50 Years of Progressive Supranuclear Palsy

CSF Biomarkers
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At the present time, progressive Supranuclear Palsy (PSP) is diagnosed clinically based on the presence of cardinal motor and oculomotor features\(^1\), but the diagnostic accuracy of PSP is only 70-75%\(^2\). No simple objective indicator or biomarker exists to support the clinical diagnosis and determine the progression of the disease. Therefore, their clinical diagnosis relies on expert opinion. Based on genetic\(^3\) and neuropathologic implications\(^4\), the characterisation of tau-protein in human body fluids represents a logical, disease-linked marker candidate to possibly separate between primary tau-related disorders from other [e.g. \(\alpha\)-synuclein (aSyn)-related] neurological diseases. Due to the progression of tau pathology in tau-related disorders\(^5\) it may also serve as a marker of the progression of the disease. These genetic and pathological links make tau a key target for therapeutic development. However, for effective translation into the clinic, there is a need to determine the exact species of tau protein in human samples and identifying which species are more prevalent in pathological disease.

Many fundamental decisions in medical practice outside the field of neurodegeneration are based on objective laboratory biomarkers. Since cerebrospinal fluid (CSF) is in direct contact with the central nervous system, it is obvious that any changes in biochemical composition of brain parenchyma should be predominantly reflected in the CSF. In fact, the permeation of brain-derived proteins is prioritized to the diffusion of blood proteins into CSF. Total tau protein in cerebrospinal fluid (CSF) is a biomarker for Alzheimer’s disease\(^6\) but is not a reliable diagnostic test for other tauopathies.

The concentration of CSF total and phosphorylated tau protein has been explored in PSP by commercially available enzyme-linked immunosorbent assay (ELISA). There no alteration of the levels between PSP and other neurodegenerative diseases was seen (Arai et al., 1997; Urakami et al., 2001 and 2002). After the detection of tau protein
fragments in brain species, the quantification of tau forms in CSF by Western/Immunoblot (after immunoprecipitation) has been established by Borroni et al. 2008 and 2009). There the ratio of 33kDa/55kDa tau forms revealed decreased levels in CSF of PSP patients compared to other neurodegenerative diseases (Borroni et al., 2009). The different tau isoforms (i.e. 3 and 4 repeat-tau) occur through alternative splicing. The imbalance of these tau isoform homeostasis characterise disease-specific pathogenesis. In fact we showed a significant decrease of 4R-tau in PSP by sensitive immune-PCR. Tau isoforms were identified and characterized within neurodegenerative disorders showing different pattern in PSP confirming a disease specific pathological progression. Especially truncated (33 kDa) and extended (55 kDa) forms of tau were detected in CSF and in cerebral cortex with a reduced ratio between the 33 kDa and 55 kDa form in CSF of PSP patients. Hence, partially proteolyzed tau is a promising marker for PSP diagnosis. Besides these known tau isoforms, other so called “surrogate” marker candidates in CSF have already been proposed for PSP like decreased β-amyloid 1-42, neurofilament light chains and increased aSyn etc.