, and 10 years as we could not estimate the onset of dementia between the two follow-ups.

We compared demographic and health characteristics for those with dementia with Mann-Whitney U test for continuous variables and with Person χ^2 test for categorical variables.

Potential predictors included in the models were age at onset of dementia (65-69, 70-79, 80-89, and ≥90 years), sex, educational level (≤9, 10-11, ≥12 years), marital status (married/cohabiting, widowed/separated, and single), social class

Table 2 | Median (IQR) survival time in years of 438 incident dementia cases

	Women	Men	All
Sex	4.6 (2.9-7.0)	4.1 (2.5-7.6)	4.5 (2.8-7.0)
Median age at onset:			
65-69	7.5 (4.8-NA)	NA (9.1-NA)	10.7 (5.6-NA)
70-79	5.8 (3.6-8.3)	4.6 (3.0-8.6)	5.4 (3.4-8.3)
80-89	4.4 (2.8-7.0)	3.7 (2.5-6.3)	4.3 (2.8-7.0)
≥90	3.9 (2.4-5.2)	3.4 (1.5-5.5)	3.8 (2.3-5.2)
Education (years):			
≤9	4.7 (3.1-7.3)	4.0 (2.8-7.0)	4.6 (2.9-7.0)
10-11	4.5 (3.0-7.1)	3.3 (2.2-6.6)	4.0 (2.8-6.6)
≥12	3.6 (2.0-6.7)	4.2 (1.9-8.6)	3.7 (2.0-6.7)
Social class:			
I/II	4.7 (2.7-6.8)	4.2 (2.2-7.0)	4.6 (2.7-6.9)
III	4.6 (3.2-7.5)	3.8 (2.5-6.6)	4.1 (2.9-7.0)
IV/V	4.9 (2.9-7.3)	5.2 (2.6-10.6)	5.0 (2.9-8.3)
Unclassified	3.3 (2.0-5.8)	4.0 (4.0-5.5)	3.8 (2.0-5.8)
Accommodation type:			
Community	4.9 (3.2-8.3)	4.6 (3.1-7.9)	4.9 (3.2-8.2)
Residential and nursing home	4.0 (2.6-5.9)	2.8 (2.0-4.1)	3.7 (2.3-5.8)
Marital status:			
Widowed	4.4 (2.8-6.5)	3.6 (2.5-5.2)	4.3 (2.8-6.4)
Married/cohabiting	7.0 (3.5-10.1)	4.2 (2.4-7.6)	5.0 (3.2-8.6)
Single	3.3 (2.5-5.9)	4.0 (2.8-9.6)	3.8 (2.6-7.0)
Third of Townsend deprivation scale:			
First	4.7 (3.2-7.0)	3.8 (2.8-7.0)	4.6 (3.0-7.0)
Second	4.9 (2.9-7.0)	4.1 (2.8-6.5)	4.7 (2.9-7.0)
Third	4.0 (2.6-7.5)	4.0 (2.2-9.6)	4.0 (2.5-7.7)
Self reported health:			
Excellent	5.0 (3.3-9.1)	4.5 (2.8-6.1)	4.9 (2.8-8.7)
Good	4.7 (3.0-7.0)	4.2 (2.6-9.1)	4.6 (3.0-7.0)
Fair	4.5 (3.0-6.5)	3.4 (2.2-6.8)	4.4 (2.8-6.6)
Poor	3.2 (2.0-5.8)	4.1 (2.4-7.6)	3.8 (2.3-6.3)
Third of Blessed dementia scale:			
First	6.4 (4.0-10.0)	6.6 (3.9-10.4)	6.4 (4.0-10.4)
Second	4.0 (3.0-6.0)	4.6 (2.6-6.3)	4.2 (2.8-6.0)
Third	3.4 (2.4-5.4)	2.9 (1.5-5.1)	3.3 (2.2-5.3)
Missing	4.8 (3.2-7.0)	3.6 (2.8-5.5)	4.6 (2.9-7.0)
Mini-mental state examination:			
26-30	NA (3.4-NA)	NA (4.6-NA)	NA (4.6-NA)
22-25	7.0 (4.6-NA)	4.6 (3.1-6.6)	6.1 (3.9-10.4)
18-21	4.9 (3.2-7.5)	4.6 (2.9-7.6)	4.7 (3.0-7.6)
0-17	4.5 (2.8-6.8)	3.8 (2.2-6.5)	4.3 (2.8-6.6)
Missing	3.9 (1.9-5.4)	3.0 (2.0-3.9)	3.6 (2.0-5.4)

IQR=interquartile range; NA=not available because of censored information on survival.

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(professionals (I), managerial and technical workers (II), skilled non-manual and manual (III), partly skilled workers (IV), and unskilled manual workers (V)), accommodation type (community *v* institution), third of Townsend deprivation score, Blessed dementia scale (least impaired, middle, and most impaired thirds), score on the mini-mental state examination (≤17, 18-21, 22-25, 26-30), and self reported health (excellent, good, fair, or poor). The values of potentially time dependent variables were taken from the interview closest to the estimated onset of dementia. For the 40% with missing data for self reported health, we took that from the closest interview.

Mortality was calculated by dividing the number of individuals who had died by person years at risk during the 14 years of follow-up. We used the Kaplan-Meier method to calculate median survival times from date of onset of dementia and log rank tests to evaluate the survival distributions of different groups. Factors associated with death were analysed with Cox's proportional hazards regression model, which included only those factors that were significant in the univariate analysis. We used Schoenfeld residual tests to evaluate the proportional hazard assumption and checked interactions between variables. This model generates regression coefficients for the independent variables, the exponents of which reflect hazard ratios. All data were analysed with Stata software, version 9.2 (Stata Corp, College Station, TX). The dataset we used was version 8.1 of the Medical Research Council's cognitive function and ageing study.

