

Clinical and Experimental Transmission of Creutzfeldt-Jakob Disease by Corneal Transplantation

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Why should we be concerned?

- CJD has been transmitted human to human by corneal transplantation:
 - **One Definite case**
 - Duffy, et al.
 - NEJM 290:692, 1974
 - **One Probable case**
 - Heckman, et al.
 - J Neurol Neurosurg Psychiat 63:388-390, 1997
 - **One Possible case**
 - Uchiyama, et al
 - Dementia 8:466-473, 1994

Three "at risk" cases from UK:

- **Donor with sporadic CJD**
 - 2 corneal transplant recipients
 - 1 scleral graft recipient
 - Allan & Turf, *BMJ* 315:1553-4, 1997
 - Sir William Stewart, Scottish Executive Office
 - Independent Investigation, 3/98
 - www.scotland.gov.uk/library/documents2/cjd-00.htm

Human-to-Human Transmission of CJD by Corneal Transplant

Case 1 Recipient

- 55 yo WF with Fuch's Dystrophy
 - » 18 months after transplant
 - progressive myoclonus, lethargy, ataxia
 - » Died 26 months after transplant
 - » Autopsy showed spongiform neuropathology

Duffy, et al., *NEJM* 290: 692, 1974

Human-to-Human Transmission of CJD by Corneal Transplant

Case 1 Donor

- 55 year old white male
- Died after 2 month history of
 - ataxia, myoclonus, progressive dementia
- Neuropathology several weeks later
 - spongiform neuropathology

Duffy, et al., *NEJM* 290: 692, 1974

Human-to-Human Transmission of CJD by Corneal Transplant

Case 2 Recipient

- 45 yo WF with keratoconus
- s/p PK 1965 & 1982
- Died after 8 month history of
 - ataxia, myoclonus, progressive dementia, flexion rigidity

Heckmann, et al., *J Neurol Neurosurg Psychiat* 63:388, 1997

Human-to-Human Transmission of CJD by Corneal Transplant

Case 2 Recipient(cont'd)

- No familial prion mutations
- Codon 129 met/met
- EEG genrl slow wave, biphasic d/c
- CSF NSE = 117 (nl<20ng/ml)
- Necropsy - no consent

Heckmann, et al., *J Neurol Neurosurg Psychiat* 63:388, 1997

Human-to-Human Transmission of CJD by Corneal Transplant

Case 2 Donor 1965

- 63 year old white female
- Died after 3 month history of
 - incoordination, myoclonus, memory loss
- Neuropath report - "spongiform changes"
 - insula and caudate, (front/occipit = mild)
- Original slides not available

Heckmann, et al., *J Neurol Neurosurg Psychiat* 63:388, 1997

Human-to-Human Transmission of CJD by Corneal Transplant

Case 2 Donor 1982

- » No information in records

Heckmann, et al., *J Neurol Neurosurg Psychiat* 63:388, 1997

Human-to-Human Transmission of CJD by Corneal Transplant

Case 3 Recipient

- 63 yo Japanese female
- Died 3 years after onset of
 - dysarthria, dysmetria, dysdiadochokinesia, myoclonus, paranoid hallucinations
- Necropsy = "typical CJD"
- s/p PK 15 months earlier

"Uchiyama K, et al., *Dementia* 8:466, 1994"

Human-to-Human Transmission of CJD by Corneal Transplant

Case 3 Donor

- » No information given

"Uchiyama K, et al., *Dementia* 8:466, 1994"

Human-to-Human Transmission of CJD by Corneal Transplant

"At risk" Cases Donor

- 53 yo Scottish female
- Died of lung Ca 2/97
 - in weeks prior to death, "falling over", "staggering gait", "like a senile old lady"
- Necropsy = cause of death as lung Ca
- No premortum CJD Dx
- Brain removed for "later review"

Stewart, 1998: www.scotland.gov.uk/library/documents2/cjd-00.htm

Human-to-Human Transmission of CJD by Corneal Transplant

"At risk" Cases Recipients

- Corneas and sclera transplanted to:
 - 3/97-cornea to man (39) from Wolverhampton
 - 3/97-cornea to woman (85) from Liverpool
 - 4/97-sclera to man (34) from Manchester

-Stewart, Sir Willam, 1998
 -www.scotland.gov.uk/library/documents2/cjd-00.htm

Human-to-Human Transmission of CJD by Corneal Transplant

"At risk" Cases

- 11/97- neuropathology of donor
 - confirmed CJD
 - (not nvCJD)
- 12/97 - transplant recipients notified
- 1/98 - transplanted tissues removed
- No clinical signs of CJD in recipients to date

-Stewart, Sir Willam 1998
 -www.scotland.gov.uk/library/documents2/cjd-00.htm

Human-to-Human Transmission of CJD by Corneal Transplant

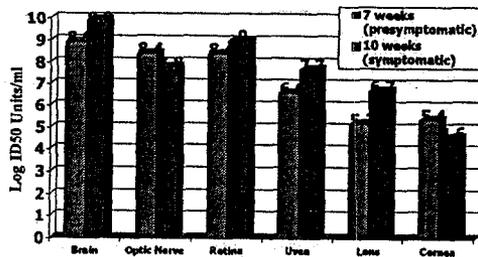
- Summary
 - 1 Definite transmission
 - 1-Probable transmission (Germany)
 - 1-Possible transmission (Japan)
- 45,000 Corneal Transplants/year US
- Why not more cases?
 - Biologic factors
 - Epidemiologic factors

