Presentation, Diagnosis and Management of Alzheimer’s Disease

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Outline

- I. CLINICAL FEATURES AND NATURAL HISTORY OF ALZHEIMER’S DISEASE
- II. DIAGNOSTIC CRITERIA FOR AD
- III. NON-COGNITIVE SYMPTOMS OF AD
- DIAGNOSTIC TOOLS IN ALZHEIMER’S DISEASE
- IV. EXISTING AND EMERGING THERAPIES FOR AD
Disorders causing dementia

- Alzheimer’s disease: > 60%
- Vascular dementia: < 20%
- Dementia with Lewy bodies: < 20%
- Other dementias: < 10%
Mixed brain pathologies account for most dementia cases in community-dwelling older persons

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ABSTRACT

Objective: To examine the spectrum of neuropathology in persons from the Rush Memory and Aging Project, a longitudinal community-based clinical-pathologic cohort study.

Methods: The study includes older persons who agreed to annual clinical evaluation and brain donation. We examined the neuropathologic diagnoses, including Alzheimer disease (AD) (NIA-
Scope of the Problem

- Of the 38 million Americans aged 65 years and older, 5.1 million suffer from AD.

- This number will reach 7.7 million by 2030, an increase of more than 50%.
Clinical features of Alzheimer’s disease
“The first noticeable symptom of illness shown by this 51-year-old woman was suspiciousness of her husband. [At times] believing that people were out to murder her, [she] started to scream loudly. At times she......seems to have auditory hallucinations.”

Alzheimer A 1907
(trans Jarvik & Greenson Alz.dis.Ass.Disord (1987) 1 7-8
November 26, 1901

- She sits on the bed with a helpless expression. What is your name?
- Auguste
- What is your husband’s name?
- Auguste, I think
- Your husband?
- Ah, my husband
- Are you married?
- To Auguste
- Mrs D?
- Yes, yes. Auguste D
“A characteristic serious disease of the cerebral cortex” 1906

In the centre of an otherwise normal cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability.
Natural history of Alzheimer's disease

- Onset
  - gradual, probably imperceptible

- Progression
  - slow and gradual but not linear

- Duration
  - less than 10 years, on average, from diagnosis to death
Clinical Presentation of AD Amnesia

- Loss of Memory is the commonest presenting symptom
- Initially affects ability to recall new information (‘episodic memory impairment’)
- Remote memory declines as the disease progresses
- Disorientation to time and place is closely related to memory impairment
Aphasia

- Reduced conversational output
- Word-finding difficulties
- Reduced vocabulary
- Increasingly non-fluent with disease progression
- Global aphasia
Apraxia

- Inability to carry out learned purposeful movements despite normal strength and coordination

- Difficulties with:
  - Utensils
  - Appliances
  - Dressing
Agnosia

- Impaired recognition of sensory stimuli not attributed to sensory loss or language disturbance
- Prosopagnosia: Inability to recognize familiar faces
- Object agnosia
- Auditory agnosia: pure word deafness or non-speech sounds
Executive dysfunction

- Problem solving
- Abstraction
- Reasoning
- Decision-making
- Judgment
Visuospatial dysfunction

- Impaired driving
- Getting lost
- Clock construction task
The non-cognitive symptomatology of Alzheimer’s disease

Behavioural and Psychological Symptoms of Dementia (BPSD)
BPSD in AD

- Symptoms of disturbed perception, thought content, mood, behavior

- Occurs in up to 50% of patients with AD
Psychological symptoms

- Depression
- Anxiety
- Persecutory ideas
- Visual hallucinations
Behavioural disturbance

- Symptoms assessed by behavioural observation
  - Wandering
  - Aggression
  - Screaming
  - Restlessness
The importance of BPSD in AD

- Carer distress
- Hospitalisation
- Morbidity and mortality
- Cost
Diagnosis of AD

- Identify elements *suggestive* of the disease from the History and Physical examination

- Exclude other causes of dementia by laboratory tests and Neuro-imaging if necessary

- Most widely used clinical criteria for AD are:
  - National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA)
  - Diagnostic and statistical manual of mental disorders IVth edition (DSM-IV)
NINCDS-ADRDA criteria for Probable AD


- Dementia by clinical exam and supported by neuropsychological testing
- Deficits in at least two areas of cognition (memory essential)
- Progressive worsening
- No disturbance of consciousness
- Onset after 40 years of age
- Absence of other systemic or brain disease that could account for the condition
NINCDS-ADRDA criteria for AD

Diagnosis of Probable AD is supported by:

- Progressive deterioration in specific cognitive areas (e.g. aphasia or apraxia)
- Impaired function and altered behaviour
- Family history
- Normal EEG, Neuroimaging and CSF
NINCDS-ADRDA
Probable AD