RESULTS

Descriptive characteristics

At baseline, 13 004 participants were included in the cohort. A total of 438 incident dementia cases were available from 1991 to 2003 (figure). Of all the participants, 41% had intervals of two years or less between the interviews that measured the transition from no dementia to dementia. Table 1 shows characteristics of the participants.

The median age at onset of dementia was 84 (interquartile range 80-88) for women and 83 (77-87) for men (P=0.001 for difference). Two thirds of individual cases were women (311, 71%). Among the 356 who died, the median age at death was 90 for women and 87 for men (P=0.001). Compared with men, women were more likely to be widowed (70% *v* 32%, P=0.001) and living in residential and nursing homes (39% *v* 29%, P=0.001). Women had lower scores on the mini-mental state examination (median 16 *v* 18, P=0.006).

Impact of dementia on median survival time and mortality

We derived all median survival times from Kaplan-Meier estimates from onset of dementia. During the

Table 3 | Hazard ratios (HR) for death of incident dementia cases, with multiple adjustments for all variables shown

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex:				
Women	1	0.7	1	0.007
Men	1.0 (0.8 to 1.3)		1.4	
Age at onset:				
65-69	1	<0.001	1	0.03
70-79	3.3 (1.4 to 7.5)		2.1 (0.9 to 4.9)	
80-89	4.5 (2.0 to 10.2)		2.7 (1.1 to 6.3)	
≥90	6.4 (2.7 to 15.0)		3.1 (1.3 to 7.5)	
Accommodation type:				
Community	1	<0.001	1	0.14
Residential and nursing home	1.6 (1.3 to 2.0)		1.2 (0.9 to 1.6)	
Marital status:				
Widowed	1	0.005	1	0.2
Married/cohabiting	0.7 (0.5 to 0.9)		0.7 (0.6 to 1.0)	
Single	0.9 (0.6 to 1.3)		0.9 (0.6 to 1.4)	
Third of Blessed dementia scale:				
First	1	<0.001	1	0.002
Second	2.1 (1.5 to 2.9)		1.8 (1.3 to 2.5)	
Third	2.9 (2.1 to 4.0)		2.1 (1.6 to 3.3)	
Missing	1.9 (1.4 to 2.6)		1.6 (1.2 to 2.2)	
Mini-mental state examination:				
26-30	0.1 (0.03 to 0.5)	<0.001	0.3 (0.1 to 1.5)	0.3
22-25	0.6 (0.4 to 0.8)		0.8 (0.5 to 1.2)	
18-21	0.9 (0.7 to 1.2)		1.2 (0.9 to 1.6)	
0-17	1		1	
Missing	1.3 (1.0 to 1.7)		1.2 (0.9 to 1.6)	

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Dementia is associated with an increased risk of death

No estimate exists for actual survival with dementia in England and Wales

WHAT THIS STUDY ADDS

People with incident dementia survive on average for 4.5 years

Survival varies between 10.7 and 3.8 years between younger old and oldest old

Sex and disability influence survival

follow-up period, 356 (81%) individuals died. Survival from estimated onset of dementia was 4.6 years for women and 4.1 years for men (table 2), with a significant trend for age.

In the univariate analysis, those with higher education had slightly shorter survival than those with lower education, but this did not reach conventional significance. Social class showed no pattern. Though those who assessed their health as "poor" before the onset of dementia had shorter survival (3.8 years) than those who assessed their health as "excellent" (4.9 years), the difference was not significant. None of these non-significant variables was put in the multivariable Cox's proportional hazards regression model. Married individuals with dementia had the longest median survival (7.0 years for married/cohabiting, 4.4 years for widowed/separated, and 3.3 years for single), while widowed men had the shortest survival (table 3).

Those who were functionally impaired, older, and male had predicted shorter survival, but accommodation type, marital status, and score on the mini-mental state examination were no longer associated with survival (table 3).

DISCUSSION

Summary of findings

In a large population based sample, survival after the estimated onset of dementia was 4.6 years for women and 4.1 years for men. Survival was influenced by age, sex, and disability before onset. Accommodation type, marital status, and self reported health were not associated with survival once we controlled for other factors. An estimate of the expected survival after the onset of dementia is a useful measure for individuals, families, and society. Clinicians and those providing care for patients with dementia are often asked to provide a sense of how long the patient might survive. There is often a delay in recognition of dementia and formal diagnosis, which clinicians need to consider when using the best estimate in each clinical case. Knowing which factors influence the length of survival is also important.

Our findings might be limited because often we did not exactly know the timing of onset of dementia and used an estimate as the midpoint between interviews. This is unlikely to have introduced bias as most individuals were captured by the design.

Limitations

In our cohort participants who died rapidly after onset could not be diagnosed and thus cannot be included in the survival analysis of those with incident dementia. This could lead to an overestimate of the survival time. Analysis of attrition for this study has shown that individuals who dropped out or refused follow-up during the study tended to have impaired cognitive ability and higher mortality.[29] We therefore potentially missed this type of incident case. Few previous studies have investigated mortality with dementia in the community based on incident cases but this is probably the measure of most value to clinicians and families[13] and can be adjusted by clinicians to take into account the lag between onset and the time a clinician estimates an individual would have fulfilled dementia criteria. We did not attempt to split the sample further by subtype as the neuropathology is often mixed in the population.[30] Clinical studies have examined the relation between particular syndrome profiles and survival, but we did not cover this and aimed to provide broad groups for easier application and which are available for all individuals.

