Prions for Neuropathology Fellows (and Friends)

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Disclosures

• I have no relevant financial relationships to disclose
• OR
• I have the following relevant financial relationships to disclose

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Learning Objectives

1. Discuss the diagnostic value of cerebrospinal fluid biomarkers for prion diseases, including why most patients with cerebrospinal fluid 14-3-3 protein do not have prion disease.

2. Describe anatomic variability in the histopathological hallmarks of prion disease.

3. Find reliable information regarding proper handling of potentially prion positive biomaterials.
Accomplishing our learning objectives

1. Helping the Doctors
2. Prions under glass
   1. Horses
   2. Zebras (or, plaques I have known)
   3. Unicorns (knowing our limitations)
3. When Prions escape
CLINICAL HISTORY: Other Comments; Concern for CJF (no history anoxic brain injury)

COMPARISON: MR brain November 09, 2021

TECHNIQUE:
Sagittal T1 weighted, axial T2 weighted, axial diffusion weighted and axial T2-weighted FLAIR images of the brain were obtained.

IMPRESSION:
Supratentorial cortical and deep nuclei restricted diffusion with T2 FLAIR hyperintense signal suggestive of status epilepticus though differentials include but not limited to Creutzfeldt-Jakob disease, encephalitis or hypoglycemic encephalopathy.
Given these prevalences, is it likely that the test result is a false positive?

Well, this chapter is on Bayes' theorem, so yes.
Subtype Diagnosis of Sporadic Creutzfeldt–Jakob Disease with Diffusion Magnetic Resonance Imaging

Alberto Bizzi, MD ©,1 Riccardo Pascuzzo, PhD ©,1 Janis Blevins, BSc,2 Marco E. M. Moscatelli, MD ©,1 Marina Grisoli, MD,1 Raffaele Lodi, MD,3,4 Fabio M. Doniselli, MD,1 Gianmarco Castelli, MSc,1 Mark L. Cohen, MD,2,5,6 Aymeric Stamm, PhD,7 Lawrence B. Schonberger, MD,8 Brian S. Appleby, MD,2,5,6,9 and Pierluigi Gambetti, MD5
Helping the Doctors II: CSF testing for prion disease

Prior probability at NPDPSC has doubled over the last decade (good)

RT-QuIC is nearly/may be 100% specific (good)

14-3-3 still sucks, and clinicians still love it (bad)

https://seeing-theory.brown.edu/bayesian-inference/index.html
76-year-old man with progressive behavioral, cognitive, and visual dysfunction.

VM CASE (HORSES)
Classic (MM/V1) CJD shows fine vacuolation involving all cortical layers, with relative sparing of the hippocampus.
Ataxic (VV2) CJD shows deep laminar cortical vacuolation with marked striatal and cerebellar degeneration.
58-year-old man with alcohol and drug abuse, two years of dizziness initiated by motion, and recent memory difficulties.

VM CASE 2 (ZEBRAS)
Sporadic CJD demonstrates *heterozygote advantage* with respect to the codon 129 polymorphism

<table>
<thead>
<tr>
<th>Disease subtype</th>
<th>Relative frequency</th>
<th>Mean survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM1</td>
<td>65%</td>
<td>4 months</td>
</tr>
<tr>
<td>VV2</td>
<td>15%</td>
<td>6.5 months</td>
</tr>
<tr>
<td>MV2</td>
<td>10%</td>
<td>17 months</td>
</tr>
</tbody>
</table>
36-year-old woman with >5 years of brainstem and cerebellar dysfunction, now with cognitive decline. Father died from spinocerebellar ataxia.
27-year-old consumer of “Vintage British Beef” with 14 months of cognitive decline
33-year-old man who developed anxiety followed by double vision, gait difficulties, nocturnal panic attacks with trouble sleeping, memory problems, dysphagia, and myoclonus.

**VM CASE 3 (UNICORNS)**
“A physician has got to know his limitations”

--Dr. C. Eastwood

- Insomnia is not a defining feature of Fatal Insomnia
- MRI & EEG can be normal
- RT-QuIC is often negative
- Brain biopsy will be negative
- Autopsy will be negative if thalamus and medulla not examined

- Polysomnography may support the diagnosis
- PrP IHC may be positive in the medial temporal lobe
- Western blot is often diagnostic
No iatrogenic CJD cases associated with exposure to the CJD agent from surfaces such as floors, walls, or countertops have been identified.
Give me one good reason I shouldn’t freak out, and not just that it hasn’t been reported.

Not good enough. How about some human data that I can share with my laboratory personnel?

**Table 3.** Inoculation of sCJD CSF samples into Tg66 mice.

<table>
<thead>
<tr>
<th>Donor</th>
<th>Inoculum dilution</th>
<th>Clinical prion disease (+/total)</th>
<th>Survival time dpi (mean +/- SD)</th>
<th>Neuropathology and PrP IHC (+/total tested)</th>
<th>RT-QuIC (+/ total tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCJD Patient 1</td>
<td>1:20</td>
<td>0/6</td>
<td>516 +/-64</td>
<td>NT</td>
<td>0/4</td>
</tr>
<tr>
<td>sCJD Patient 2</td>
<td>1:1</td>
<td>0/6</td>
<td>547 +/-74</td>
<td>NT</td>
<td>0/4</td>
</tr>
<tr>
<td>sCJD Patient 8</td>
<td>1:20</td>
<td>0/5</td>
<td>518 +/-89</td>
<td>NT</td>
<td>0/2</td>
</tr>
<tr>
<td>Non-CJD</td>
<td>1:1</td>
<td>0/6</td>
<td>550 +/-73</td>
<td>0/3</td>
<td>0/5</td>
</tr>
</tbody>
</table>

**Table 4.** Inoculation of sCJD-seeded RT-QuIC products into Tg66 mice.

<table>
<thead>
<tr>
<th>RT-QuIC product inoculum</th>
<th>Total PrP inoculated</th>
<th>Clinical prion disease (+/total)</th>
<th>Survival time dpi (mean +/- SD)</th>
<th>Atypical neuropathology and PrP IHC (+/total tested)</th>
<th>RT-QuIC (+/total tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CJD Patient 2-seeded</td>
<td>5 µg</td>
<td>0/5</td>
<td>644 +/-7</td>
<td>4/4</td>
<td>2/2</td>
</tr>
<tr>
<td>CJD Patient 8-seeded</td>
<td>0.5 µg</td>
<td>0/6</td>
<td>554 +/-104</td>
<td>2/3</td>
<td>NT</td>
</tr>
<tr>
<td>CJD Patient 8-seeded</td>
<td>5 µg</td>
<td>0/5</td>
<td>560 +/-62</td>
<td>2/2</td>
<td>1/1</td>
</tr>
<tr>
<td>Control Patient-seeded</td>
<td>2.5 µg</td>
<td>0/4</td>
<td>526 +/-36</td>
<td>3/4</td>
<td>0/4</td>
</tr>
</tbody>
</table>

NT: not tested.

Minimise transmission risk of CJD and vCJD in healthcare settings

Prevention of CJD and vCJD by the Advisory Committee on Dangerous Pathogens' Transmissible Spongiform Encephalopathy (ACDP TSE) subgroup.

From: Department of Health and Social Care
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Are we there yet?

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