- III other clinical features compatible with probable AD
  - Plateau in progression
  - Other neurological features such as gait disorder, myoclonus or abnormal primitive reflexes, especially late in the disorder
  - Seizures
  - Atrophy on CT
NINCDS-ADRDA
Probable AD

- IV features making the diagnosis of probable AD unlikely
  - Sudden apoplectic onset
  - Focal neurological features
  - Seizures or gait disturbance early in the disease
NINCDS-ADRDA
Possible AD

- Atypical onset and/or course of cognitive decline
- Focal neurological findings
- Co-existing disorders that may themselves produce dementia
NINCDS-ADRDA
Definite AD

Definite AD = Probable AD + Neuropathology

• May only be made in the presence of a clinical diagnosis of probable AD together with neuropathological evidence of AD
DSM-IV Criteria

- Insidious onset and progressive decline in cognition with impairment in social/occupational functioning
- Impairment in recent memory, and one of:
  - Aphasia
  - Apraxia
  - Agnosia
  - Executive functioning
- Absence of other neurological, psychiatric, metabolic, systemic disease causing cognitive decline
- No delirium
Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS–ADRDA criteria


“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 become available.”

…the criteria do not take into account the unprecedented growth of scientific knowledge concerning the existence of reliable markers of Alzheimer’s disease…
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

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


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_{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 Pittsburgh compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family
Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS–ADRDA criteria


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
Hypothetical sequence of temporal changes in biomarkers of Alzheimer’s disease


Structural neuroimaging in AD

- Hippocampal atrophy predicts cognitive decline
  - Rate of hippocampal atrophy in healthy subjects 0.1-0.2% a year at 30-50 years
  - 0.8% in mid-70s
  - 1.5-2% between 80-90 years
  - Hippocampal atrophy rates are 4-8% a year in early AD
  - Hippocampal atrophy accelerates several years before diagnostic criteria for AD are met

Scahill RI and Fox NC
Whole Brain Atrophy in AD

- Early event in AD
- Excellent discriminator between AD and control
- Correlates well with cognitive decline
- Longitudinal measures used in a clinical trial setting (AN 1792)

Chen et al.

Neuroimage

(2004) 22, 134-143
Functional Neuroimaging in AD
FDG-PET

- Reduced metabolism in the posterior cingulate cortex, precuneus and tempo-parietal cortices is an early event.

- Good discriminant between AD and control as well as other dementias (FTD).

Herholz et al.  
*Br J Radiology*  
(2007) 80, S160-S167
Functional Neuroimaging in AD

$^{11}$C-PIB

- Binds fibrillar Aβ
- High sensitivity for Aβ in plaques and vascular amyloid *in vivo*
- In AD, specific binding observed in frontal, temporal and parietal association cortices
- Bimodal distribution of increased PIB retention in MCI and control subjects

Herholz et al.  
*Br J Radiol*  
(2007) 80, S160-S167
CSF $A\beta_{1-42}$

- In independent studies, mean $A\beta_{42}$ levels are decreased by 30-50% in those with a clinical diagnosis of AD relative to age-matched non-demented controls.

- Also reduced in subjects with amnestic MCI but substantial overlap with controls.

- Approximately 2000 subjects in multiple centers with sensitivity and specificity around 86% and 89% for AD versus controls.
CSF Total tau

- >40 independent studies with >2000 AD cases and >1000 controls have reported approximately 300% increase in mean total CSF tau in AD relative to controls.

- Sensitivity and specificity for AD versus controls approaching 80 and 89% respectively.

- Significant overlap in individual values between AD/MCI versus control in early stages.
**Phosphorylated-tau (p-tau)**

- Mean increase in p-tau in AD versus controls 245%
- Sensitivity (74%), specificity (92%) for AD versus normal aging
- Higher specificity for discriminating AD from other dementias (compared to $A\beta_{42}$ and t-tau)
Utility of core CSF tests

- **Alzheimer’s disease**
  - $\text{A}_42$, t-tau and p-tau each differentiate AD from healthy elderly with 80-90% sensitivity and specificity
  - Performance is better in combination
  - $\text{A}_42 + t$-tau together increase sensitivity to 86% (78-84% stand-alone) and specificity to 97% (84-90% stand-alone)
  - CSF p-tau aids differentiation from other dementias including FTD and LBD

