MEASURING NOVEL CSF BIOMARKERS IN FRONTOTEMPORAL DEMENTIA

Foiani M.S.[1,2], Cicognola C.[3], Jackson-Morgan, T. [2], Ermann N.[4], Woollacott, I.O.C.[5], Heller C.[1], Heslegrave A.J.[1], Keshavan A.[5], Paterson R.W.[5], Ye, K.[6], Kornhuber, J.[4], Fox N.C.[5], Schott J.M.[5], Warren J.D.[5], Lewczuk P.[4,6], Zetterberg H.[1,3], Blennow K.[3], Höglund K.[3], Lashley, T. [2], Rohrer J.D.[5]

[1] Dementia Research Institute, University College London, London, UK
[2] Queen Square Brain Bank (QSBB), University College London, London, UK
[3] Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
[4] Department of Psychiatry and Psychotherapy, University of Erlangen and Friedrich-Alexander, Erlangen, Germany
[5] Dementia Research Centre, Institute of Neurology, University College London, London, UK
[6] Pathology & Laboratory Medicine, Experimental Pathology, Emory University School of Medicine, Atlanta, Georgia, USA

Background

About 40% of patients with frontotemporal dementia (FTD) have tau-positive inclusions at post-mortem with a variety of different pathologies found. Unique conformations of tau are hypothesized to underlie the distinct morphological and cellular distribution of pathological tau aggregates. In this study we measured novel tau species as possible biomarkers to detect specific forms of FTD and to allow differentiation from non-tau pathologies. In the first phase, we screened newly developed tau antibodies to identify the exposed epitopes on the protein tau on post mortem brain tissue (figure 1). Subsequently, we developed sandwich ELISAs using combinations of the antibodies to measure levels in cerebrospinal fluid (CSF) (figure 2).

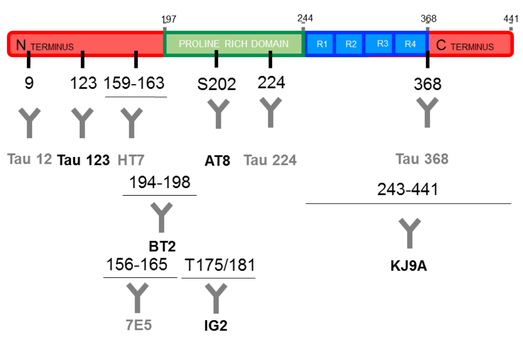

Fig. 1 Schematic of tau 441 protein with the approximate location of various linear epitope antibodies.

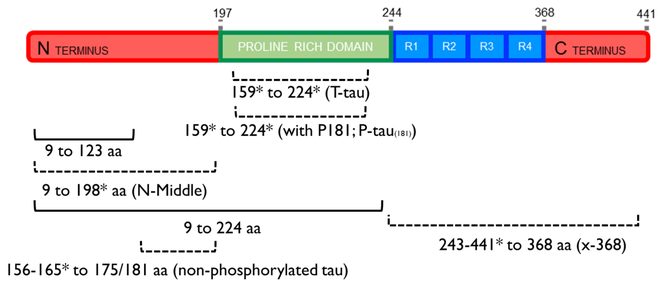

Fig. 2: Schematic of tau 441 aa protein with the approximate location of epitopes of capture and detection antibodies in developed and established immunoassays.

Methods

Ten anti-tau antibodies spanning the length of the protein were used for IHC staining on 5 FTLD cases from the Queen Square Brain Bank (UK) with CBD, PSP, PiD, GGT and AD as a control (table 1). Consequently, sandwich ELISAs using a combination of the antibodies were developed targeting tau fragments N-123, N-mid-region, N-224 and X-368, as well as a non-phosphorylated form of tau. Established T-tau and P-tau$_{(181)}$ were used too. CSF concentrations were measured in 86 participants, which were grouped based on their Aβ42 level into those likely to have underlying Alzheimer's disease (AD) pathology (n=20), those with likely frontotemporal lobar degeneration (FTLD) pathology (n=46) and healthy controls (n=20). The FTLD group was then grouped based on their underlying clinical and genetic diagnoses into those with likely tau (n=7) or TDP-43 (n=18) pathology (table 2).