Findings in context of the literature

The Canadian Study of Health and Ageing used estimated survival from incidence by basing an analysis on prevalent cases but measuring survival from an estimated earlier time of onset. Median survival times are shorter, perhaps because of this design feature and the shorter duration of follow-up (five years).[19] The estimates from a French epidemiological study on brain ageing (PAQUID) are similar to ours.[13] A further study from the US did not include institutions, possibly leading to longer estimated survival times than ours.[10]

As expected, we found significant trends of decreasing survival with increasing age for women and men, in line with others.[3 10 13] The absolute differences are large, with more than five years' difference between the youngest and oldest groups. Women with dementia have longer survival than men in our study and others.[10 13]

We did not find strong educational effects. Univariate analysis suggests shorter survival for people with more education, as reported in some of the literature[13] but not in other studies.[31] These discrepancies might be caused by variation in the nature of variables adjusted in multivariable analysis. Although individuals in institutions do live for a shorter time, this is also accounted for by other factors measured in this study.[13 21]

Lower cognitive function and dementia shorten survival, but our analysis shows that once other factors are controlled for, cognitive level within dementia is no longer significant. It is useful to know survival for specific mini-mental state examination bands as these can be applied directly for clinical use. Survival is lower by more than two years in those who cannot do the

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mini-mental state examination compared with those with higher scores, perhaps highlighting a more aggressive course. Severe comorbidity is unlikely to account for these findings as such individuals are less likely to be interviewed and are under-represented.

Disability with dementia is still associated with shorter survival, even when other factors are taken in account, as found in other studies,[32] with around a three year absolute reduction in survival between the most and least disabled. This does suggest that the frailer individuals are at higher risk even after age is considered.

Other studies have estimated associations between mortality and baseline variables without taking into account changes in these variables during follow-up.[10 32] Our analysis uses values from the interview closest to onset with the intention of providing more clinically useful estimates. The major strengths of our study include its representative sampling from the population (including institutions), prospective study design, detailed measures on individuals before onset of dementia, and length of follow-up (14 years). Our analyses provide robust population based estimated survival for incident dementia by age, sex, and setting. Some of these results may seem self evident but they answer questions asked by those caring for and advising people with dementia. We hope the estimates will be valuable to patients, clinicians, carers, service providers, and policy makers.

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DEVELOPMENT AND VALIDATION OF A GERIATRIC DEPRESSION SCREENING SCALE: A PRELIMINARY REPORT

JEROME A. YESAVAGE, T. L. BRINK

Department of Psychiatry and Behavioral Sciences, Stanford University of Medicine, Stanford, CA 94305, U.S.A.

TERENCE L. ROSE

Veteran's Administration Medical Center, Palo Alto, CA 94304, U.S.A.

OWEN LUM

Geriatric Treatment Team, Santa Clara County Mental Health

VIRGINIA HUANG, MICHAEL ADEY and VON OTTO LEIRER

Veteran's Administration Medical Center, Palo Alto, CA 94304, U.S.A.

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Summary—A new Geriatric Depression Scale (GDS) designed specifically for rating depression in the elderly was tested for reliability and validity and compared with the Hamilton Rating Scale for Depression (HRS-D) and the Zung Self-Rating Depression Scale (SDS). In constructing the GDS a 100-item questionnaire was administered to normal and severely depressed subjects. The 30 questions most highly correlated with the total scores were then selected and readministered to new groups of elderly subjects. These subjects were classified as normal, mildly depressed or severely depressed on the basis of Research Diagnostic Criteria (RDC) for depression. The GDS, HRS-D and SDS were all found to be internally consistent measures, and each of the scales was correlated with the subject's number of RDC symptoms. However, the GDS and the HRS-D were significantly better correlated with RDC symptoms than was the SDS. The authors suggest that the GDS represents a reliable and valid self-rating depression screening scale for elderly populations.

INTRODUCTION

MOST EXISTING depression rating scales have been developed and validated in younger populations and their applicability with older persons has not yet been demonstrated. The scale described in this article was specifically designed to measure depression in the aged, primarily as a screening instrument, and validated within this population.

MEASURING DEPRESSION IN THE AGED

The need for a geriatric depression scale is obvious. Between 5 and 20% of the 20 million aged Americans are estimated to be depressed (GURLAND, 1976). Although one could apply existing general psychiatric depression scales to this population, the aged present unique problems for clinicians and researchers interested in the study and treatment of depression (SALZMAN and SHADER, 1978).

A major problem is the confusion of dementia with depression in the elderly. The syndrome of "pseudodementia", with psychomotor retardation and passive refusal to

respond appropriately to cognitive tests is depression mistaken for dementia (WELLS, 1979; JARVIK, 1976). Depression in the elderly often is accompanied by subjective experiences of memory loss and cognitive impairment (KAHN *et al.,* 1975), symptoms seen less frequently in the young.

Conversely, somatic symptoms which are usually a key to diagnosis of depression in the young are less useful in the elderly. For instance, sleep disturbances are a common symptom of endogenous depression; but such disturbances are also common in the nondepressed elderly (COLEMAN *et al.,* 1981), while rare in younger persons not suffering from depression. A host of other examples include the normal decline of sexual function, constipation, and the aches and pains associated with arthritis in the aged.

The high prevalence of somatic complaints among the elderly and their unique cognitive complaints present both a problem and an opportunity in screening for depression in the elderly. The problem is that most existing scales are heavily loaded toward measuring the somatic symptoms of depression. Although somatic complaints are clearly part of major depressive disorders, this will not necessarily be the case in milder forms of depression. Moreover, to the extent one is interested in screening for depression rather than formal diagnosis or description, discrimination between depressed and nondepressed persons or between different degrees of depression would seem to be the primary concern. For this reason it may be necessary to weight somatic symptoms of depression less heavily than psychological symptoms having greater discriminative power. On the other hand, the unique cognitive complaints of the elderly may present an opportunity to devise screening instruments with enhanced discriminative power in the elderly.

