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

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iCJD vs. sCJD

- Acquired vs. spontaneous: corneal transplant, depth electrodes, neurosurgical instruments, human pituitary hormones, human dura grafts, blood and tissue donations

- Differential diagnosis of iCJD: important

- Difference in the PrP$^{Sc}$ profile between iCJD and sCJD: none
Hypothesis

There are differences in the levels of PrP\textsuperscript{Sc} and residual PrP\textsuperscript{C} as well as conformations, converting activity and infectivity of PrP\textsuperscript{Sc} between iCJD and sCJD due to distinct origins of their PrP\textsuperscript{Sc}.
Application of sophisticated methods
(quantitative and qualitative analysis of PrP)

- **PrP level**: total PrP; PrP\textsuperscript{C}; PK-sensitive/resistant PrP\textsuperscript{Sc}
- **Converting activity**
- **Oligomeric state**
- **PK-resistant fragments**
- **Transmissibility**
PrP\textsuperscript{Sc} typing by conventional methods

PK-treated
Size-exclusion chromatography (SEC) or gel filtration of PrP
Size-exclusion chromatography (SEC), also called gel-filtration, uses porous particles to separate molecules of different sizes.
Western blotting of PrP from fractions of FPLC with sCJD and non-CJD brain homogenates

- CJD: PrP eluted before fractions 35 and after fractions 49.
- PrP eluted after fractions 49 represents small oligomers or monomers (PrP\textsubscript{C}).
- PrP eluted before fractions 33 represents abnormal large aggregates (PrP\textsubscript{Sc}).
Comparison of PrP oligomeric state of PrP species from iCJD and sCJD

No significant difference in PrP profile of FPLC is detectable between iCJD and sCJD
Distribution of various PrP species from iCJD and sCJD
Velocity sedimentation of PrP in sucrose step gradients
Without density gradients

- Centrifugation
- Bulk flow path

With density gradients

- Centrifugation
- More centrifugation

In the diagram, the process with density gradients involves an additional step of centrifugation after the initial centrifugation, which is not present in the process without density gradients. The bulk flow path is indicated by a yellow arrow, while the red arrows represent centrifugation steps. The images depict laboratory equipment and samples, indicating the practical application of these processes.
Distributions in sucrose gradients of various PrP species

- Non-CJD: fractions 1-3
- sCJD: fractions 9-11
- vCJD: fractions 9-11/1-2
- GSS: fractions 1-3/10-11

**Top:** a normal monomeric form \((\text{PrP}^\text{C})\).

**Bottom:** an abnormal aggregated form \((\text{PrP}^\text{Sc})\).
Sucrose step gradients of PrP

Fractions 1 2 3 4 5 6 7 8 9 10 11

iCJD

sCJD
Sucrose step gradients of PrP

No significant difference in PrP profile of sucrose gradients is detectable between iCJD and sCJD
Transmission study

Brain homogenates from 2 iCJD and 2 sCJD cases were inoculated into 32 transgenic mice expressing human PrP with 129MM in the middle of January 2008. Currently, these animals are being monitored daily.
Visions & Reflections (Minireview)

Prion: the chameleon protein

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Accessibility of a critical prion protein region involved in strain recognition and its implications for the early detection of prions


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A Novel Human Disease with Abnormal Prion Protein Sensitive to Protease

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Objective: To report a novel prion disease characterized by distinct histopathological and immunostaining features, and associated with an abnormal isoform of the prion protein (PrP) that, contrary to the common prion diseases, is predominantly sensitive to protease digestion.

Methods: Eleven subjects were investigated at the National Prion Disease Pathology Surveillance Center for clinical, histopathological, immunohistochemical, genotypical, and PrP characteristics.

Results: Patients presented with behavioral and psychiatric manifestations on average at 62 years, whereas mean disease duration was 20 months. The type of spongiform degeneration, the PrP immunostaining pattern, and the presence of microplaques distinguished these cases from those with known prion diseases. Typical protease-resistant PrP was undetectable in the cerebral neocortex with standard diagnostic procedures. After enrichment, abnormal PrP was detected at concentrations 16 times lower than common prion diseases; it included nearly 4 times less protease-resistant PrP, which formed a distinct electrophoretic profile. The subjects examined comprised about 3% of sporadic cases evaluated by the National Prion Disease Pathology Surveillance Center. Although several subjects had family histories of dementia, no mutations were found in the PrP gene open reading frame.

Interpretation: The distinct histopathological, PrP immunohistochemical, and physicochemical features, together with the homogeneous genotype, indicate that this is a previously unidentified type of disease involving the PrP, which we designated "protease-sensitive prionopathy" (or FSP). Protease-sensitive prionopathy is not rare among prion diseases, and it may be even more prevalent than our data indicate because protease-sensitive prionopathy cases are likely also to be classified within the group of non-Alzheimer’s dementias.

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