Pathological diagnosis	Gender	AAO	Disease duration
PiD	M	60	7
PSP	F	75	9
CBD	M	57	7
GGT	M	78	5
AD	M	72	16

Table 1: Pathological information on 5 cases of FTLD

Clinical subgroup	N	Male gender N (% group)	Age at CSF (years) Mean (SD)
Healthy Control	20	10 (50)	63.9 (6.5)
$Aβ_{42}$<550μl	21	10 (52.6)	65.5 (6.2)
$Aβ_{42}$>550μl	45	36 (75)	64.2 (6.8)
Probable tau pathology	7	5 (71.4)	64.8 (8.1)
Probable TDP-43 pathology	18	13 (72.2)	62.3 (5.7)

Table 2: Clinical information and analysis subdivision of 86 participants

Results

AT8 is the gold standard tau antibody and stained all pathological inclusions. **Tau 12** faintly stained Pick bodies (PB) in 3R Pick's disease. No other tauopathies were stained. **Tau 123** showed no staining in any tauopathies. **HT7** showed immunoreactivity for PB. **BT2** displayed immunoreactivity for PB, globular oligodendroglial inclusions (GOI) and normal cytoplasmic staining in CBD. **Tau 224** mirrored the AT8, staining all tau pathological inclusions. **Tau 368** stained total tau, so all pathological inclusions, albeit fainter, and normal cytoplasmic staining was observed. **KJ9A** stained PB in PiD and reacted to 3R&4R AD by staining neurofibrillary tangles (NFTs)and neurophil threads and to 4R tauopathies by staining tufted astrocytes in PSP and GGI in GGT. Astrocytic plaques were only stained in the frontal cortex of CBD. Finally, **IG2** stained all pathological inclusions in all tauopathies and **7E5** stained PB in PiD, NFTs and neurophil threads in AD and GOI in GGT (figure 3).

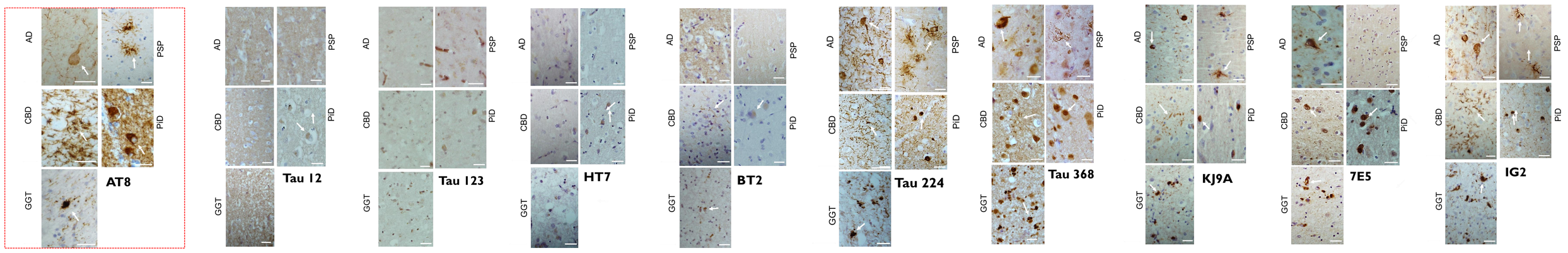

Figure 3: Representative images of IHC staining taken from frontal cortex slides of FTLD cases. Arrows point at tau inclusions positively stained for the respective antibody

The majority of measures (apart from N-123 and X-368) were raised in the AD group compared tocontrols. Only T-tau and P-tau$_{181}$ showed a significant difference between AD and FTLD. T-tau, N-mid-region, Tau 224 and non-phosphorylated tau were raised in the FTLD group compared to controls, but none of these measures nor any of the other differentiated primary tauopathies from TDP-43 proteinopathies (figure 4). 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-tau$_{(181)}$/T-tau, which itself only had a sensitivity of 61.1% and specificity of 85.7% (data not shown).