Another problem in the assessment of geriatric depression and other disorders experienced by the aged is that the elderly are typically more resistant to psychiatric evaluation than younger patients (SALZMAN and SHADER, 1978; WELLS, 1979). Consequently, one needs to design the items comprising a scale to fit this population; questions appropriate for use with the young may not be appropriate for the old. For example, questions about sexuality often make the elderly defensive, and yet they are included on many existing scales. Other questions may pose problems of patient acceptance as well as leading to problems of interpretation (BLUMENTHAL, 1975). For example, questions about suicidal intent, whether life is worth living, or whether one is hopeful about the future obviously have different meaning in those reaching the end of their lifespan. Of course these problems of patient resistance and unique interpretation can probably be dealt with adequately if an experienced interviewer administers the depression scale, and the scale is designed to elicit more open-ended responses from the patient in an atmosphere fostering good rapport. However, in designing a self-rating depression scale for the aged, these issues need to be adequately addressed in the scale's initial development.

It is also essential to provide a simple, easily understood format in the development of a geriatric depression scale. Several of the self-rating scales presently available may be too difficult for the elderly to complete by themselves. For example, Zung's (1965) self-rating scale for depression uses a four-point scale that is likely to be more confusing than a yes/no format, because it involves a greater number of choices and subtle discriminations that must be made by the person.

The scale reported here was designed to avoid most of these problems associated with

the measurement of geriatric depression by developing the scale with the aged in mind and by selecting items for the scale based on their performance within this population. Questions that proved to have inadequate power to discriminate depressed from non-depressed elderly were not incorporated into the scale while uniquely discriminating items that might not be as useful with younger groups were included. Furthermore, a yes/no format was used in order to make the scale a simple one that could be used in nearly all instances as a self-rating scale and one that would be acceptable to patient and physician alike.

EXISTING DEPRESSION SCALES

There are numerous depression rating scales currently available. These have been subject to several reviews (CARROLL *et al.*, 1973; KOCHANSKY, 1979; MCNAIR, 1979; HEDLUND and VIEWEG, 1979) and include: Hamilton Rating Scale for Depression (HRS-D), Zung Self-Rating Depression Scale (SDS), Beck Depression Inventory, Phenomena of Depression Scale, Grading Scale for Depressive Reactions, Psychiatric Judgment of Depression Scale, NIMH Collaborative Depression GDS, SAD-GLAD, Verdum Depression Rating Scale, CES-D, SCL-90 Profile of Mood States, and the MMPI Depression Scale.

These scales represent a mixture of observer-rated and self-rating scales. In some cases the same scale may also have been designed to function in either manner or an observer-rated measure of depression has been adapted for use as a self-rating scale. CARROLL *et al.*'s (1973) adaptation of the HRS-D represents an example of the latter approach. A problem with adapting a scale from one format to the other, however, is that questions which may have been acceptable to respondents in an interview setting where good rapport is established by the interviewer may no longer be accepted by the respondent when the same questions are asked using a self-rating scale. We have found this to be the case, for example, with Carroll *et al.*'s scale; mildly depressed subjects dislike the disease-oriented questions and have difficulty with questions which assume they are in a hospital setting.

However, the primary problem with these depression scales is that they were not originally designed for use with the elderly and rarely have they been properly validated in this population. There are some exceptions. There has been an attempt to validate the SDS in the aged, but the ability of the SDS to discriminate nondepressed from depressed elderly was found to be limited (ZUNG and GREEN, 1973). Zung suggested using a classification criterion of 40 for depression; although this would correctly identify 88% of depressives, it leads to the false identification of normal elderly as being depressed in 44% of the cases. Other comprehensive reviews suggest that there are still no better criteria that would reduce the number of false positives associated with the SDS (CARROLL *et al.*, 1973; CARROLL, 1978). Thus, although this represents the best validation efforts in this population to date, the SDS still has limitations as a geriatric depression screening device.

Despite the virtual absence of studies aimed at validating existing depression scales within elderly populations, these scales may prove to be useful even though they were not originally designed with the aged in mind. For this reason two of the existing scales were included in the present research. Their inclusion also was desirable so that comparisons between the GDS with currently existing measures could be made. The present research

was not aimed, however, at demonstrating the superiority of the proposed scale over those currently available. Indeed, the enormous number of existing scales would make this a tremendous undertaking. Rather, existing scales were included in order to provide additional information about the convergent validity of the GDS and to enable tentative norms for the GDS to be compared to those for other, more extensively researched measures.

The first of these was the Hamilton Rating Scale for Depression or HRS-D (HAMILTON, 1960). It was intended to be a measure of treatment outcome rather than as a screening device. Unlike the GDS it is designed to be completed by an experienced observer after a 30 min clinical interview which assays most phenomena associated with "endogenous" depression, e.g. insomnia, decreased libido, loss of appetite (LYERLY, 1978). The HRS-D is probably the most widely accepted clinical interview for depression. It has been shown to be a rapidly learned and reliable measure (HAMILTON, 1967) capable of distinguishing between different degrees of depression (CARROLL *et al.*, 1973; BIGGS *et al.*, 1978; KNESEVICH *et al.*, 1977) and to be one of the few scales available that is also useful as a diagnostic instrument (SCHNURR *et al.*, 1976).

The other scale included in the present research was the Zung Self-Rating Scale for Depression or SDS (ZUNG, 1965). It was administered because of its popularity and the availability of norms for elderly subjects. The SDS has been found to be internally consistent with split-half reliability coefficients in the range of 0.73–0.79. However, validity coefficients have shown greater variability across studies; correlations with the HRS-D have ranged from 0.22 to 0.95 (HEDLUND and VIEWEG, 1979). Although quite widely used among clinicians and researchers working psychiatry, the SDS has recently come under criticism as both a research measure and clinical screening device (CARROLL *et al.*, 1973).

