Tau without T181 phosphorylation as new biomarker of Alzheimer's Disease

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BACKGROUND

In contrast to diagnostic ability of P181 in cerebrospinal fluid (CSF) virtually nothing is known about a potential diagnostic role of Tau fraction without phosphor at this position.

OBJECTIVE

Analytical and clinical validation of the first assay capable to measure concentrations of Tau without phosphor at T181 in human CSF.

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METHODS

An antibody (1G2) preferentially binding non-phosphorylated Tau at position T181 was used in establishing a sandwich ELISA capable to measure Tau without phosphor at T181 in human CSF, following analytical and clinical validation of the method.

RESULTS

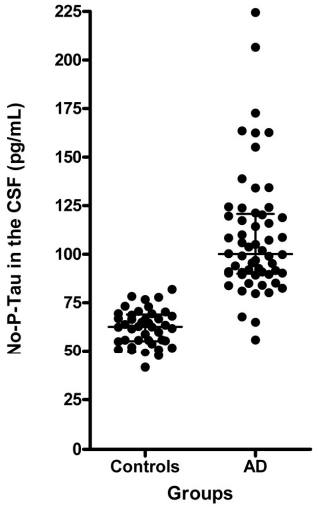

Figure 1:
Concentration of Tau w/o P181 in CSF from controls (n=42) and from MCI/AD patients (n=58).

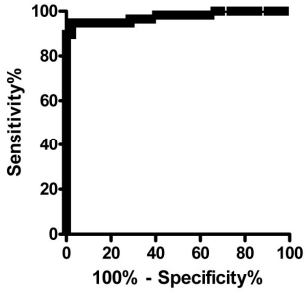

Figure 2:
ROC curve analysis of Tau w/o P181 with cut-off of 78 pg/ml for discrimination of controls (n=42) and MCI/AD (n=58) patients.

For the clinical validation, the analyses were performed in the CSF samples from very carefully selected and characterized patients with dementia due to AD (n=32) or MCI with AD pathology (MCI-AD, n=26) (Positive Group, n=58) and Non Demented Controls (Control Group, n=42). AD/MCI patients were diagnosed and sub-classified according to the current recommendations from the NIA-AA working groups.

First, linear regression model was fitted modelling Non-P-Tau as a function of age and diagnoses (categorical variable with three categories: Controls, MCI, and AD-dementia).
In this model, we did not observe significant effect of age (β=−0.039, p=0.81), and similarly difference between effects of AD-dementia and MCI was insignificant (β=4.42, p=0.61); highly significant differences were observed between effects of Controls and AD-dementia (β=−45.9, p<0.001) and between Controls and MCI (β=−50.3, p<0.001). Therefore, for further analyses we combined MCI and AD-dementia categories into one group (MCI/AD). Figure 1 shows that concentrations were highly significantly increased in the AD/MCI group (109.2 ± 32.0 pg/ml) compared to the Controls (62.1 ± 9.3 pg/ml, p<0.001).
At a cut-off of 78.3 pg/ml, the sensitivity and the specificity were 94.8% and 97.6%, respectively. As shown in figure 2 the area under the ROC curve was 0.976 (95% CI: 0.923 to 0.996).

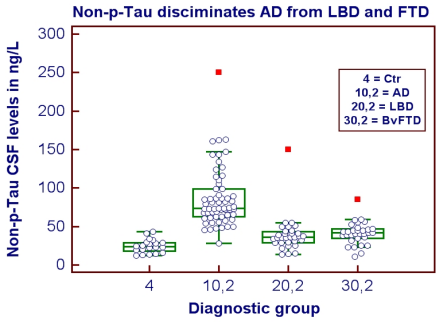

Figure 3:
CSF concentrations of Tau w/o P181 for the different patients' groups. Boxplots present median, 25-75 and 5-95 percentiles

To study ability of Tau w/o P181 to discriminate between different neuro-degenerative diseases compared to AD cases cohorts of 20 control, 61 AD, 31 BvFTD and 31 LBD patients, respectively, were analyzed using sandwich-ELISA named pTAU rel ELISA. The concentration of Tau w/o P181 was significantly higher in *AD* compared to *LBD and FTD* group (p<0.0001) and between controls compared to AD and FTD (p<0.0001) shown in figure 3.
Good sensitivity and specificity were obtained between :

- *AD and LBD+FTD* groups (88.5% and 87.1%, respectively) at the cut off of 52.8 ng/L, ROC curve area of 0.941 (fig. 4)
- *AD and FTD* groups (86.95% and 84.9%, respectively) at the cut off of 52.5 ng/L, ROC area of 0.940 (data not shown).

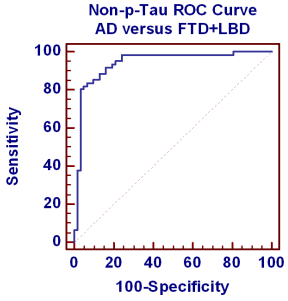

Figure 4:
The Receiver Operating Characteristic Curve of of Tau w/o P181 AD versus FTD+LBD groups

TAKE HOME MESSAGE

For the first time, an assay is reported to reliably measure concentrations of Tau without T181 phosphorylation in human CSF. Results suggest this Tau fraction to be a very good candidate biomarker for discrimination of MCI/AD from healthy patients as well as differential diagnosis of AD against BvFTD and also LBD.

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