

Differential longitudinal dynamics of p-tau217 and Nfl across Alzheimer's Disease and Dementia with Lewy Bodies copathology

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BACKGROUND

Plasma p-tau217 is a validated biomarker of Alzheimer's disease (AD), and its longitudinal dynamics may reflect progression of AD biology. Neurofilament light chain (NFL) reflects axonal injury and neurodegenerative severity. Their trajectories may be modulated by concomitant proteinopathies such as α -synuclein (asyn).

We aimed to characterize longitudinal changes (at 36 months) in plasma p-tau217 and NFL according to underlying disease and assess the impact of AD/asyn copathology within AD and DLB.

METHODS

Prospective cohort study of participants with cognitive impairment. CSF AD biomarkers (Lumipulse) and asyn pathology (RT-QuIC) were assessed at baseline. Plasma p-tau217 and NFL (Lumipulse) were measured at baseline and 36 months. Between-group differences at each time point and longitudinal change (Δ) were assessed using linear mixed-effects models adjusted for age, sex, and APOE $\epsilon 4$.

RESULTS

- The study included 224 participants (107 AD, 30 DLB, 48 FTLD, 39 NNCI). Plasma p-tau217 differed strongly across diagnoses at both baseline and follow-up, showing the highest concentrations in AD (0.70 ± 0.52 to 1.00 ± 1.37 pg/mL) and clearly lower values in DLB, FTLD and NNCI. While absolute change in p-tau217 did not significantly differ, AD showed the largest relative increase (+42.9%) compared with smaller increases in DLB (+31.8%), FTLD (+18.8%) and NNCI (+26.7%). Plasma NFL levels were highest in FTLD and increased the most over time (33.3 ± 17.2 to 53.9 ± 36.8 pg/mL; +62.5%). AD showed the next largest rise (+45.6%), DLB had intermediate change (+29.4%), and NNCI remained lowest with minimal longitudinal variation (+20.9%). Figure 1.
- CSF biomarkers indicated AD copathology in nearly half of DLB participants (48.1%, classified as DLB-AD) and α -synuclein copathology in a subgroup of AD (13.9%, classified as AD-aSyn+).

RESULTS

- Baseline p-tau217 was highest in AD-aSyn+ (0.95 ± 0.71 pg/mL) and AD (0.67 ± 0.49), intermediate in DLB-AD (0.33 ± 0.13), and lowest in DLB/FTLD (negative range). Differences persisted at follow-up, with AD-aSyn+ showing the largest rise (+131.6%), versus modest increases in AD (+22.0%) and DLB-AD (+30.3%) and minimal change in DLB/FTLD. Figure 2A.
- Baseline and follow-up NFL were highest in FTLD and AD-aSyn+. Longitudinally, increases were greatest in AD-aSyn+ (+86.3%) and FTLD (+62.5%), smaller in AD (+36.8%), and limited in DLB-AD (+22.4%) and DLB. LME models confirmed a steeper p-tau217 slope in AD-aSyn+ and the strongest NFL increases in FTLD and AD-aSyn+ (overlapping trajectories vs DLB groups). Figure 2B
- Within AD, the A+T+aSyn+ profile was associated with the largest increases in both p-tau217 (+131.6%) and NFL (+86.3%), whereas A+T+aSyn- and A+T-aSyn- showed more modest biomarker changes. Figure 3.

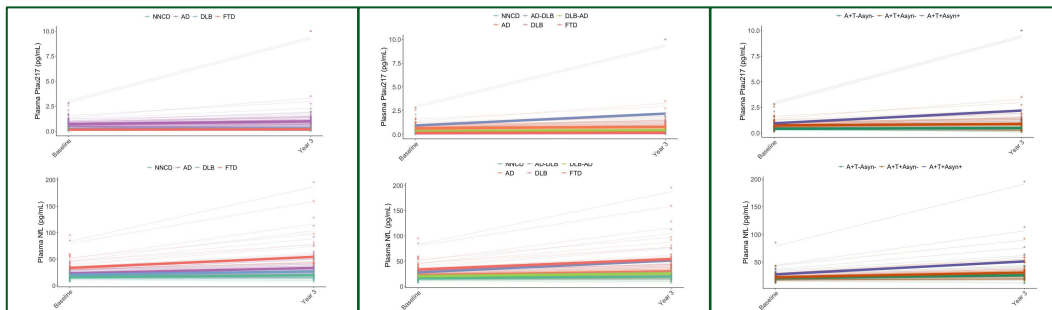


Fig. 1: Biomarker levels evolution across timepoints according to diagnosis groups

Fig. 2: Biomarker levels evolution across timepoints according to copathology groups

Fig. 3: Biomarker levels evolution across timepoints according to A-T-Asyn status in AD group

CONCLUSIONS

Overall, copathology meaningfully shaped both clinical progression and biomarker trajectories. AD-aSyn+ showed the most aggressive longitudinal profile, with the steepest increase in plasma p-tau217 and a marked rise in NFL, alongside poorer follow-up cognition. DLB-AD displayed older age and a mixed AT pattern with intermediate p-tau217 levels, consistent with variable AD-related biological burden within DLB.