Two studies were conducted in the process of developing and validating the Geriatric Depression Scale (GDS). In the first study, a large pool of items were constructed and then tested for the extent to which they appeared to measure depression in the aged. In the second subject, a subset of these items were selected, readministered to a new sample of subjects, and validated against an independent criterion of depression. The latter study also provided a basis for comparing properties of the GDS to other existing measures of depression due to the inclusion of the SDS and HRS-D. These studies will be discussed in turn. Finally, after describing the results of these studies, a number of recent investigations aimed at demonstrating the performance of the GDS in more specific elderly populations will be discussed.

STUDY ONE: ITEM SELECTION

Methods

A team of clinicians and researchers involved in geriatric psychiatry selected 100 questions believed to have potential for distinguishing elderly depressives from normals. In choosing these questions care was taken to include material covering a wide variety of topics relevant to depression, such as somatic complaints, cognitive complaints, motivation, future/past orientation, self-image, losses, agitation, obsessive traits, and mood itself. A yes/no format was chosen for ease of administration since our experience

with the SDS indicated that a range of possibilities often confused elderly patients. Questions also were phrased in a format that would not alarm patients or make them overly defensive. We thought that these features of the scale would maximize its use as a self-rating instrument of depression in the elderly.

After selecting these items for inclusion in the questionnaire, it was administered in its self-rating form to 47 subjects. The subjects were either normal elderly living in the community with no complaints of depression and no history of mental illness, or subjects hospitalized for depression. Both male and female patients were included from a number of hospitals in Santa Clara County California. All subjects were over 55 years old.

Results

Data analysis was based on the rationale that the 100 item scale should have *prima facia* validity for depression and that those items which correlated best with the total score would be most likely to measure depression. The 30 items (Table 1) correlated highest and most significantly with the total score were chosen for inclusion in the GDS. The median correlation among these items was 0.675 (range = 0.47–0.83). For the 100-item, the median correlation was 0.51 (range = −0.07 to 0.83).

TABLE 1. GERIATRIC DEPRESSION SCALE

Choose the best answer for how you felt over the past week

1.	Are you basically satisfied with your life?	yes / no
2.	Have you dropped many of your activities and interests?	yes / no
3.	Do you feel that your life is empty?	yes / no
4.	Do you often get bored?	yes / no
5.	Are you hopeful about the future?	yes / no
6.	Are you bothered by thoughts you can't get out of your head?	yes / no
7.	Are you in good spirits most of the time?	yes / no
8.	Are you afraid that something bad is going to happen to you?	yes / no
9.	Do you feel happy most of the time?	yes / no
10.	Do you often feel helpless?	yes / no
11.	Do you often get restless and fidgety?	yes / no
12.	Do you prefer to stay at home, rather than going out and doing new things?	yes / no
13.	Do you frequently worry about the future?	yes / no
14.	Do you feel you have more problems with memory than most?	yes / no
15.	Do you think it is wonderful to be alive now?	yes / no
16.	Do you often feel downhearted and blue?	yes / no
17.	Do you feel pretty worthless the way you are now?	yes / no
18.	Do you worry a lot about the past?	yes / no
19.	Do you find life very exciting?	yes / no
20.	Is it hard for you to get started on new projects?	yes / no
21.	Do you feel full of energy?	yes / no
22.	Do you feel that your situation is hopeless?	yes / no
23.	Do you think that most people are better off than you are?	yes / no
24.	Do you frequently get upset over little things?	yes / no
25.	Do you frequently feel like crying?	yes / no
26.	Do you have trouble concentrating?	yes / no
27.	Do you enjoy getting up in the morning?	yes / no
28.	Do you prefer to avoid social gatherings?	yes / no
29.	Is it easy for you to make decisions?	yes / no
30.	Is your mind as clear as it used to be?	yes / no

Although twelve of the 100 original items assessed somatic complaints (e.g. sleep disturbance, anorexia, weight loss, cardiac or gastrointestinal symptoms), none of these were among the 30 items which correlated strongest with the total score. The median correlation between the somatic items and the total score was 0.33 (range = 0.02–0.45). Thus, these items were excluded from the final scale, because they did not meet the purely empirical criterion adopted as a basis for an item's inclusion.

Of the 30 questions selected for inclusion in the GDS, 20 indicated the presence of depression when answered positively while ten others (Nos 1, 5, 7, 9, 15, 19, 21, 27, 29 and 30) indicated depression when answered negatively. The questions were arranged in a 30 item, one-page format and ordered so as to maximize patient acceptance of the questionnaire. Having arrived at a final version of the GDS, a validation study was implemented.

STUDY TWO: VALIDATION

Method

Two groups of geriatric subjects were chosen for the validation phase. The first of these ($n = 40$) consisted of normal elderly persons recruited at local senior centers and housing projects. These subjects had no histories of mental illness and were functioning well in the community. The second group ($n = 60$) consisted of subjects under treatment for depression. These subjects were both inpatients and outpatients, male and female, and in Veterans Administration, county and private treatment settings.

The subjects under treatment were further differentiated into mild and severe depression groups. The frequently used criteria of outpatient vs inpatient groups was not used because in some settings, such as the county mental health service, many severe depressives were outpatients while in other settings, such as the Veterans Administration, many mild depressives were inpatients. Instead, it was decided to divide our group of clinically depressed subjects into mild and severe groups on the basis of whether or not they met Research Diagnostic Criteria (RDC) for a major affective disorder (depressed) (SPITZER *et al.*, 1978). These criteria, elicited during a clinical interview, involve eight symptoms: weight loss, sleep difficulty, loss of energy, psychomotor retardation, loss of interest or pleasure in usual activities, feelings of self-reproach or guilt, complaints of diminished ability to concentrate and recurrent thoughts of death or suicide. Five are required to make the diagnosis. Using these criteria it was possible to separate the depressives into a "mild" group ($n = 26$), having an average of 3.4 RDC criteria symptoms, and a "severe" group ($n = 34$) with an average of 5.9 RDC criteria symptoms. These two groups then became our second and third subject groups, respectively.