- **Prodromal AD**
  - Combination of $\text{A}_42$, t-tau and p-tau have a high predictive value for identifying conversion from MCI to AD
  - 180 consecutive MCI patients with 137 lumbar punctures at baseline and 4-6 year follow-up
  - 39 healthy controls
  - 42% developed AD, 41% remained stable, 15% other dementias
  - $\text{A}_42 + t$-tau at baseline gave 95% sensitivity, 83% specificity for incipient AD
  - Greatly increased relative risk with ‘pathological’ concentrations of $\text{A}_42 + t$-tau for AD (HR 17.7, p<0.0001)
Diagnostic biomarkers in CSF

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in total tau</td>
<td>90%</td>
<td>81%</td>
</tr>
<tr>
<td>Increase in phospho-tau</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>Decrease in $A\beta_{1-42}$</td>
<td>86%</td>
<td>90%</td>
</tr>
</tbody>
</table>

- Predict progression to both MCI and AD
Recommendations to Update Diagnostic Criteria

Accelerating scientific discovery has increased our understanding of Alzheimer's disease. In response to the pace of insight, the National Institute on Aging (NIA) and the Alzheimer's Association convened three workgroups to explore the need for new diagnostic criteria that better reflect the full continuum of the disease from its earliest effects on mental and physical function.

These workgroups have proposed recommendations to update diagnostic criteria for Alzheimer's disease and mild cognitive impairment (MCI). Additional recommendations propose criteria for "preclinical Alzheimer's disease," a new diagnostic category representing the earliest changes that occur even before MCI. These preclinical criteria would currently be used only in research settings and not in medical practice.

All of the recommendations propose a potential diagnostic role for biomarkers based on emerging understanding of characteristic brain imaging patterns and changes in molecular benchmarks, including beta-amyloid and tau.

The proposed recommendations were released at the 2010 Alzheimer's Association International Conference on Alzheimer's Disease (AAICD). Following release, the recommendations were posted here until Oct. 30, 2010 for public comment. After revision to reflect comments, the recommendations will again be publicly available here.

To read the press release, please click here.

Backgrounders / FAQs for the proposed revisions to diagnostic criteria for Alzheimer's disease

View workgroups

- Workgroup members: Proposed criteria for Alzheimer's disease dementia
- Workgroup members: Proposed criteria for mild cognitive impairment due to Alzheimer's disease
- Workgroup members: Proposed criteria for preclinical Alzheimer's disease

"The NIA and the Alzheimer's Association hope this process of updating and revising the diagnostic criteria with the latest advances will provide standards that move the field further in the direction of early detection and treatment."

- William H Thies, Ph.D., Alzheimer's Association Chief Medical and Scientific Officer
Clinical Approach to AD

- History obtained from patient *and* reliable informant/caregiver
  - Changes from prior levels of cognitive performance
  - Decline in functional abilities
  - Personality changes
  - Confirm insidious onset and slow progression

- Cognitive testing:
  - Memory
  - Language
  - Attention
  - Orientation
  - Executive function
  - Visuo-spatial
Clinical Approach to AD

- Neurological examination:
  - Primarily to rule out other conditions
  - Focal deficits suggest VaD
  - Prominent rigidity, tremor, bradykinesia suggest PD, LBD
  - Myoclonus
  - Primitive reflexes

- Rule out poly-pharmacy
Laboratory evaluation

Mainly to exclude other causes and/or treatable conditions:

- Complete blood count
- Chemistry panel
- Thyroid function
- Vitamin B12 level
- Syphilis serology
- Heavy metals
- Chest X-ray
- EEG
Role of Neuroimaging in clinical evaluation of dementia

- American Academy of Neurology recommends structural neuroimaging to rule out:
  - NPH
  - Space occupying lesions
  - Subdural hematoma
  - Non contrast CT or MRI

*Neurology.* 2001 May 8;56(9):1143-53.
Treatments for AD

Disease specific treatment for Alzheimer’s disease
Acetylcholinesterase inhibitors (ACHEIs)

- Approved in US and Europe 1995 onwards
- Modestly efficacious
- Effects on cognition, global change, function and behavior
Donepezil

Change in ADAS-cog

High dose (10 mg/day)
Low dose (5 mg/day)
placebo

Burns et al 1999
ACHEIs in AD

- Donepezil, Galantamine, Rivastigmine
- Most common side effects are GI, sleep disturbances
- Comparable safety and efficacy profiles
- First choice as monotherapy in mild AD
- Which ACHEI to use is up to the treating clinician and is governed by tolerability and efficacy
Memantine in AD

- Non-competitive NMDA antagonist
- Blocks Glutamate-induced excitotoxicity
- Approved for moderate-severe AD
- May be used in combination with the AChE-inhibitors
Box 2. Possible drug targets for disease-modifying therapies for Alzheimer’s disease.

