Comparative study of prions associated with iatrogenic and sporadic CJD: An update

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Background

- Spontaneous vs. acquired: sporadic CJD (sCJD) and familial CJD (fCJD); variant CJD (vCJD) and iatrogenic CJD (iCJD)

- Iatrogenic CJD: corneal transplant, depth electrodes, neurosurgical instruments, human growth hormone, human dura graft, blood and tissue donations

- Differential diagnosis of iCJD: important

- Difference in the PrP\textsuperscript{Sc} profile between iCJD and sCJD: none, by conventional methods
Aim

To search for differences in prions between iCJD and sCJD
PrP<sub>Sc</sub> typing by conventional methods
Application of sophisticated methods
(quantitative and qualitative analysis of PrP)

- PrP levels: total PrP, PrP<sub>C</sub>, PK-sensitive/resistant PrP<sub>Sc</sub>
- Oligomeric state
- Converting activity
- Enzymatic fragmentation
- Transmissibility
Oligomeric state of various PrP species from iCJD and sCJD by FPLC

No significant difference in PrP profile of FPLC is detectable between iCJD and sCJD
Oligomeric state of PrP in sucrose step gradients

No significant difference in PrP profile of sucrose gradients is detectable between iCJD and sCJD
Amplification of PrP\textsuperscript{Sc} from iCJD and sCJD by PMCA \textit{in vitro}

The converting activity of PrP\textsuperscript{Sc} from iCJD is higher than that from sCJD.
Amplification of PrP<sub>Sc</sub> from iCJD and sCJD by PMCA in vitro

The converting activity is not completely determined by the amount of PrP<sub>Sc</sub> template.
PrP-CTF in variant CJD (vCJD)

PK PNGaseF

sCJD  vCJD

Anti-C

48- 36- 29- 19- 13- 6-

PK PNGaseF + + + + + +
PrP-CTF12/13 is undetectable in some of iCJD
**Inoculation of Tg mice with prions from iCJD and sCJD**

**Prion transmission in transgenic mice**

<table>
<thead>
<tr>
<th>Prion inoculum</th>
<th>Mice</th>
<th>Incubation Time (SEM)</th>
<th>Transmission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>iCJD case 1</td>
<td>Tg 40</td>
<td>181 ± 3</td>
<td>8/8</td>
</tr>
<tr>
<td>iCJD case 2</td>
<td>Tg 40</td>
<td>170 ± 7</td>
<td>8/8</td>
</tr>
<tr>
<td>sCJD case 1</td>
<td>Tg 40</td>
<td>185 ± 5</td>
<td>8/8</td>
</tr>
<tr>
<td>sCJD case 2</td>
<td>Tg 40</td>
<td>185 ± 3</td>
<td>8/8</td>
</tr>
</tbody>
</table>

No difference in incubation time in Tg mice inoculated with iCJD and sCJD
Comparison of PrP from Tg mice inoculated with prions of iCJD or sCJD

No difference in PrP$^\text{Sc}$ in Tg mice inoculated with brain homogenates from iCJD and sCJD
Conclusions

- No differences in the PrP levels, gel mobility of PrPres, oligomeric state, transmissibility are observed between iCJD and sCJD

- PrPSc from iCJD may be more readily amplified by PMCA compared to sCJD

- Detection of PrP-CTF12/13 may be used to distinguish acquired CJD including some of iCJD from sCJD
Future studies

- To develop a PrP<sub>Sc</sub> enzymatic fragmentation-based assay for distinguishing iCJD from sCJD

- To distinguish iCJD from sCJD by comparing converting efficiency of PrP<sub>Sc</sub> associated with iCJD and sCJD using PMCA
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