Plasma p-tau181 and p-tau231 in probable Dementia with Lewy bodies

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Key Points

Question: Are plasma p-tau concentrations related to cognitive decline and AD pathology in probable dementia with Lewy bodies?

Findings: In this study of 987 participants from the European DLB consortium, concentrations of plasma p-tau181 and p-tau23 were significantly higher in DLB compared with healthy controls and lower compared with Alzheimer's disease (AD) patients. Plasma p-tau181 and p-tau231 levels were associated with cognitive impairment at baseline and more rapid cognitive decline during follow-up while adjusting for sex and age.

Meaning: Plasma p-tau has the potential to act as a cost-effective and accessible biomarker of AD pathology and a prognostic marker in DLB.

Abstract

Importance: Plasma p-tau has proven to be an accurate biomarker for Alzheimer's disease (AD) pathology. This offers a cheaper and less invasive alternative to cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers for amyloid-β and tau. AD co-pathology is common and leads to more rapid cognitive decline in DLB; therefore, it is anticipated that plasma p-tau may have utility in predicting cognitive impairment in this disorder.

Objective: To measure the concentrations of plasma p-tau (p-tau181 and p-tau231) and their associations with cognitive decline in probable DLB.

Design, setting: This is a multicenter longitudinal cohort study including participants from the European DLB (E-DLB) consortium cohort enrolled at ten centers from the year 2002 to 2020 with up to five years of follow up.

Participants: E-DLB centres with harmonized diagnostic procedures were invited to participate in this study. A total of 1122 participants with plasma samples were available. Participants with acute delirium, terminal illness, and patients with other previous major psychiatric or neurological disorders were excluded, leaving a cohort of clinically diagnosed participants with probable DLB (n=371), Parkinson's disease (PD) (n=204), AD (n=207), and healthy controls (HC) (n=205).

Main Outcomes and Measures: Plasma p-tau181 and p-tau231 measured with in-house Single molecule array assays was the main outcome. Mini-Mental State Examination (MMSE) was used to measure cognition.

Results: This cohort of DLB patients (with mean age 71.84 ± 8.04, 57.1% of them being males and mean years of education 9.16 ± 4.23) did not differ significantly regarding age, sex or years of education with the AD group, but the DLB group was older than the HC and included more men than the AD and HC groups. Plasma concentrations of p-tau181 and p-tau231 were higher in DLB patients than in HC (p-tau181 2.58 pg/ml; 95% CI, 1.79 – 3.37

P=.007 and p-tau231 1.96; pg/ml 95% CI, 1.37 – 2.56 P=.007), and lower than in the AD group (p-tau181 -3.53 pg/ml; 95% CI, -4.31 – -2.76 P<.001 and p-tau231 -3.30 pg/ml; 95% CI, -3.98 – -2.71 P<.001) but similar to the PD group. Higher plasma concentrations of both p-tau markers were found in a subgroup of DLB patients with abnormal CSF Aβ42 levels compared to those with normal levels (difference in the groups in p-tau181 -3.619 pg/ml; 95% CI, -5.43– -1.79 P=.049 and p-tau231 -2.51 pg/ml; 95% CI, -3.63 – -1.39 P=.02). There was no difference between p-tau181 and p-tau231's performance across confirmed AD pathology based on reduced Aβ42 on CSF in DLB. In DLB, a significant association was found between higher plasma p-tau181 and p-tau231 levels and lower MMSE scores at baseline (for p-tau181, -0.092 MMSE points; 95% CI, -0.12 – -0.06 P=.001 and for p-tau231 -0.16 MMSE points; 95% CI, -0.21 – -0.12 P<.001), as well as more rapid MMSE decline overtime. Plasma p-tau181 predicted a decline of -0.094 MMSE points per year (-0.094 MMSE points per year; 95% CI, -0.144 – -0.052 P=.015), whereas plasma p-tau231 predicted an annual decline of -0.130 MMSE points (-0.130 MMSE points per year; 95% CI, -0.201 – -0.071 P=.018) after adjusting for sex and age.

Conclusions and Relevance: Plasma p-tau181 and p-tau231 levels can be cost-effective and accessible predictors of cognitive decline in DLB.

Introduction

Dementia with Lewy bodies (DLB) is the second most frequent neurodegenerative dementia after Alzheimer's disease (AD) [1]. The prognosis of DLB is usually poor[2], even compared to AD; however, a large variation in the rate of decline is observed[3].