**Aβ production**
- α-secretase enhancement
- β-secretase inhibition
- γ-secretase inhibition
- γ-secretase modulation

**Aβ degradation**
- Neprilysin activation
- Insulin-degrading enzyme activation

**Aβ removal**
- Vaccination
- Passive immunization
- Receptor-mediated removal from CNS
- Prevent entry from periphery

**Preventing Aβ toxicity**
- Prevent aggregation by binding Aβ
- Prevent oligomerization through metal protein attenuation

**Tau**
- Prevent tau aggregation
- Prevent tau hyperphosphorylation
- Facilitate tau phosphatases
- Microtubule stabilization

**Neuroprotection**
- Ensure neuronal health with growth factor treatment or growth factor receptor activation
- Prevent cell death with anti-apoptotic agents
- Ensure mitochondrial health
- Block inflammatory disease processes

Aβ: Amyloid-β.
Amyloid and amyloid deposition in the brain

G. William Rebeck
Georgetown University
AD: Pathological Hallmarks

Amyloid Plaques and Neurofibrillary Tangles
Distribution of tangles and plaques in Alzheimer’s disease
Aβ plaques in brain cortex
Production of Aβ from APP
Mutations in APP cause a small percentage of familial Alzheimer’s disease.

Also: Down syndrome, gene duplication.
Tangles are downstream of Aβ accumulation in AD

Down syndrome (trisomy 21)

APP \xrightarrow{\beta\text{-secretase}} A\beta \xrightarrow{\text{inflammation, oxidative stress, excitotoxicity, direct toxicity}} Neuron death

Tangles

\text{APP mutations}

\text{PS1, PS2 mutations}

Amyloid cascade hypothesis
Temporal course of AD neuropathology

Aβ
NFT
Neurons/synapses

Aging prodromal MCI AD

Progression of Neuropathology
Different types of Aβ deposition in AD brain
Staining for Aβ plaques

Thioflavin S (amyloid)  Aβ immunostain (protein)
Aβ amyloid in blood vessels

Cerebral Amyloid Angiopathy

risk of cerebral hemorrhage
Amyloid consists of proteins containing β sheets

Fowler et al, TIBS 2007

Amyloid dyes

Congo Red
Thioflavin S
Methyl violet
Binding of amyloid dyes

Some non-amyloid staining.

May interfere with amyloid formation.

Frid et al. Brain Res Review 2006
Aβ assembly into amyloid

Temporal course of AD Neuropathology

Aβ

NFT

Neurons/synapses

Aging prodromal MCI AD

Progression of Neuropathology
$\alpha$-amyloid in normal aging

39 cognitively normal people

Age 74-95

Knopman et al. JNEN 2003
### Amyloid-forming proteins

<table>
<thead>
<tr>
<th>CNS</th>
<th>Periphery</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aβ</td>
<td>• Transthyretin</td>
</tr>
<tr>
<td>– Plaques</td>
<td>• Serum amyloid A</td>
</tr>
<tr>
<td>– Blood vessels</td>
<td>• Immunoglobulin light chain</td>
</tr>
<tr>
<td>• tau</td>
<td>• Islet amyloid polypeptide</td>
</tr>
<tr>
<td>ː α-synuclein</td>
<td>• Lysozyme</td>
</tr>
<tr>
<td>• Prion protein</td>
<td>• Gelsolin</td>
</tr>
<tr>
<td>• TDP-43</td>
<td>• Lactoferrin</td>
</tr>
<tr>
<td>• Cystatin C</td>
<td>ː β2-microglobulin</td>
</tr>
<tr>
<td>• Abri/ADan</td>
<td>• ApoAI</td>
</tr>
<tr>
<td></td>
<td>[119x153] [171x206] [206x79] [240x115] [274x115] [309x79]</td>
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</tbody>
</table>
Prion protein

normal folding  amyloid

$\beta$ sheet

Helix A
Helix B
Helix C

a

b
Neurofibrillary Tangles (NFT)

Hippocampus

Basal forebrain
Non-AD brain amyloidoid diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Amyloid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease</td>
<td>$\alpha$-synuclein</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>tau, TDP-43</td>
</tr>
<tr>
<td>Amyotrophic Lateral Sclerosis</td>
<td>tau, TDP-43</td>
</tr>
<tr>
<td>Diffuse Lewy Body Disease</td>
<td>$\alpha$-synuclein</td>
</tr>
<tr>
<td>Prion Diseases</td>
<td>prion protein</td>
</tr>
</tbody>
</table>

Symptoms reflect which brain areas are affected.
Conclusions

- Alzheimer’s disease is characterized neuropathologically by plaques (made up of Aβ) and tangles (made up of tau).
- Accumulation of Aβ in the brain is a primary event in Alzheimer’s disease.
- Other proteins also form amyloids, but generally in smaller amounts or more restricted brain areas than Aβ.