The subjects in all groups were given a clinical interview lasting 30–60 min which involved a rating of the HRS-D and the administration of the two self-rating scales, the SDS and our GDS. The interviews were conducted by trained observers, the authors. Interrater reliability on the HRS-D was 0.9. For those subjects who were unable to complete the self-rating scales without assistance, the examiner read the questions orally, elicited answers from the subject, and recorded his or her responses. The order in which the scales were administered was randomly determined for each subject.

Results

Internal consistency and reliability

Four measures of internal consistency were computed for each of the three depression scales. These included: (1) the median correlation between the individual items comprising a scale and the corrected-item total score (total score minus score on the particular time involved); (2) the average intercorrelation among the scale's individual items; (3) CHRONBACH's (1951) alpha coefficient; and (4) the split-half reliability coefficient. Each of these measures or indices of interanl consistency provides a basis for judging the extent to which the scale's items all measure the same underlying construct. In addition to computing these various indices of internal consistency, test–retest data are reported for the GDS. These data provide information regarding the reliability, i.e. stability, of GDS scores over time.

The results of the internal consistency analyses are displayed in Table 2. Each of the indices computed for the depression scales are discussed in turn below.

TABLE 2. COMPUTED INDICES OF INTERNAL CONSISTENCY FOR THE GDS, SDS AND HRS-D

Index	Scale GDS	SDS	HRS-D
Median correlation with total score	0.56	0.44	0.56
Mean interitem correlation	0.36	0.25	0.34
Alpha coefficient	0.94	0.87	0.90
Split-half reliability	0.94	0.81	0.82

Correlation with total score. The median correlation between the items of the GDS and the corrected-item total scores was 0.56 (range = 0.32–0.83), suggesting that all of the items on this scale do, in fact, measure a common latent variable. The comparable values for the SDS and HRS-D were 0.44 (range = 0.24–0.71) and 0.56 (range = 0.16–0.81), respectively. Based on these data it would appear that the GDS, HRS-D and SDS are all internally consistent measures.

Inter-item correlations. The mean intercorrelation among items from the GDS was 0.36; the computed values for the SDS and HRS-D were 0.25 and 0.34, respectively. These values are in a range necessary for a high degree of internal consistency for each scale as a whole, as confirmed by the analyses which follow.

Alpha coefficient. CHRONBACH's (1951) alpha coefficient was utilized in order to provide an overall measure of the internal consistency of the GDS. The computed value of the alpha coefficient was 0.94, suggesting a high degree of internal consistency for the GDS. Computed values of the alpha coefficient for the SDS and HRS-D were 0.87 and 0.90, respectively.

Split-half reliability. An alternative index of internal consistency is the split-half reliability coefficient. This measure is typically derived by splitting a scale into two equivalent forms, calculating their intercorrelation, and then estimating the reliability of the composite scale using the Spearman–Brown formula (NUNNALLY, 1967). Employing this procedure, the reliability coefficients for the GDS, SDS, and HRS-D were found to be 0.94, 0.81, and 0.82, respectively. These values are reported in order to allow comparisons with previous research.

Test–retest reliability. Test–retest reliability was calculated for the GDS by having 20 subjects complete the questionnaire twice, one week apart. A correlation of 0.85 was obtained ($p < 0.001$), suggesting that, at least within the time frame considered here, scores on the GDS reflect stable individual differences.

Validity

The primary test of the validity of the GDS as a measure of depression was provided by the classification of subjects as normal (i.e. nondepressed), mildly depressed, or severely depressed on the basis of RDC for major affective disorder. If both this classification variable and the GDS are valid indices of depression, one would expect normal subjects to receive the lowest GDS scores whereas severely depressed subjects should score the highest on this measure. As a test of this hypothesis, an analysis of variance was conducted in which the classification variable served as a between-subjects factor while the subjects' total scores on the GDS served as the dependent measure. Similar analyses were also performed on the SDS and HRS-D. The results of these analyses provided evidence for each of the scales' validity. In each analysis the main effect for the classification variable was highly significant [GDS: F (2, 97) = 99.48, $p < 0.001$; SDS: $F(2, 97) = 44.75$, $p < 0.001$; HRS-D: $F(2. 97) = 110.63$, $p < 0.001$], and as seen in Table 3, in each case the means were ordered as predicted. t-Tests conducted between each pair of means within the same row of this table showed that subjects classified as normal scored significantly lower on each of the scales compared to the mildly and severely depressed subjects while the severely depressed group scored higher than each of the other two groups (all $p < 0.001$). These findings, then, provide evidence

TABLE 3. MEANS AND STANDARD DEVIATIONS FOR THE GDS, SDS, AND HRS AS A FUNCTION OF SUBJECT CLASSIFICATION

Scale	Normal	Group Mildly depressed	Severely depressed	Total sample
GDS	5.75	15.05	22.85	13.98
	(4.34)	(6.50)	(5.07)	(9.02)
SDS	34.31	44.15	52.79	43.15
	(6.66)	(11.39)	(7.51)	(11.53)
HRS	5.43	13.35	25.42	14.29
	(4.98)	(5.98)	(6.45)	(10.35)

*Standard deviations appear in parentheses.

for the validity of the GDS as a measure of depression as well as validating the SDS and HRS-D.

