Prion Disease Overview
Patient with RPD

- Blood: CBC, chemistry (including Ca, Mg, phosphorus); LFTs; RPR; rheumatology screen (ESR, ANA, RF and CRP); thyroid function; B12; homocysteine; anti-thyroglobulin and anti-thyroperoxidase antibodies; HIV; Lyme; paraneoplastic antibodies & non-paraneoplastic antibodies (eg. VGKC, anti-GAD65...)
- Urine analysis
- LP: Cell count & differential Protein; Glucose; IgG index; OCB; VDRL
- Imaging: Brain MRI (including FLAIR and DWI) with and without contrast

Further evaluation (Fig 13.2)

- R/O Infectious
- R/O Autoimmune
- R/O Malignancy
- R/O Vascular
- R/O Toxic-metabolic

If CSF and body & brain imaging findings do not allow a definitive diagnosis.

Brain Biopsy

What is a prion?

- *protein* and *infectious*
- *-ion* (infectious, e.g. *virion*)
- No nucleic acid (e.g., DNA, RNA, “building blocks of life”)
- Non-degradable by typical sterilization
PrP: prion protein
PrP\textsubscript{C}: normal prion protein (c=cellular)
PrP\textsubscript{Sc}: disease causing protein (Sc=scrapie)

Soto C, *Trends Biochem Sci*
2006
Animals

• Scrapie: sheet & goat
• Bovine spongiform encephalopathy (BSE): cow
• Chronic wasting disease (CWD): deer, elk, moose, caribou
Etiologies

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

- 1-2 new cases per million individuals per year across the entire population (all ages)
- 1/10,000 US deaths per year
- OH=10.5 million people
  - 10.5 new cases/yr
  - ~2.5 cases living past one year
  - Would not be unusual to have 13 active cases in OH

Age at Onset

Adapted from: Appleby BS, J Neuropsychiatry Clin Neurosci 2007
Survival Time in Sporadic Creutzfeldt-Jakob Disease (n=90)

Cumulative Survival

Time (years)

Adapted from: Appleby BS, Arch Neurol 2009
Definite Diagnosis - Neuropathology

H & E Staining
(spongiform changes)

Immunohistochemistry
(abnormal prion protein)
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 spinal fluid and disease duration < 2 years
3. Abnormal findings in basal ganglia or at least two cortical (e.g., outside) regions on specific sequences on brain MRI

Electroencephalogram (EEG)

Periodic sharp wave complexes
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)
Real-Time Quaking-Induced Conversion (RT-QuIC)
RT-QuIC: Highly Specific

### CSF Samples from sCJD Cases

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>Japan</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT-QuIC</td>
<td>14-3-3</td>
<td>14-3-3</td>
<td>14-3-3</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>89%</td>
<td>94%</td>
<td>88%</td>
</tr>
<tr>
<td>Specificity</td>
<td>99%</td>
<td>65%</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?

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
Genetic Prion Disease

Table 1 Variations in the human prion protein gene coding region

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent</td>
<td>Influential</td>
</tr>
<tr>
<td>P68P</td>
<td>M129V</td>
</tr>
<tr>
<td>A117A</td>
<td>N171S?</td>
</tr>
<tr>
<td>G124G</td>
<td>E219K?</td>
</tr>
<tr>
<td>V161V</td>
<td>24bp deletion?</td>
</tr>
<tr>
<td>N173N*</td>
<td>I138M*</td>
</tr>
<tr>
<td>H177H</td>
<td>G142S*</td>
</tr>
<tr>
<td>T188T*</td>
<td>Y145s</td>
</tr>
<tr>
<td>D202D</td>
<td>Q160s</td>
</tr>
<tr>
<td>Q212Q</td>
<td>D178N–129V</td>
</tr>
<tr>
<td>R228R</td>
<td>D178N–129M</td>
</tr>
<tr>
<td>S230S</td>
<td>V180I</td>
</tr>
<tr>
<td></td>
<td>V180I + M232R</td>
</tr>
<tr>
<td></td>
<td>T183A</td>
</tr>
<tr>
<td></td>
<td>H187R</td>
</tr>
<tr>
<td></td>
<td>T188R</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)
Clinical Features of Genetic Prion Disease

- **Genetic CJD**
  - Resembles classic sporadic CJD

- **Fatal Familial Insomnia**
  - Insomnia
  - Neuropsychiatric symptoms (anxiety, hallucinations)
  - Dementia typically late in the illness

- **Gerstmann-Straussler-Scheinker Syndrome**
  - Cerebellar signs and symptoms early
  - Parkinsonian symptoms early
  - Dementia usually later in the illness
  - Longer duration (e.g., years)
Acquired Prion Disease

- Kuru
- Iatrogenic CJD (iCJD)
- Variant CJD (vCJD)
Kuru
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 has 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
• Negative 14-3-3, unrevealing EEG
• Different brain MRI findings
• Tonsil biopsy

Will RG, Lancet 1996
Pulvinar Sign

Zeidler M, Lancet 2000
## VARIANT CJD CASES WORLDWIDE

<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 (1)</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>
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<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Netherlands</td>
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<td>-</td>
<td>0</td>
</tr>
<tr>
<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.
MM

MV: 1 symptomatic case

BSE 1980's

Creutzfeldt-Jakob Disease in the UK, 20th Annual Report, 2011
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

Gill ON, BMJ 2013
Chronic Wasting Disease in North America

- **Areas with CWD infected Cervid populations**
- **States/Provinces where CWD has been found in captive populations**

02/2016

www.cwd-info.org
sCJD subtypes

A. Polymorphism (differences in code) at position 129 of the prion protein gene (MM, MV, or VV)
B. Prion protein type (differ by size/weight) (e.g., 1 or 2)

sCJD subtype = A + B (MM1, VV2, etc)

Subtypes vary in neuropathology and clinical characteristics.
Thank you!
Questions?