Prion Titers of Ocular Structures

- Based on hamster scrapie data
- Titers (highest to lowest)
 - Brain
 - Optic Nerve
 - Retina
 - Uvea
 - Lens
 - Cornea

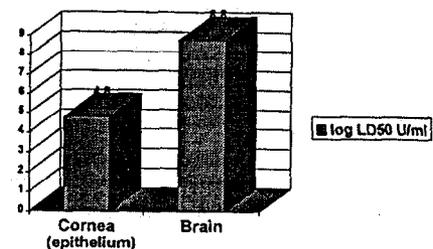
Hogan, et al., *Ophthalmic Res*, 18:230-235, 1986

Regional Ocular Titers Scrapie Agent in Hamsters (IC inoculation)



Hogan, et al., *Ophthalmic Res*, 18:230-235, 1986

Titers of Agent in Transmissible Mink Encephalopathy



Marsh & Hanson, *Science* 187:656, 1974.

Experimental Corneal Transmission of CJD

- Manuelidis (1977)
 - Emulsified CJD infected guinea pig cornea
 - Injected into anterior chamber of 6 guinea pigs
 - 4/6 developed "clinical disease"
 - 2/6 asymptomatic after 600 days
 - 6/6 with spongiform encephalopathy

Manuelidies, et al., *NEJM* 296:1334-7, 1977

Experimental Corneal Transmission of CJD

- Herzberg (1979)
 - Transplanted CJD infected capuchin corneas to 2 recipient monkeys
 - Recipients clinically free of disease after 55 months
 - Grafts clear and without rejection
 - No spongiform neuropathology

Herzberg, *Med J Aust* 1:248, 1979

Experimental Corneal Transmission of CJD

- Tateishi (1985)
 - Emulsified CJD infected mouse cornea
 - Injected into brains of 6 mice
 - All mice clinically free of disease after 2.8 years
 - 1/6 mice with spongiform neuropathology

Tateishi, *Lancet* 2:1074, 1985

Genetic Sequestration of Iatrogenic CJD Transmissibility

- 56 cases of iatrogenic CJD transmission
 - 92% with allelic homozygosity
 - (met/met or val/val)
 - at polymorphic codon 129
 - of chromosome 20 amyloid gene
- 110 normal controls
 - 49% homozygous at codon 129
 - $p < 0.001$

Brown, et al., *Neurol*, 44:291-3, 1994

Genetic Sequestration of CJD Transmissibility

- Homozygosity at codon 129
 - May accelerate pathogenesis
 - Does heterozygosity protect From iatrogenic transmission?

Non-Transmissible CJD

- Traub (1977)
 - 56 transmission attempts
 - clinically and biopsy proven CJD
 - 8 cases considered untransmissible (14%)
- Brown (1994)
 - 396 transmission attempts
 - clinically and biopsy proven CJD
 - 35 cases considered untransmissible (9%)

Traub, et al., *Aging and Dementia*, Spectrum Press, pp91-172, 1977
Brown, et al., *Ann Neurol* 35:513-529, 1994

Non-Transmissible CJD

- Apparent earlier age of disease onset
 - mean = 53 years
- Apparent longer duration of illness
 - mean = 28 months
- Reason for lack of virulence unclear

Exclusionary Criteria for Corneal Tissue Donors

*Tissue from donors with the following...shall not be offered for surgical purposes:

- Death of unknown cause
- Death with (unknown) neurologic disease
- Creutzfeldt-Jakob Disease
- Rabies
- Hepatitis B or C seropositivity

EBAA Medical Standards, October 1994, p. 9

Exclusionary Criteria for Corneal Tissue Donors

Donor History of:

- Acute viral encephalitis
- Encephalitis of unknown origin
- Progressive encephalopathy
- History of receiving human pituitary hormone
- HTLV-I, HTLV-II, or HIV seropositivity

EBAA Medical Standards, October 1994, p. 9

Exclusionary Criteria for Corneal Tissue Donors

- Only 1 definite CJD transmission
 - In 25 years
 - Occurred prior to institution of donor screening criteria
 - Risk under current banking system small
 - Adequate tissue numbers critical

Hogan, et al., *Cornea* 14:547-53, 1995
Hogan, et al., *Cornea* 18:2-11, 1999
Kennedy, et al., *In Press*

Conclusions

The risk of transmission of CJD by corneal transplant is extremely small because:

- Lower titers of agent in cornea
 - Low rate of experimental ocular transmission in animals
- Apparent genetic transmission restriction
 - homozygosity at codon 129 of chromosome 20
- Low numerical risk of transmission
 - based on population/epidemiology data
- Lack of transmission of 10% of CJD cases