What’s new in prion diseases?

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The National CJD Research & Surveillance Unit

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Session: Disorders at the interface of neurology and psychiatry
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What are prion diseases?

- Prion diseases or transmissible spongiform encephalopathies are fatal neurodegenerative diseases that affect both animals and humans
- Human prion diseases: rapid cognitive decline, ataxia, myoclonus, visual and/or cerebellar disturbance

**Animal TSEs**

- Scrapie of sheep and goats
- Transmissible mink encephalopathy
- Bovine spongiform encephalopathy
- Chronic wasting disease of cervids
  - ERA – Dr Fiona Houston, Roslin Institute
- Camel Prion Disease
  - CAMENET (Camel Middle East Network)
  - EFRAN (Enhancing Research for African Network)

**Human TSEs**

- Creutzfeldt-Jakob disease
  - Sporadic: (85%)
  - Genetic: mutations PRNP gene (10%)
  - Iatrogenic: cadaveric hormone therapy, dura mater graft
  - Acquired: Kuru and variant CJD

- Gerstmann-Straussler-Scheinker syndrome

- Variable Protease sensitive prionopathy (VPSPr)
Neuropathology of TSEs

- Defined by the neuropathological deposition of an abnormal prion protein
New developments

- Updates on the diagnosis of sporadic CJD
  - New diagnostic criteria introduced in 2017
    - Cortical Ribboning on MRI
    - CSF Real-Time Quaking Induced Conversion (RT-QuIC)

- Variant CJD update

- Variably Protease Sensitive Prionopathy
Diagnosis of sporadic Creutzfeldt-Jakob disease prior to 2017

• Rapidly progressing dementia
  • Rare: 1-2 cases/million population/year
  • Age onset 60s
  • Death usually occurs within 6 months

• Other clinical features
  • Myoclonus
  • Visual or cerebellar problems
  • Pyramidal or extrapyramidal features
  • Akinetic mutism

• Neuropathological features
  • Neuronal loss
  • Astrocytosis
  • Deposition of an abnormal form of prion protein (PrP\textsuperscript{Sc})

• Supportive Investigations
  • MRI
  • EEG
  • CSF 14-3-3
Diagrammatic scheme of RT-QuIC reaction

- Non-fluorescent ThT
- Fluorescent ThT
- Recombinant hamster PrP(Substrate)
- Seeding agent in CSF or brain homogenate (Seed)

Lag Phase

Aggregation Phase
RT-QuIC analysis of brain and CSF from sCJD cases
<table>
<thead>
<tr>
<th>Cases</th>
<th>Controls</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermann et al (2018)**&lt;sup&gt;1&lt;/sup&gt;</td>
<td>65</td>
<td>Definite sporadic Creutzfeldt-Jakob disease and genetic Creutzfeldt-Jakob disease</td>
<td>14</td>
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<td>62</td>
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<tr>
<td>Focini et al (2020)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>102</td>
<td>Probable and definite sporadic Creutzfeldt-Jakob disease</td>
<td>80</td>
<td>Rapidly progressive dementia</td>
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<tr>
<td>Manimana et al (2020)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>24</td>
<td>Probable and definite sporadic Creutzfeldt-Jakob disease</td>
<td>12</td>
<td>Rapidly progressive dementia</td>
</tr>
<tr>
<td>Rhodes et al (2020)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>459</td>
<td>Definite sporadic Creutzfeldt-Jakob disease</td>
<td>69</td>
<td>Rapidly progressive dementia</td>
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</table>

**Table: Diagnostic accuracy of CSF RT-QuIC in retrospective and prospective studies**

*Definite sporadic Creutzfeldt-Jakob disease is defined as neuropathologically confirmed diagnosis. Probable sporadic Creutzfeldt-Jakob disease is defined as clinical diagnosis based on syndrome and biomarkers. Some other neurological diseases include dementia syndromes, Non-Creutzfeldt-Jakob diseases including non-neurological disorders, neurological disorders, and dementia syndromes. 1st generation first generation tests. 2nd generation second generation tests. RT-QuIC real-time quaking induced conversion. This study investigated two different cohorts, overall sensitivity and specificity are summarised here. These studies applied two different protocols and used the same control group for both investigations. This protocol used hamster-sheep chimeric recombinant PrP as substrate (instead of hamster PrP) and test positivity was indicated by two out of three positive replicates (instead of two of four).
MRI in sCJD

- DWI and FLAIR MRI display restricted diffusion in at least two cortical regions (ribboning) or restricted diffusion predominantly in the caudate nucleus, or both, followed by putamen and thalamus
MRI: CJD mimics

- Seizures + status epilepticus
- Vascular encephalopathy
- Immune mediated encephalitis
- Infectious encephalitis
- Metabolic/toxic encephalopathy
- Cerebral neoplasia
- Cerebral hypoxia
- Storage diseases and mitochondrial cytopathies

Red flags:
1. Prominent limbic involvement
2. Swelling
3. Isolated region (Dx criteria require *multifocal* disease)
4. White matter involvement
## Impact of RT-QuIC and MRI on sCJD diagnosis in UK

<table>
<thead>
<tr>
<th>Definite/probable sCJD (131)</th>
<th>RT-QuIC Positive</th>
<th>RT-QuIC Negative</th>
<th>MRI in RT-QuIC Negative cases (7) or cases with no CSF (24)</th>
<th>Post-mortem undertaken</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSF received 107 (82%)</strong></td>
<td></td>
<td></td>
<td>Basal ganglia changes and cortical ribboning (4)</td>
<td>1 case (confirmed sCJD MM2)</td>
</tr>
<tr>
<td></td>
<td>100 (94%)</td>
<td>7 (6%)</td>
<td>Basal ganglia changes only (1)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Cortical ribboning only (1)</td>
<td></td>
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<tr>
<td><strong>No CSF received 24 (18%)</strong></td>
<td></td>
<td></td>
<td>Basal ganglia changes and cortical ribboning (14)</td>
<td>5 cases (all confirmed sCJD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Basal ganglia changes only (1)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Cortical ribboning only (4)</td>
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</tbody>
</table>
Box 1 | European Creutzfeldt–Jakob Disease Surveillance Network diagnostic criteria for sCJD

**Definite sCJD:**
Progressive neurological syndrome and either neuropathological, immunocytochemical or biochemical confirmation.