Given previous findings indicating that the SDS (ZUNG, 1965; HEDLUND and VIEWEG, 1979) and HRS-D (CARROLL *et al.*, 1973; HAMILTON, 1960, 1967; BIGGS *et al.*, 1978; KNESEVICH *et al.*, 1977) are valid measures of depression, positive correlations between these measures and the GDS would provide evidence for the scales' convergent validity. The obtained correlation between the GDS and the SDS was found to be 0.84 while a correlation of 0.83 was found between the GDS and the HRS-D. The correlation between the SDS and the HRS-D was 0.80. All of these correlations were statistically reliable at or beyond the 0.001 level.

These analyses provided additional evidence of the validity of each of these depression scales. However, given the criticism that the SDS often may not adequately distinguish between different levels of depressive symptomatology (CARROLL *et al.*, 1973) a comparison was also made across the three scales to determine the relative strength with which each one was related to the RDC. The correlation of each of the depression scales with the classification variable derived from these criteria was computed, and then, following FERGUSON (1971), the magnitude of each correlation was compared to the other two. The obtained correlations between the classification variable and the GDS, SDS, and HRS-D were 0.82, 0.69, and 0.83, respectively. All of these represented statistically reliable correlations (all p's < 0.001). However, comparing each of these correlations to the others showed that, whereas those associated with the GDS and the HRS-D did not differ significantly from each other, $t\ (97) < 1$, both of these were significantly greater in magnitude than that associated with the SDS [GDS vs SDS: $t\ (97) = 3.83$, $p < 0.001$; HRS-D vs SDS: $t\ (97) = 3.85$, $p < 0.01$]. It thus appears that, compared to the other two measures, the SDS discriminates less effectively between the normal, mildly depressed, and severely depressed subjects.

DISCUSSION

These results provide evidence that the GDS is a reliable and valid measure of geriatric depression. A high degree of internal consistency was found for the scale, and total scores on the GDS were reliable over a one-week interval. Evidence for the validity of the scale came from a comparison of the mean scores associated with subjects classified as normal, mildly depressed, or severely depressed based on RDC criteria for depression; the three groups' means were reliably different and ordered as one would expect given their differing RDC scores.

The primary purpose for constructing the GDS was to provide a reliable screening test for depression in elderly populations that would be simple to administer and not require the time or skills of a trained interviewer. The fact that the GDS was found to discriminate between groups of normal, mildly depressed, and severely depressed subjects is encouraging in this regard. However, one would ultimately desire information on the percentage of individuals correctly and incorrectly classified using particular scores on this measure. This can be accomplished by computing indices of *sensitivity* and *specificity* for the measure, where in this case sensitivity refers to the number of depressed persons correctly classified as depressed based on a particular criterion and where specificity refers

to the number of nondepressed persons correctly classified as such. Sensitivity is lowered to the extent depressed persons are missed using a criterion and classified incorrectly as nondepressed whereas specificity declines to the extent nondepressed persons are incorrectly labelled as suffering from depression.

Sensitivity and specificity of the GDS was examined in a recent study conducted by our research group (BRINK *et al.*, 1981). It was found that among elderly persons drawn from the same centers as those used in the present study, a cut-off score of 11 on the GDS yielded a 84% sensitivity rate and a 95% specificity rate. A more stringent cut-off score of 14 yields a slightly lower, 80%, sensitivity rate, but results in the complete absence of nondepressed persons being incorrectly classified as depressed, i.e. a 100% specificity rate. Based on these findings BRINK *et al.* (1981) suggested that a score of 0–10 be viewed as within the normal range while 11 or greater being a possible indicator of depression. Criteria for the SDS and HRS-D were also offered; these were scores of 46 and 11, respectively. A score of 46 on the SDS achieves 80% sensitivity and 85% specificity whereas a score of 11 on the HRS-D achieves 86% sensitivity and 80% specificity. The three scales, however, are best compared by holding either sensitivity or specificity constant. With specificity held constant at 80%, the sensitivities of the GDS, SDS and HRS-D were found to be 90, 82, and 86%, respectively.

A geriatric depression scale should not only be applicable for screening depression in the physically healthy elderly but should also be useful with the physically ill, and cognitively impaired. There is some evidence that the GDS may fulfill this criterion. Using data from a study by GALLAGHER *et al.* (1981), we found that the GDS differentiated depressed from nondepressed elderly in a sample of subjects who all suffered from physical illness. These subjects were elderly arthritics who had been given the GDS after having been classified as either depressed or nondepressed based on a comprehensive clinical interview. Comparing the GDS scores of these two groups of arthritics it was found that the mean score of the depressed subjects (13.1, S.D. = 7.14) was indeed significantly higher than that of the nondepressed subjects (5.10, S.D. = 4.21), $t\,(47) = 4.94$, $p < 0.001$. These data, then, provide evidence that the validity of the GDS is not limited to elderly subjects who are physically healthy.

In another recent study the GDS was found to differentiate depressed from nondepressed elderly undergoing cognitive treatment for senile dementia. These subjects were classified as demented by criteria of FOLSTEIN *et al.*'s (1975) Mini-Mental Status Exam. It was found that those subjects categorized as depressed by a therapist blind to GDS scores received a mean score of 14.72 (S.D. = 6.13) on the GDS vs a mean of only 7.49 (S.D. = 4.26) for nondepressed subjects, $t\,(41) = 4.4$, $p < 0.001$. Although the results of this study should only be viewed as suggestive since the number of subjects was small ($n = 43$), this study provides preliminary evidence that the GDS is a valid measure of depression with demented, as well as normal, elderly subjects.

