Is protease-sensitive prionopathy (PSPr) the sporadic form of Gerstmann-Sträussler-Scheinker disease (GSS)?

Preliminary data

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Proteinase-sensitive prionopathy (PSPr) is a novel human prion disease characterized by:

- Dementia associated with parkinsonism and ataxia
- Long(er) disease duration
- Abnormal prion protein displaying different levels of resistance to proteases and forming a distinctive ladder-like electrophoretic profile
- Distinctive pattern of PrP immunoreactivity

PSPr mimics some of the features of GSS including clinical features, the presence of PrP-microplaques and the electrophoretic profile
# Comparative study of GSS and PSPPr

## Clinical features

### GSS (117; 198; 217)

- **Age at onset:** generally begins between 30 and 70 years of age
- **Duration:** variable, up to 11 years
- **Cardinal signs at onset:** cerebellar ataxia variably combined with Parkinsonism and dementia.
- **Cardinal signs during disease course:** Increased severity of above rigidity, and dementia.

### PSPPr

- **Age at onset:** 61±8 years (range 48-77)
- **Duration:** 25±17 months (10-60)
- **Cardinal signs at onset:** behavioral and psychiatric signs (77%) often associated with aphasia (62%) and ‘frontal’ dementia (60%)
- **Cardinal signs during progression:** ataxia [70%] and Parkinsonism[46%]
Comparative study of GSS and PSPr

**Histopathology**

**GSS (Mut)**

PrP-amyloid deposits are either round and sharply defined resembling kuru plaques, or more often *multicentric* because of the presence of several amyloid cores (a, b).

**PSPr**

As GSS, the new disease has less conspicuous spongiform degeneration (a) and a very distinctive PrP immunostaining pattern characterized by clusters of positive granules forming a target-like pattern in the cerebral cortex (b). There are much fewer plaques but structures suggestive of microplaques are present in the molecular layer of the cerebellum (c, d).
Comparative study of GSS and PSPr

**Conclusion:**

GSS patients with 117,217,198 mut share a ladder like PrP WB profile after protease digestion, which is similar to that of PSPr.
## BUT

### Genetic features

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<th>GSS</th>
<th>PRNP coding region:</th>
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<td>Mutations:</td>
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**Conclusion:**

GSS is very heterogeneous due to the presence of different mutations that are associated with distinct disease types; we selected three types (underlined) that have more similarities with PSPr.

In these three mutations, in addition to the presence of multicentric amyloid plaques characteristic of GSS, there is also a significant tauopathy.
“Is PSPr the sporadic form of GSS?”

How to assess it?

1. By searching for the presence of PrP-amyloid, which is the distinctive feature of GSS

2. By comparing the tau pathology
The study

Total number of cases: 26
Cod.129 subtypes: 19 Val/Val, 5 Met/Val, 2 Met/Met

**Genetical analysis for tau gene** was carried out on three out of the cases with positive family history: all cases sequenced for exons 1,9,10,11,12 and 13 of the human tau gene, as well as the flanking intronic sequences, were wild type.

**Phospho-Tau Immunostaining** was present in all MM and MV cases, and in 17 out of 19 VV cases (3 cases showed a mild immunostaining).

Furthermore we looked at:

- cell type affected by tau-degeneration
- topographic distribution
- composition (3- and 4-repeats) of phospho-tau deposits
- presence of neuro-fibrillary-tangles (NFT)
- tau profile in Western blot
- ultra-structural morphology of tau filaments
Conclusion:
All the cases shared a similar pattern of topographic distribution of tau-immunoreactivity involving the deep temporal structures. Hippocampus, subiculum and parahippocampus are mainly affected by tauopathy. Generally, no phospho-tau immunostaining in frontal cortex.
Conclusion:
As in GSS, phospho-tau deposits were present predominantly in the form of *neuronal inclusions*; rare thorn-shaped astrocytes and glial plaques.
Comparison of 3R, 4R, and phospho-tau immunoreactivity in PSPr

Conclusion:
As in GSS, phospho-tau deposits in PSPr are composed by both 3-repeats and 4-repeats tau isoforms.
Neurofibrillary Tangles in PSPr

Conclusion:
Some of phospho-tau neurons in PSPr are tangles
Conclusion:
Several PrP\textsuperscript{Sc} aggregates in the cerebellum are amyloid plaques; while PrP\textsuperscript{Sc} granules organized in clusters in the cerebral cortex are unstained by FSB.
The biochemical signatures
(preliminary data)
(The GSS blot is terrible)

Conclusion
By Western Blot, PSPr seems to be associated with the same insoluble tau profile observed in GSS and Alzheimer’s disease
Conclusions

• As in several GSS subtypes, hyper-phosphorylated insoluble tau deposits represent a consistent feature of PSPr.

• The tau pathology is predominantly evident in deep temporal cortex and is expressed as ‘neuronal’ inclusions; rarely as glial plaques and astrocytic inclusions.

• Neuro-Fibrillary-Tangles in PSPr are composed by both 3-repeats and 4-repeats tau isoforms as in GSS and AD.

• In PSPr, hyperphosphorylated tau in the insoluble fraction by Western blot analysis discloses the same electrophoretic profile observed in GSS and AD.

• As observed in GSS, some of PrPSc aggregates are amyloid plaques in PSPr. They are exclusively visible in the cerebellar cortex.

• We do not yet know whether the PrPSc granules organized in clusters in the cerebral cortex are unstained by thyoflavin or FSB because of their small size or because they really are not amyloid.

• Further studies are ongoing to define the ultrastructure of pathological tau and PrP-microplques in PSPr.
The presence in PSPr of PrP-amyloid and tau pathology with characteristics similar to those observed in GSS further supports the possibility that PSPr is related to GSS, perhaps representing the long sought sporadic form of GSS.
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