**Probable sCJD:**
Rapidly progressive cognitive impairment; two of myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism; and typical EEG<sup>a</sup>.

OR
Rapidly progressive cognitive impairment; two of myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism; and typical MRI brain scan<sup>b</sup>.

OR
Rapidly progressive cognitive impairment; two of myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism; and positive cerebrospinal fluid 14–3–3 protein test.

OR
Progressive neuropsychiatric syndrome and positive real-time quaking-induced conversion (RT-QuiC) in cerebrospinal fluid or other tissues.

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Impact on surveillance data UK

Deaths from definite or probable CJD referred to NCJDRSU
1 May 1990 – 31st December 2018

Age-specific mortality rates from sporadic CJD in the UK 1970-2019

Post-mortem rate in all referrals of suspected CJD to NCJDRSU
1 May 1990 – 31st December 2019
Variant CJD
Occupational risk for vCJD

- 24y;F; Laboratory technician
- Working with sheep-adapted BSE
- 2010: Needle stick injury
- 2017: Burning pain left shoulder/neck, progressed over 6 months
- 2018: Routine CSF investigations: normal,
  - MRI: increased signal in caudate/thalami
- 2019: Depression, hallucinations, memory impairment,
  - CSF 14-3-3 and RT-QuIC: Negative;
  - PRNP-codon 129:MM;
  - PMCA CSF and plasma: positive for vCJD
- Died 2019: PM showed classical vCJD

- 2016: Italian laboratory technician
- Working with BSE infected brain material
- Died with PM confirmed variant CJD
- No reported laboratory accident

Variably protease sensitive prionopathy (VPSPr)

- First identified 2008
- Further characterised in 2010
- 37 cases reported in literature
- Neuropathological studies suggest prevalence 0.7%-1.7% of all sporadic prion diseases
- Not associated with mutations in PRNP gene, commonly associated with PRNP-codon 129:VV
- Clinically: median 2-year duration and presentation with psychiatric signs, speech/language impairment, or cognitive decline
- Often diagnosed as atypical or non-Alzheimer’s dementia
- Neuropathy: moderate spongiform degeneration, PrP amyloid mini-plaques
- Transmission to animal models has been demonstrated
Neuropathology of VPSPr

**H + E**

**Anti-PrP**

**PrP^Sc Western blot**

- kDa
- VPSPr MV
- sCJD VV2
## Characteristics of VPSPr

<table>
<thead>
<tr>
<th></th>
<th>PRNP-codon 129:MM</th>
<th>PRNP-codon 129:MV</th>
<th>PRNP-codon 129:VV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of cases</strong></td>
<td>8%</td>
<td>25%</td>
<td>67%</td>
</tr>
<tr>
<td><strong>Age at onset (years, range)</strong></td>
<td>78 (64-87)</td>
<td>74 (65-81)</td>
<td>67 (48-77)</td>
</tr>
<tr>
<td><strong>Duration (months, range)</strong></td>
<td>41 (10-73)</td>
<td>34 (9-71)</td>
<td>18 (10-60)</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>psychiatric symptoms, aphasia, parkinsonism, ataxia</td>
<td>psychiatric symptoms, cognitive impairment</td>
<td>psychiatric symptoms, cognitive impairment, aphasia</td>
</tr>
<tr>
<td><strong>Advanced clinical symptoms</strong></td>
<td>Cognitive decline, aphasia, myoclonus</td>
<td>Ataxia, parkinsonism</td>
<td>Ataxia, parkinsonism, myoclonus</td>
</tr>
<tr>
<td>Suggestive EEG</td>
<td>50%</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td>Positive CSF 14-3-3/tau</td>
<td>50%</td>
<td>0%</td>
<td>37%</td>
</tr>
<tr>
<td>Positive CSF RT-QuIC</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Suggestive MRI</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Clinical features

- Psychiatric symptoms: disinhibition, euphoria, impulsivity, and apathy
- Speech and language impairments: anomic or semantic aphasia with or without dysarthria.
- Cognitive impairment: frontal lobe dysfunction

**Proposed clinical criteria for variable protease-sensitive prionopathy**

A. Symptoms (both 1 and 2)
   1. Cognitive impairment
   2. Two or more of the following:
      (a) Psychiatric symptoms
      (b) Parkinsonism or aphasia
      (c) Ataxia or myoclonus

B. Duration < 8 years

C. Lack of alternative etiology or phenotype divergence from other neurodegenerative atypical dementias
Conclusions

• Introduction of CSF RT-QuIC and updated MRI criteria identify 95% of sCJD cases
• Increase in the prevalence of sCJD – worldwide, related to improved ascertainment
• No new cases variant CJD in UK since 2016
• No evidence of a second wave of vCJD
• Evidence for occupational risk for laboratory workers working with BSE/vCJD
• VPSPr is a new form prion disease, under recognised
• VPSPr presents can present with psychiatric features and often classified as atypical dementia/non-AD dementia
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