However, despite evidence for each of the three scales' validity, they did not appear to perform equally well with respect to the task of differentiating between various RDC defined degrees of depression. Because the GDS and HRS-D were correlated with the number of RDC symptoms each subject had to a significantly greater extent than the SDS, one could argue that, among the two self-rating scales, the GDS appears to provide a

more sensitive screening instrument. Although the SDS was found to correlate more poorly with the RDC than either the GDS or HRS-D, differences in the content and format of the three scales should be considered in making this comparison. It is important to recognize, first of all, the similarity between the three scales and the criterion, the RDC. The HRS-D would be expected to be more strongly related to the RDC, and the group classification variable, than the other two scales simply because the RDC are heavily represented on the HRS-D. Thus, the GDS and SDS are at a disadvantage in the analyses undertaken in the present study, because they do not measure all of the symptoms comprising the RDC while measuring others (e.g. diurnal symptom variation) which are not reflected in these criteria. Moreover, the poorer performance of the SDS may have been due partly to the fact that the RDC measure the severity of depression while the SDS measures the frequency of symptoms, and the two may not correspond closely (CARROLL *et al.*, 1973).

The RDC were chosen as the basis for classifying the level of depression in subjects because of a consensus among researchers that it appears to capture the essential aspects of depressive disorders. Given its wide acceptance, and the lack of a better set of criteria, the failure of a scale to correlate well with the RDC probably reflects more upon the scale in question than the RDC. However, despite the differences in content between the RDC and the GDS, the GDS total score was found to still correlate as strongly with the number of RDC symptoms as the HRS-D whose content corresponds more closely with these criteria. Thus, emphasizing the subjective aspects of depression rather than the somatic and behavior aspects does not seem to have detracted from the validity of the GDS as it may have in the case of the SDS. Despite the differences in content betwen the GDS and HRS-D, the former scale did nevertheless appear to be as valid as the HRS-D in the present research. This finding is somewhat surprising given the absence of somatic symptoms on the former and reliance upon them in the latter. This may be explained in part by the fact that both scales assay mood dysphoria and other psychological symptoms of depression, which seem to best discriminate between the depressed and nondepressed aged.

The issue of how well somatic items measure depression in the elderly and discriminate the depressed from nondepressed is one which deserves further attention. In the first study of the present series, the somatic items' median correlation with the total score was only 0.33, compared to 0.68 for the selected questions. A similar pattern emerged for both the SDS and HRS-D in the second study. On the SDS the items most highly correlated with the corrected-item total score were those concerned with the subjective, psychological aspects of depression while the items most poorly correlated with the total score were those dealing with the somatic aspects of depression. The four lowest correlations were those measuring constipation, decreased libido, appetite decrease, and somatic anxiety while the four highest correlations were those measuring personal devaluation, emptiness, depressed mood, and dissatisfaction. Nearly identical findings have been obtained by STEUER *et al.* (1980). They found total scores on the SDS to be most highly correlated with those items measuring dissatisfaction, depressed mood, emptiness and personal devaluation whereas the lowest correlations occurred with those items measuring constipation, somatic anxiety, decreased libido, and agitation. Moreover, they found

further evidence that the somatic items of the SDS may measure depression more poorly than subjective states in elderly patients by computing four sets of factor scores labelled well being, depressed mood, optimism, and somatic symptoms. Not only was the somatic factor correlated the least strongly with the SDS total score, but this factor was the only one found to be significantly correlated with physician health ratings. Thus, this study demonstrates how, even among individuals screened for serious illness, the poorer health of the aged may undermine the power of somatic symptoms to detect depression.

Of course it is possible that the SDS simply does not contain good measures of those somatic symptoms accompanying depressive illness. But this interpretation does not explain the findings in which other measures of depression have been utilized. For example, although less marked than the results found with the SDS, a similar pattern of results was found in the present research when the items from the HRS-D were correlated with the total score: the somatic items generally correlated less strongly than the items measuring loss of interests, depressed mood and anxiety. Similarly, DESSONVILLE *et al.* (1981) using the Schedule for Affective Disorders and Schizophrenia (SADS) have found that, even though the somatic aspects of depression differentiated depressed from nondepressed elderly, the mean differences between the two groups were smaller on the somatic items than those measuring the subjective states of depression.

Clearly more research is needed on the expression of depression within elderly subjects. The fact that the subjects in the present research were all relatively healthy, as were subjects in these additional studies, may have preserved the discriminability of some somatic questions. It remains to be determined whether the somatic items on these scales adequately measure depression in elderly persons who are less healthy. The GDS appears to avoid many of these problems by focusing on the psychological aspects of depression. This is not meant to imply that somatic symptoms should not be measured in cases of depressive illness. Such symptoms need to be assessed when one is concerned with formal diagnosis or when there is the desire to examine changes in the expression of depressive illness. However, when screening is the goal, discrimination between levels of depression is of primary important and somatic questions may be less powerful in this regard than items chosen empirically for their ability to differentiate the nondepressed from the depressed.

Finally, it is important to distinguish instruments to be used for screening, diagnosis and assessment of change. As the above data indicate, all three may find use as screening instruments, even if this was not their original intent. None, however, is a diagnostic tool. Positive results on any of the three scales on screening should be followed up by a clinical interview if significant levels of depressive symptomatology are found and treatment is being considered. On the other hand, the HRS-D has also been shown to be quite sensitive to changes in the level of symptomatology over time (KNESEVICH *et al.*, 1977), and thus, may serve well, as it was originally intended, as a means of gauging changes in the severity of depression. The use of the SDS in outcome research is more controversial (CARROLL *et al.*, 1973; CARROLL, 1978). It remains to be determined if the GDS may be useful for measuring changes in the severity of depression following treatment.

In conclusion, though not a substitute for observer-rated scales or indepth diagnostic interviews, and not yet shown to be treatment sensitive, the GDS appears to be a promising and simple screening instrument which may find other applications through further research.

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