Creutzfeldt-Jakob disease & Laboratory Tests

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Case Definition For Possible & Probable sCJD

Possible sCJD
Dementia or Rapid Progressive Dementia with at least 2 clinical signs:
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)

Probable sCJD
Satisfies possible sCJD definition AND at least 1 of the following:
- 1. Periodic sharp wave complexes (PSWC) on electroencephalogram (EEG) (looks at brain waves)
- 2. Elevated protein 14-3-3 in spinal fluid and disease duration < 2 years
- 3. Abnormal findings in basal ganglia or at least two cortical regions on specific sequences on brain MRI

Comparison of findings by Prion disease

Typical Features of sCJD by Subtype (Polymorphism (129th codon) & Glycoform)

Table 1: Genetic subtypes of sCJD and typical features

<table>
<thead>
<tr>
<th>Features</th>
<th>sCJD</th>
<th>vCJD</th>
<th>iCJD</th>
<th>fCJD</th>
<th>OS</th>
<th>PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at onset</td>
<td>65-75 yrs</td>
<td>75 yrs</td>
<td>65 yrs</td>
<td>65 yrs</td>
<td>65 yrs</td>
<td>65 yrs</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>5 yrs</td>
<td>16 yrs</td>
<td>5 yrs</td>
<td>5 yrs</td>
<td>5 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td>Predominant clinical features</td>
<td>Rapid cognitive decline, myoclonus, pyramidal symptoms</td>
<td>Rapid cognitive decline, myoclonus, pyramidal symptoms</td>
<td>Rapid cognitive decline, myoclonus, pyramidal symptoms</td>
<td>Rapid cognitive decline, myoclonus, pyramidal symptoms</td>
<td>Rapid cognitive decline, myoclonus, pyramidal symptoms</td>
<td>Rapid cognitive decline, myoclonus, pyramidal symptoms</td>
</tr>
<tr>
<td>EEG findings</td>
<td>FPaS negative</td>
<td>FPaS positive</td>
<td>FPaS positive</td>
<td>Similar to sCJD</td>
<td>Similar to sCJD</td>
<td>Similar to sCJD</td>
</tr>
<tr>
<td>14-3-3 testing</td>
<td>Positive in 100%</td>
<td>Positive in 100%</td>
<td>Positive in 100%</td>
<td>Positive in 100%</td>
<td>Positive in 100%</td>
<td>Positive in 100%</td>
</tr>
<tr>
<td>MRI findings</td>
<td>GM1 ganglioside in basal ganglia or cortex</td>
<td>GM1 ganglioside in basal ganglia or cortex</td>
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<td>GM1 ganglioside in basal ganglia or cortex</td>
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<td>GM1 ganglioside in basal ganglia or cortex</td>
</tr>
<tr>
<td>Percentage of sCJD</td>
<td>60-70%</td>
<td>60-70%</td>
<td>80%</td>
<td>60-70%</td>
<td>60-70%</td>
<td>60-70%</td>
</tr>
</tbody>
</table>

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Supportive Tests for Prion Disease

**Labs:**
- Tau Protein - CSF
- 14-3-3 Protein - CSF
- Real Time-Quaking Induced Conversion (RT-QuIC) - CSF

**Imaging:**
- Magnetic Resonance Imaging (MRI)
- Electroencephalogram (EEG)

**Confirmatory Path Criteria**
- Diagnosis by standard neuropathological techniques
- Immunohistocytochemistry (IHC) AND/OR Western blot (WB) AND/OR Presence of scrapie-associated fibrils from biopsy or autopsy obtained brain tissue

**Diseases that may have positive 14-3-3 and/or Tau protein CSF Test Results**
- Herpes simplex & other viral encephalitides
- Recent stroke
- Subarachnoid hemorrhage
- Hypoxic brain hemorrhage
- Metabolic encephalopathy after barbiturate intoxication
- Glioblastoma
- Cerebromedullary meningitis from small-cell lung cancer
- Paraneoplastic encephalopathy
- Corticobasal degeneration

**CSF Protein Markers**
- Non-specific for disease
- Elevated in presence of active neuron destruction due to any cause
- False positive due to blood in the CSF
  - Red or pink appearing CSF
  - Hematocrit above normal range
  - fibrin-looking CSF
  - HGB counts >500 cells per μL
  - WBC counts >10 cells per μL
  - Clinical correlation is required
  - Positive results without clinical findings consistent with CJD do not carry weight in the diagnosis of CJD
  - Sensitivity: 14-3-3 = Tau; Specificity: Tau > 14-3-3

**Supportive Lab Criteria**
- ELISA reported as elevated or above normal limits (>1.5 pg/ml)
- Western blot (WB) reported positive

