Prion Disease Overview

Brian Appleby, MD
Objectives

• Provide an overview of the biology underlying prion disease
• Discuss the clinical presentation and work-up of prion disease
• Discuss the various forms of prion disease
What is a prion?

- **proteaceous** and **infectious**
- -**ion** (infectious, e.g. *virion*)
- No nucleic acid
- Non-degradable by typical sterilization
PrP: prion protein
PrP<sub>C</sub>: normal prion protein (c=cellular)
PrP<sub>Sc</sub>: disease causing protein (Sc=scrappie)
Neuropathology

H & E Staining (spongiform changes)

Immunohistochemistry (abnormal prion protein)
Western blot

Loading (ul):
½ sample buffer + ½ TH (10%)

+: proteinase K treated

F: Frontal  O: Occipital  C: Cerebellum
Animals

- Scrapie: sheep & goat
- Bovine spongiform encephalopathy (BSE): cow
- Chronic wasting disease (CWD): deer, elk, moose, caribou
- Camels: Camel prion disease
**Human Etiologies**

- **Sporadic**
- **Genetic**
  - Genetic CJD
  - Fatal familial insomnia
  - Gerstmann-Sträussler-Scheinker
- **Acquired**
  - Kuru
  - Iatrogenic CJD
  - Variant CJD

- 14%
- 85%
- 1%
Survival Time in Sporadic Creutzfeldt-Jakob Disease (n=90)

Adapted from: Appleby BS, Arch Neurol 2009
Age at Onset

Adapted from: Appleby BS, J Neuropsychiatry Clin Neurosci 2007
Human Epidemiology

• 1-2 new cases per million individuals per year across the entire population (all ages) (incidence)
• 1/7,000 US deaths per year (lifetime risk)
• OH: 11 million people
  – 11-22 new cases/yr
  – ~2-4 cases living past one year
  – Would not be unusual to have 13-26 active cases in OH

Creutzfeldt-Jakob disease age-specific and age-adjusted death rates, United States, 1979-2006*

- Deaths obtained from the multiple cause-of-death data for 1979-1998 are based on ICD-9 codes. Deaths beginning in 1999 are based on ICD-10 codes with available computerized literal death certificate data. Death information was also obtained from other surveillance mechanisms. Rates are adjusted to the US standard 2000 projected population.
Criteria for Probable sCJD

At least two clinical signs with dementia:
1. Myoclonus (e.g., twitches)
2. Cerebellar or visual symptoms (e.g., “drunken” walking, incoordination, depth misperception)
3. Pyramidal or extrapyramidal symptoms (e.g., weakness, tremors, Parkinson’s disease like walking)
4. Akinetic mutism (lack of voluntary speech & movement)

At least one of the following:
1. Periodic sharp wave complexes on electroencephalogram (EEG) (looks at brain waves)
2. 14-3-3 in CSF and disease duration < 2 years
3. Abnormal findings in basal ganglia (e.g. middle) or at least two cortical (e.g., outside) regions on specific sequences on brain MRI
New Diagnostic sCJD Criteria

- Neuropsychiatric disorder
- + Real-time quaking induced conversion (RT-QuIC)

https://www.cdc.gov/prions/cjd/diagnostic-criteria.html
sCJD Clinical Presentations

- Cognitive: 31%
- Heidenhain (Visual): 15%
- Affective: 17%
- Classic CJD: 15%
- Oppenheimer-Brownell (Ataxic): 9%
- Undetermined: 13%

Adapted from Appleby BS et al., Arch Neurol 2009
Electroencephalogram (EEG)

Periodic sharp wave complexes
Brain MRI

basal ganglia

cortex
Cerebrospinal Fluid Tests

Markers of brain cell damage:
1. 14-3-3: positive, negative, or ambiguous
2. Tau: result is a number (0-tens of thousands)

Disease specific test:
1. RT-QuIC: detects abnormal prion protein (very specific)
Problem with 14-3-3/tau

• Markers of brain cell injury
• Often seen in other conditions:
  – Stroke
  – Seizure
  – Head injury
  – Multiple sclerosis
  – Rapidly progressive Alzheimer's disease
Real-Time Quaking-Induced Conversion (RT-QuIC)
RT-QuIC: Highly Specific for sCJD

<table>
<thead>
<tr>
<th></th>
<th>14-3-3</th>
<th>Tau</th>
<th>RT-QuIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>81%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Specificity</td>
<td>43%</td>
<td>71%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Sensitivity: How good is the test at detecting a disease?

