Searching for novel CSF biomarkers of primary tauopathies

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Primary tauopathies (PT) are pathologically heterogeneous neurodegenerative disorders associated with unique conformations of tau protein and include frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). Currently there are no biomarkers able to diagnosis the underlying pathology during life. In this study we aimed to investigate the potential of novel tau species within cerebrospinal fluid (CSF) as biomarkers for tauopathies.

Methods
86 participants were included: 20 healthy controls, 21 patients with low CSF Ab42 consistent with Alzheimer’s disease (AD), and 45 with a diagnosis within the FTLD/PSP/CBD spectrum and normal Ab42. Within the last group, 7 patients had available genetic or pathological data confirming a likely primary tauopathy, whereas 18 had a likely TDP-43 proteinopathy. Immunoassays targeting tau fragments N-123, N-mid-region, N-224 and X-368, as well as a non-phosphorylated form of tau were measured in CSF, along with total-tau (T-tau) and phospho-tau (P-tau181). Groups were compared using a linear regression model with 95% bootstrapped confidence intervals.

Results
The majority of measures (apart from N-123 and X-368) were raised in the AD group compared with controls. Only T-tau, N-mid-region, Tau 224 and non-phosphorylated tau were raised in the FTLD/PSP/CBD group. However, only T-tau and P-tau181 showed a significant difference between AD and FTLD/PSP/CBD. Of the novel assays, only tau-N-mid-region and N-224 showed a difference between the primary tauopathy group and controls, but neither of these two measures nor any of the other measures differentiated primary tauopathies from TDP-43 proteinopathies. In a sub-analysis, normalising for total-tau, none of the novel tau species provided a higher sensitivity and specificity to distinguish between tau and TDP-43 pathology than P-tau181/T-tau, which itself only had a sensitivity of 61.1% and specificity of 85.7%.

Conclusion
Despite investigating multiple novel CSF tau fragments, none show promise as a primary tauopathy biomarker and so the quest for in vivo markers of non-AD tau pathology continues.

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