**Confirmatory Path Criteria**
- CSF-14-3-3 Protein:
  - >1.5 pg/ml
  - Presence of 14-3-3 protein

**Real-Time Quaking Induced Conversion (RT-QuIC)**
- Positive

**Host PrP = Normal Prion Protein = PrPsen**
- Infectious PrPsc = Abnormal Prion Protein = PrPres

**PrP**
- Prion protein
- PrPsen: normal prion protein (normal lucid)
- PrPres: disease causing prion protein (bicoreceptor)

Soda C, Tendler, Bloem, Surf 2008

Christina D. Orru; Jason M. Wilham; Sarah Vascellari; Andrew G. Hughson; Byron Caughey; Prion 2012, 6, 147-152.
DOI: 10.4161/pri.19430
Copyright © 2012 Landes Bioscience
Plate-based fluorescence detection of prion-seeded PrP Amyloid – RT-QuIC

RT-QuIC detection of 28 types of prion seeds from 5 different species using new BV-rPrP substrate

Potential mechanisms of substrate replacement effect
difference between generation I & II RT-QuIC

Sensitivity and specificity of RT-QuIC, 14-3-3 & Tau testing performed in RT-QuIC retrospective study of 294 patients

A universal prion protein substrate?

Bank Vole prion protein?

Western blot of products from RT-QuIC reactions

Antemortem diagnosis and confirmation of prion disease is in-sight!
Diagnostic performance of 2nd generation CSF RT-QuIC, 14-3-3, & T-Tau; prospective cohort

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Mutation</th>
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<tbody>
<tr>
<td>Prion diseases</td>
<td>PRNP</td>
<td>Point mutations &amp; octapeptide repeats</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>APP</td>
<td>Point mutations</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>SNCA</td>
<td>Point mutations</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>TAU</td>
<td>Point mutations</td>
</tr>
<tr>
<td>Fick’s disease</td>
<td>TAU</td>
<td>Point mutations, deletions</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>SOD1</td>
<td>Point mutations</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>HTT</td>
<td>Polyglutamine expansions</td>
</tr>
<tr>
<td>Spinocerebellar ataxia</td>
<td>Type 1</td>
<td>SCA1</td>
</tr>
<tr>
<td></td>
<td>Type 2</td>
<td>SCA2</td>
</tr>
<tr>
<td>Machado-Joseph disease</td>
<td>Type 3</td>
<td>SCA3</td>
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Typical EEG findings for sporadic Creutzfeldt-Jakob disease (sCJD)

Periodic sharp wave complexes (PSWCs)
Conditions that may mimic EEG findings typical for sporadic CJD

- Alzheimer disease
- Lewy body disease
- Binswanger disease
- AIDS dementia hypernatremia
- Multiple cerebral abscesses
- MELAS syndrome
- Post-oxicencephalopathy

Hyperammonemia
Hyperparathyroidism
Hypo- and hypernatremia
Hypoglycemia
Hepatic encephalopathy
Baclofen, mianserin, metrizamide and lithium toxicity

The presence of periodic sharp-wave complexes (PSWCs) is reported to have a sensitivity of 67% and a specificity of 86% for vCJD, the remaining cases being noted to have only nonspecific slow-wave abnormalities.

The MRI – "Cortical Ribboning" is also a finding that can be seen in vCJD.

Head of caudate

Brain MRI – FLAIR imaging, axial view – Findings Seen in vCJD

A) Normal FLAIR image; Thalamus
- Slight symmetrical hyperintensity of pulvinar (posterior) thalamic nuclear

B) Pulvinar sign of vCJD; FLAIR image
- Marked, symmetrical hyperintensity of the pulvinar (posterior) thalamic nuclear

C) "Hockey-stick" sign of vCJD - FLAIR image
- Symmetrical pulvinar and dorsomedial thalamic nuclear hyperintensity
- This combination gives a characteristic, "hockey-stick" appearance
- In a study of 98 confirmed vCJD cases, the sign was present in 93% of cases by FLAIR imaging


Conditions with thalamic hyperintensity on MRI

- Causes of thalamic high signal (involving whole thalamus or other thalamic nuclei except pulvinar)
  - Carbon monoxide poisoning
  - Japanese Niposituencephalitis
  - Wernicke encephalopathy
  - BI-thalamic glioma
  - Thalamic infarction

- Causes of pulvinar and dorsomedial nuclear group hyperintensity
  - Benign intracranial hypertension (BIH)
  - Cat-scratch disease
  - Alpers syndrome
  - Post-Infectious encephalitis

Normal sCJD MM1 sCJD MM2
Microscopic View of the Cerebral Cortex