The neuropathology of DLB is heterogeneous. In addition to the defining α-synucleinopathy in the brainstem, limbic system, and cortical areas, there is often co-existing AD neuropathology[4]. Cerebrospinal fluid (CSF) concentrations of the core AD biomarkers

(Aβ42/40, total tau and phosphorylated tau (p-tau)) are associated with molecular imaging of Aβ plaques and tau tangles and are usually within normal ranges in non-AD dementias[5]. In DLB, however, about 50% of individuals have low CSF Aβ42 concentration, which is indicative of amyloid plaque pathology, *i.e.*, the key feature of AD neurodegeneration [5]. The degree, type, location, and spread of neurodegenerative changes in DLB are highly variable, which may explain the heterogeneous clinical presentation and rate of cognitive decline observed in clinical studies[6]. Notably, imaging and CSF biomarker studies support the concept that the presence of AD pathology can predict the rate of cognitive decline in DLB[7,8].

There is now substantial evidence that blood biomarkers can predict AD neuropathology with high accuracy[9,10]. In this regard, p-tau species, including p-tau181 and p-tau231, have emerged as leading candidates, and the diagnostic and prognostic markers first shown in CSF have been widely replicated in blood[11]. Limited comparison data have suggested either subtle no difference between p-tau181 and p-tau231 in AD; however, these biomarkers have never been compared in DLB[12]. In this study, we sought to assess plasma p-tau181 and p-tau231 and their association with cognition in a large international multicenter DLB cohort from the European DLB (E-DLB) consortium.

Methods

A total of 1122 participants with plasma samples were available for this study with overall 371 probable DLBs from 10 participating E-DLB centers with harmonized diagnostic procedures[13]. Participants were referrals from outpatient clinics including memory, movement disorders, geriatric medicine, psychiatric, and neurology clinics. Additional information on the diagnostic examination program, inclusion and exclusion criteria, p-tau blood measurements and statistic procedures for this study can be found in e-Methods. Patients with AD, Parkinson's disease (PD), and healthy controls (HC) were included for comparison (see e-supplementary table 1). A subgroup of AD (n=113 / 47.0%) had CSF confirmation based

on reduced Aβ42 concentrations. Likewise, 34% (n=126) of the DLB group had Aβ42 results on CSF according to local reference values (see supplementary table 2). Global cognitive function was assessed using the Mini-Mental State Examination (MMSE). A subgroup of probable DLB participants (n=182, see e-supplementary figure 1) had annual longitudinal cognitive assessments for up to 5 years. Details of sample collection procedures in each center are available in e-supplementary table2. The local ethics committee at each center has approved the incorporation of data in this study and the analysis of samples abroad. The participating subjects gave their written consent to use the unidentified results of their clinical, instrumental, and laboratory data for research purposes.

Plasma p-tau181 and p-tau231 biomarker concentrations were measured using clinically validated in-house Single molecule array (Simoa) methods at the Clinical Neurochemistry Laboratory Sahlgrenska University Hospital, Mölndal, Sweden (see e-Supplementary table 3).

Statistical Analysis

We reported baseline characteristics of the cohort as appropriate. After a significant one-ANOVA, differences between groups at baseline were evaluated using a Bonferroni post hoc test. The receiver operating characteristic curve (ROC) explored the overall biomarker performance across confirmed AD pathology based on reduced Aβ42 on CSF in DLB providing the area under the curve (AUC). We used DeLong's test to contrast the change in the AUC of both biomarkers. MMSE score was transformed using the squared root of 30 minus the MMSE score to achieve normal distribution. We fitted a linear regression with MMSE score at baseline to evaluate the association between plasma p-tau181 and p-tau231 and cognition. We analyzed the longitudinal MMSE decline by fitting a linear mixed-effect model with random intercept and slope for each subject, adjusted by potential confounders such as age, gender and years of education.

Results

The baseline characteristics can be found in table 1. The DLB and AD groups did not differ significantly regarding age, sex, years of education, duration of symptoms, or MMSE baseline scores, but the DLB group was older than HC and included more men than the AD and HC groups. In the DLB group with CSF analyses available, 63 patients (50%) had Aβ 42 values below the threshold.

Associations of plasma p-tau with diagnoses

Plasma p-tau181 and p-tau231 concentrations in the different groups are shown in figure 1. DLB patients had increased plasma concentrations for both p-tau181 and p-tau231 (p-tau181 2.58 pg/ml 95% CI, 1.79 – 3.37 P=.007 and p-tau231 1.96 pg/ml 95% CI, 1.37 – 2.56 P=.007) compared with HC, but concentrations were lower than in AD (p-tau181 -3.53 pg/ml; 95% CI, -4.31 – -2.76 P<.001 and p-tau231 -3.30 pg/ml; 95% CI, -3.98 – -2.71 P<.001); the numerical difference between DLB and AD increased when the analyses were done only using the AD patients (n=113) with confirmation of diagnosis based on low CSF Aβ42 concentration. These results remained statistically significant after correcting for age and sex. When comparing DLB and AD patients with biomarker confirmation based on low CSF Aβ42, a greater effect size was seen for p-tau181 (Cohen's d=0.53) compared with the full AD group (Cohen's d=0.39). Effect sizes (Cohen's d) for DLB compared with HC were rather similar for both plasma markers: 0.25 (p-tau231) and 0.23 (p-tau181). There were no statistically significant differences in either of the plasma p-tau concentrations between PD and DLB. The DLB group with abnormal CSF Aβ42 levels had higher plasma concentrations of both p-tau markers compared to those with normal CSF values (difference in p-tau181 -3.61 pg/ml 95% CI, -5.43– -1.79 P=.049 and p-tau231 -2.51 pg/ml CI, -3.63 – -1.39 P=.02, see figure 1). AUC values of the ROC curves indicating the overall biomarker performance across AD pathology confirmed cases based on reduced Aβ42 on CSF in DLB were larger for