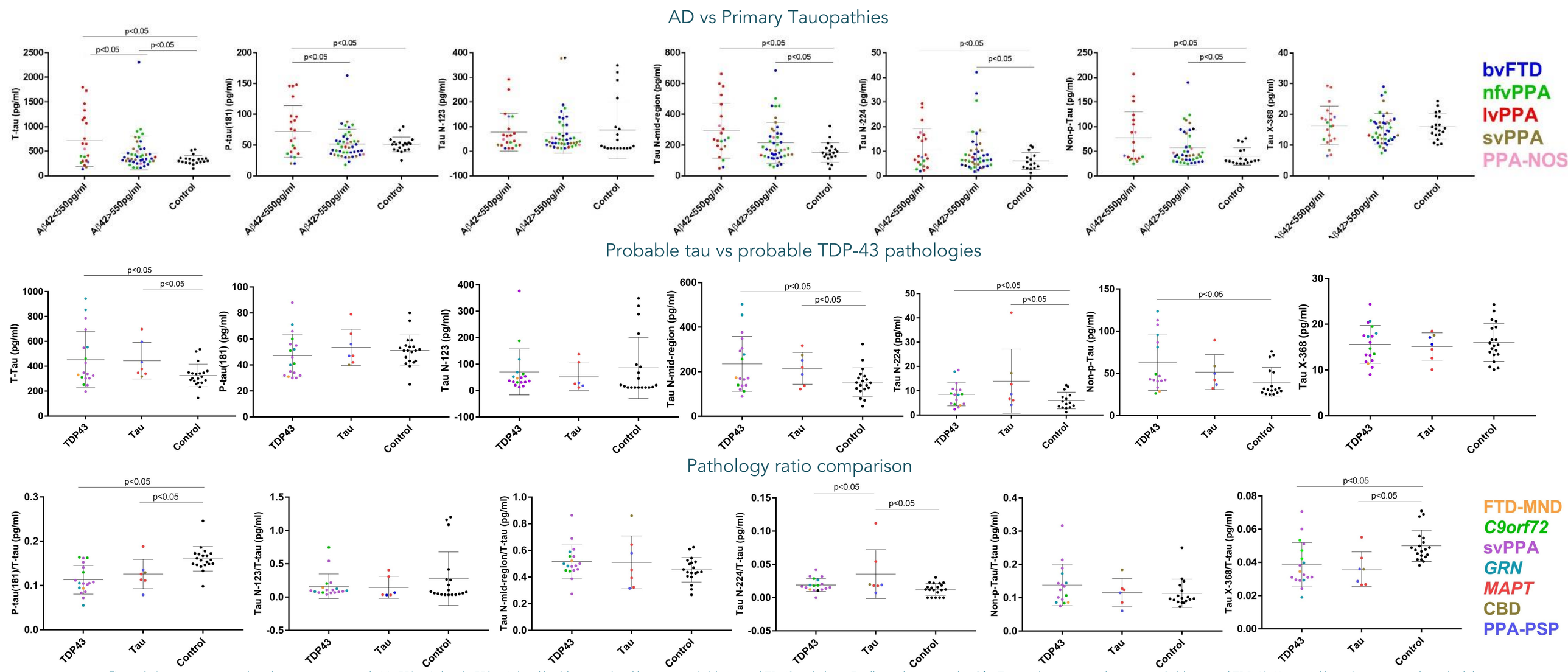

Figure 4: Comparison tau analytes between patients with Aβ<550pg/ml and >550pg/ml and healthy control and between probable tau and TD-43 pathology. Finally, analytes normalised for T-tau with comparison between probable tau and TDP-43 Horizontal bars show mean and standard deviation.

Conclusion

Despite investigating multiple novel CSF tau species, 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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