Specificity: How sure are you that it is the disease you are trying to detect?

Foutz A, Ann Neurol 2017
NPDPSC vs Mayo CSF 14-3-3 Testing

- 14-3-3 is done differently
- Mayo: must order tau separately
- RT-QuIC only available via NPDPSC
- Will automatically be contacted regarding interest in autopsy program if positive
sCJD Molecular Subtypes

<table>
<thead>
<tr>
<th>sCJD</th>
<th>Codon 129 Polymorphism</th>
<th>Prion Protein Type</th>
<th>Molecular Subtype</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MM</td>
<td>Type 1</td>
<td>MM1</td>
<td>Classic CJD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 2</td>
<td>MM2</td>
<td>Longer duration</td>
</tr>
<tr>
<td></td>
<td>MV</td>
<td>Type 1</td>
<td>MV1</td>
<td>Classic CJD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 2</td>
<td>MV2</td>
<td>Atypical dementia</td>
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<tr>
<td></td>
<td>VV</td>
<td>Type 1</td>
<td>VV1</td>
<td>Young onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 2</td>
<td>VV2</td>
<td>Early balance difficulties</td>
</tr>
</tbody>
</table>
Genetic Prion Diseases

PrP\(_c\)  PrP\(_m\)  PrP\(_{Sc}\)

Genetic Prion Disease
**Table 1** Variations in the human prion protein gene coding region

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Silent</th>
<th>Influential</th>
<th>Mutation</th>
<th>Insertional</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Point</td>
<td></td>
</tr>
<tr>
<td>P68P</td>
<td>M129V</td>
<td>P102L</td>
<td>T188A</td>
<td>24bp</td>
</tr>
<tr>
<td>A117A</td>
<td>N171S?</td>
<td>P105L</td>
<td>T188K</td>
<td>48bp</td>
</tr>
<tr>
<td>G124G</td>
<td>E219K?</td>
<td>A117V</td>
<td>E196K</td>
<td>96bp</td>
</tr>
<tr>
<td>V161V</td>
<td>24bp deletion?</td>
<td>G131V</td>
<td>F198S</td>
<td>120bp</td>
</tr>
<tr>
<td>N173N*</td>
<td>I138M*</td>
<td>E200K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H177H</td>
<td>G142S*</td>
<td>D202N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T188T*</td>
<td>Y145s</td>
<td>V203I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D202D</td>
<td>Q160s</td>
<td>R208H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q212Q</td>
<td></td>
<td>D178N—129V</td>
<td>V210I</td>
<td></td>
</tr>
<tr>
<td>R228R</td>
<td></td>
<td>D178N—129M</td>
<td>E211Q</td>
<td></td>
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<tr>
<td>S230S</td>
<td></td>
<td>V180I</td>
<td>Q212P</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>V180I + M232R</td>
<td>Q217R</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T183A</td>
<td>M232R</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>H187R</td>
<td>M232T</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T188R</td>
<td>P238S</td>
<td></td>
</tr>
</tbody>
</table>

*(Bold indicates CJD phenotype, underlined indicates GSS, italics indicate FFI. Others are not categorised, as the published data are insufficient, or findings are unusual to the known disease subtypes. * Referred from: http://www.mad-cow.org/prion_point_mutations.html)*

Kovács GG, J Neurol 2002
**Penetrance**

“The likelihood that you will become ill if you have the mutation”

<table>
<thead>
<tr>
<th>Variant(s)</th>
<th>Ancestry</th>
<th>Comparison (allele frequencies)</th>
<th>Lifetime risk (95% CI)</th>
<th>Positive family history in cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>M232R</td>
<td>Japanese</td>
<td>Cases (2.2%) vs. ExAC (0.38%)</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cases (2.2%) vs. 23andMe (0.54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V180I</td>
<td>Japanese</td>
<td>Cases (7.2%) vs. ExAC (0.15%)</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cases (7.2%) vs. 23andMe (&lt;0.094%*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V210I</td>
<td>Italians</td>
<td>Cases (8.1%) vs. ExAC (0.021%)</td>
<td></td>
<td>12%</td>
</tr>
<tr>
<td>P102L</td>
<td></td>
<td>Cases (4.9%) vs. ExAC (0%)</td>
<td></td>
<td>49% (E200K)</td>
</tr>
<tr>
<td>A117V</td>
<td></td>
<td>Cases (4.9%) vs. 23andMe (&lt;0.00049%*)</td>
<td></td>
<td>70% (GSS†)</td>
</tr>
<tr>
<td>D178N</td>
<td></td>
<td>Cases (4.9%) vs. 23andMe (&lt;0.00049%*)</td>
<td></td>
<td>88% (FFI‡)</td>
</tr>
<tr>
<td>E200K</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**population baseline risk**