p-tau181 (p-tau181 AUC= 0.62 vs. p-tau 231 AUC= 0.56), but the change in the AUC of both biomarkers was not statistically significant (see e-supplementary figure 2).

Associations of plasma p-tau with baseline and longitudinal MMSE in DLB

We found that higher baseline plasma p-tau181 and p-tau231 concentrations were associated with lower MMSE score at baseline (p-tau181 -0.092 MMSE points; 95% CI, -0.12 – -0.06 P=.001 and p-tau231 -0.16 MMSE points; 95% CI, -0.21 – -0.12 P<.001) while adjusting for age and sex. When adjusting the model for years of education, p-tau231, but not p-tau 181, remained a significant predictor for MMSE decline (p-tau231 -0.049 MMSE points; 95% CI, -0.15 – -0.04 P= .049). The average change estimated for the other diagnostic groups can be found in the e-Supplementary Table 4.

In the longitudinal model (DLB subgroup with longitudinal measurements of cognition n=182 mean follow up 3.53 years and SD 1.67), plasma p-tau181 predicted a decline of -0.094 MMSE points per year (95% CI, -0.144 – -0.052 P=.015) whereas plasma p-tau231 predicted an annual decline of -0.130 MMSE points (95% CI, -0.201 – -0.071 P=.018) (see figure 2).

Discussion

Here we examined the concentrations of plasma p-tau181 and p-tau231 in 987 patients from the E-DLB. We found that the baseline concentrations of plasma p-tau181 and p-tau231 in DLB were significantly higher than those in HC but lower than in AD. In addition, we found that both markers were associated with more cognitive impairment in the DLB group at baseline, as well as with more pronounced cognitive worsening over time during follow-up. Significance was lost after including years of educations, possibly because of the smaller sample size with longitudinal follow-up and education data available. Overall, plasma p-tau181 had a greater effect size when comparing DLB and AD, although it shouldn't be used

in isolation to make a clinical diagnosis. There was no difference between p-tau181 and p-tau231's performance across confirmed AD pathology based on reduced Aβ42 on CSF in DLB. Moreover, plasma p-tau231 had a larger effect on cognition than p-tau181. While there was a statistically significant effect, the impact on the decline in MMSE was small, and the clinical relevance may be questionable. Previously, plasma p-tau has shown to be a strong predictor of cognitive decline in AD[14] and is associated with AD neuropathology. However, in DLB, plasma p-tau has only been examined in small cohorts[9,15]. Hall *et al.* revealed that plasma p-tau had a high correlation with abnormal tau and amyloid PET scans in DLB, highlighting its usefulness as a marker for AD co-pathology DLB[15]. Lantero-Rodriguez *et al.*, in neuropathologically confirmed cases, demonstrated increased plasma p-tau levels in those who had mixed AD and Lewy body pathologies a decade before death. In the small number of Lewy body cases without AD pathology, plasma p-tau was not increased[9]. In this study, we report that the levels of p-tau in DLB are intermediate between HC and AD and significantly associated with cognitive decline in DLB patients, suggesting that both p-tau181 and p-tau231 blood assays could be useful as predictors of disease progression. Similar to Hall et al., we also demonstrate that plasma p-tau is elevated in DLB cases with AD co-pathology. Further studies are needed to assess whether plasma p-tau can predict response of DLB patients to treatments targeting AD pathophysiology[16].

Limitations

A limitation of this study is that not all patients had a biomarker confirmation of the diagnosis. However, it has been shown that the clinical diagnosis of probable DLB has a very high specificity[17]. This is one of the largest DLB cohorts with biomarker data ever reported. However, due to the retrospective multi-centre design, there were missing data for some variables, including longitudinal data, CSF dementia markers, and years of education, which led to reduced statistical power for these analyses. Future studies should compare p-tau

species with other candidate blood markers of progression, *e.g.*, Aβ42/40, NfL, or GFAP, and explore their predictive power in prodromal DLB.

Conclusions

In conclusion, plasma concentrations of p-tau181 and 231 are increased in DLB and further in DLB cases with confirmed AD co-pathology. Plasma p-tau represents a promising biomarker to identify AD pathology and a faster cognitive decline in this neurological disorder.

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Conflict of Interest

The authors have no potential conflicts of interest to declare regarding research, authorship, and/or publication of this article

Author Contributions

MCG, NJA: Conception of work, methods, writing- reviewing, and editing. DA, HZ: Preparation of the initial draft, manuscript writing, supervision, review, and approval. NJA, HZ, BFG, KB, TKK: performed the plasma measurements. DAT- R, MCG: processed the data, performed the analysis, and designed the figures. FB, BM, AP, AL, CP, CA, MK, LB, and RV: contributed to clinical data collection and sample preparation. All authors discussed the results and contributed to the final manuscript.

Access to Data Statement

Dr. Aarsland had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability

Qualified external researchers can request access to anonymized patient-level data, respecting patient informed consent, from the corresponding author on reasonable request.

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Table and Figure Legends

Figure 1. Plasma p-tau181 and p-tau231 concentrations in the different diagnostic groups and Aβ42 on CSF status in DLB

a) This plot shows plasma p-tau181 and p-tau231 distribution across the different diagnostic groups. Dots represent means and the whiskers their confidence intervals. Baseline concentrations of plasma p-tau181 and p-tau231 in DLB

were significantly higher than those in the HC group but lower than in the AD group. These differences between groups at baseline were evaluated using a Bonferroni post hoc test. b) This plot shows plasma p-tau181 and p-tau231 distribution in DLB with CSF Aβ42 status. Baseline concentrations of plasma p-tau181 and p-tau231 in DLB were significantly higher in the DLB group with abnormal CSF Aβ42 levels in both p-tau markers compared to those with normal CSF values.

Abbreviations: (DLB) Dementia with Lewy bodies, (AD) Alzheimer's disease, (PD) Parkinson's disease, (HC) Healthy control, (pg/mL) picograms per milliliter, (Aβ42) amyloid-β42.

Figure 2. Associations between plasma p-tau181 and p-tau231 and MMSE scores decline in DLB

In this figure, the solid line shows the estimated marginal model for the MMSE scores for a typical subject at mean age and 1.5 years of follow-up in relation to plasma levels of a) p-tau181 and b) p-tau231. The gray area represents the CIs. 95% around the averages. Both graphs show the MMSE scores decline in function of the increase in plasma values of p-tau181 and p-tau231.

Abbreviations: (MMSE) Mini-Mental State Examination, (pg/mL) picograms per milliliter.

Table 1. Baseline characteristics of the cohort

	DLB	AD	PD	HC	Total	P-value
	n (%) or mean ± sd					
Total	371 (37.6)	207 (20.9)	204 (20.7)	205 (20.8)	987 (100)	
Gender						
Female n (%)	159 (42.8)	121 (58.5)	79 (38.7)	116 (56.6)	475 (48.2)	<.001
Male n (%)	212 (57.2)	86 (41.5)	125 (61.3)	89 (43.4)	512 (51.8)	
Age	71.84 ± 8.04	71.74 ± 8.00	69.16 ± 9.87	65.12 ± 8.04	70.04 ± 8.75	<.001[ab]
Year of education	9.2 ± 4.2	9.0 ± 4.0	9.9 ± 4.7	12.9 ± 3.6	9.79 ± 4.5	<.001[a]
Duration of symptoms [d]	25.2 ± 30.3	25.6 ± 26.6	71.5 ± 62.9	53.6 ± 61.1	41.2 ± 49.1	<.001[b]
MMSE	21.7 ± 6.0	21.4 ± 5.3	26.9 ± 3.7	28.5 ± 1.7	23.2 ± 5.8	<.001[ab]
Plasma p-231, pg/mL	12.8 ± 6.6	16.9 ± 12.1	12.3 ± 6.8	11.0 ± 6.9	13.2 ± 8.4	<.001[ac]
Plasma p-181, pg/mL	18.2 ± 9.5	28.7 ± 28.4	17.0 ± 8.5	16.7 ± 18.5	18.1 ± 17.2	<.001[ac]
Abnormal CSF Aβ42 levels (%)	63 (17.0%)	113 (47.0%)	-	-	-	

[a] Differences between DLB and HC, [b] Differences between DLB and PD, [c] Differences between DLB and AD, [d] Duration in months from first motor or cognitive symptom.

Abbreviations: (SD) Standard deviation, (DLB) Dementia with Lewy bodies, (AD) Alzheimer's disease, (PD) Parkinson's disease, (HC) Healthy control, (MMSE) Mini-Mental State Examination, (pg/mL) picograms per milliliter, (CSF) Cerebrospinal fluid.