**complete penetrance**
Clinical Features of Genetic Prion Disease

- Genetic CJD (multiple different mutations, e.g. E200K)
  - Resembles classic sporadic CJD
- Fatal Familial Insomnia (D178N-129M mutation)
  - Insomnia
  - Neuropsychiatric symptoms (anxiety, hallucinations)
  - Dementia typically late in the illness
- Gerstmann-Straussler-Scheinker Syndrome (several mutations)
  - Cerebellar signs and symptoms early
  - Parkinsonian symptoms early
  - Dementia usually later in the illness
  - Longer duration (e.g., years)
Preimplantation genetic diagnosis (PGD) for genetic prion disorder due to F198S mutation in PRNP gene

Alice Uflacker, MD,1 P. Murali Doraiswamy, MBBS, FRCP,1 Svetlana Rechitsky, PhD,2 Tricia See, CGC,3,4 Michael Geschwind, MD,3 and Ilan Tur-Kaspa, MD2,5

- Only implant embryos that do not have mutation
- Eliminate disease from the family
- Can do even if the parent does not wish to know their genetic status
Acquired Prion Disease

- Kuru
- Iatrogenic CJD (iCJD)
- Variant CJD (vCJD)
Iatrogenic CJD

Two criteria for acquired prion disease*:
1) Taken from central nervous system
2) Placed in central nervous system, injected into body, or ingested

*Only vCJD is known to have been transmitted by blood transfusions

Brown P, Neurology 2006
vCJD Characteristics

- Young age at onset (~20s)
- Longer duration (> 1 year)
- Psychiatric and sensory symptoms at presentation
- Often have negative 14-3-3, unrevealing EEG
- Different brain MRI findings

Will RG, Lancet 1996
<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)</th>
<th>TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)</th>
<th>RESIDENCE IN UK &gt; 6 MONTHS DURING PERIOD 1980–1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>175 (0)</td>
<td>3 (0)</td>
<td>178†</td>
</tr>
<tr>
<td>France</td>
<td>27 (0)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Republic of Ireland</td>
<td>4 (0)</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Italy</td>
<td>3 (0)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>USA</td>
<td>4† (0)</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Canada</td>
<td>2 (0)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1 (0)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Japan</td>
<td>1* (0)</td>
<td>-</td>
<td>0</td>
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<tr>
<td>Netherlands</td>
<td>3 (0)</td>
<td>-</td>
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<td>Portugal</td>
<td>2 (0)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Spain</td>
<td>5 (0)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1 (0)</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

† The third US patient with vCJD was born and raised in Saudi Arabia and has lived permanently in the United States since late 2005. According to the US case-report, the patient was most likely infected as a child when living in Saudi Arabia. The completed investigation of the fourth US patient did not support the patient’s having had extended travel to European countries, including the United Kingdom or travel to Saudi Arabia. It confirmed that the case was in a US citizen born outside the Americas and indicated that his infection occurred before he moved to the United States; the patient had resided in Kuwait, Russia and Lebanon (see [http://wwwnc.cdc.gov/eid/article/21/5/pdfs/14-2017.pdf](http://wwwnc.cdc.gov/eid/article/21/5/pdfs/14-2017.pdf)).

* The case from Japan had resided in the UK for 24 days in the period 1980–1996.

† Case 178 from the UK was heterozygous at codon129 of the PRNP gene.
“mad cow epidemic” 1980’s
Asymptomatic vCJD Carriers

- Survey of UK appendices
- 16/32,441 were prion positive
- No difference by birth cohort
- All codon 129 polymorphisms represented
- Estimated infection prevalence of 1:2000
CWD Questions

• Transmissible to humans?
  – No known cases
  – CDC has various studies
  – NPDPSC collects data and looks for atypical cases
  – Some evidence that it can be transmitted to primates

• Effect on environment (e.g., contamination)

• How to stop the spread?

• Are other animals at risk?
Summary

- Prion diseases are caused by a misfolded protein and can be transmissible in certain circumstances
- There are 3 causes of prion disease: sporadic, genetic, and acquired
- Brain tissue allows us to definitely diagnosis prion disease and its type, but clinical tests are often useful in making a diagnosis in the right clinical setting
My Lab
National Prion Disease Pathology Surveillance Center

Thank you!