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Cerebrospinal Fluid Alzheimer's Disease Biomarkers Across the Spectrum of Lewy Body Diseases: Results from a Large Multicenter Cohort

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Abstract

Background—Concomitant Alzheimer's disease (AD) pathology is observed in Lewy body diseases (LBD), but the clinical impact is unknown. Only a few biomarker studies in LBD exist and have included small cohorts from single centers.

Objective—We aimed to evaluate the prevalence of abnormal cerebrospinal fluid (CSF) AD biomarkers across the spectrum of LBD in a large multicenter cohort and to assess whether an AD

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SUPPLEMENTARY MATERIAL

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biomarker profile was associated with demographic and clinical differences in dementia with Lewy bodies (DLB).

Methods—We included 375 DLB patients, 164 Parkinson's disease (PD) patients without dementia, and 55 PD patients with dementia (PDD) from 10 centers. CSF amyloid-beta42 ($A\beta_{42}$), total tau (t-tau), and phosphorylated tau (p-tau) values were dichotomized as abnormal or normal according to locally available cut-off values. A CSF AD profile was defined as abnormal $A\beta_{42}$ combined with abnormal t-tau and/or p-tau.

Results—A substantial proportion of DLB patients had abnormal values for CSF $A\beta_{42}$, t-tau, and p-tau, while abnormal values were uncommon in PD without dementia. Patients with PDD had values in between. A CSF AD profile was observed in 25% of DLB patients, compared with only 9% of PDD and 3% of PD without dementia. Within DLB, patients with a CSF AD profile were older, more often female, performed worse on the Mini-Mental State Examination, and had shorter disease duration compared with patients with normal CSF.

Conclusion—A CSF AD profile is more common in DLB compared with PDD and PD, and is associated with more severe cognitive impairment in DLB.

Keywords

Amyloid beta-protein (1–42); biomarkers; cerebrospinal fluid; dementia with Lewy bodies; Lewy body disease; tau protein

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative disease in the elderly after Alzheimer's disease (AD), accounting for 10–15% of the dementia cases at autopsy and 15–20% of dementia cases seen in dementia cohorts [1]. Recognizing DLB remains challenging due to the highly variable presentation of clinical symptoms, which include cognitive fluctuations, visual hallucinations, parkinsonism, sleep disorders and autonomic dysfunction [2], and the fact there is considerable clinical and pathological overlap with both AD and Parkinson's disease (PD) and PD with dementia (PDD).

Pathologically, DLB is characterized by Lewy bodies and Lewy neurites composed of α-synuclein aggregates in the brain, which are also the pathological hallmarks for PD and PDD [3]. In addition, a frequent finding in DLB is a varying degree of concomitant AD pathology (i.e., amyloid-β plaques and neurofibrillary tangles (NFT) [2, 4]. The role of AD pathology in the pathogenesis of DLB and its clinical impact remains unclear. Autopsy studies have suggested that DLB patients with concomitant AD pathology exhibit a more aggressive disease course and more pronounced cognitive dysfunction compared with pathologically pure AD or DLB patients [5–7].

CSF biomarker analysis provides a means to evaluate antemortem the underlying neuropathology in neurodegenerative diseases. The relevance of CSF biomarkers, amyloid-β 1–42 ($A\beta_{42}$), total tau protein (t-tau), and tau phosphorylated at threonine 181 (p-tau) for the diagnosis of AD is clearly established [8], and these markers have been included in the proposed research criteria for the clinical diagnosis of AD [9]. Recently, evidence was

provided that antemortem CSF $A\beta_{42}$ is correlated with pathologically proven concomitant AD pathology in DLB [10]. On the other hand, the accuracy of CSF biomarkers for the differential diagnosis of α-synucleinopathies is less well demonstrated. A number of studies have evaluated the potential value of CSF α-synuclein as a diagnostic marker for Lewy body diseases (LBD), however, large variations in the absolute levels α-synuclein have been reported and the results were conflicting (see [11] for review).

To date, there are no specific CSF biomarkers for DLB, despite decades of research. This is partly related to the heterogeneity of DLB, the considerable overlap with AD and PD, and the lack of a reliable biomarker for α-synuclein deposition in the brain. A few AD CSF biomarker studies in DLB have reported reduced levels of $A\beta_{42}$ compared with non-demented controls (see [12] for review). Similarly, reduced CSF $A\beta_{42}$ levels predict cognitive decline in patients with PD [13, 14]. Most CSF biomarker studies have included small cohorts from single centers, and few studies across the full spectrum of LBD (DLB, PDD, and PD) have been performed [15, 16]. Therefore, the aim of the current study was to describe the prevalence of abnormal AD CSF biomarkers across the spectrum of LBD in a large multicenter cohort. In addition, we assessed whether a CSF AD biomarker profile was associated with demographic and clinical differences in DLB.

METHODS

Study population

From a European multicenter DLB study, we included 594 patients with a clinical diagnosis of probable DLB, PDD, or PD with available CSF biomarker data from 10 participating centers (academic memory clinics and movement disorder clinics) in eight countries. Detailed demographic data on DLB, PDD, and PD patients from different centers are presented in Supplementary Table 1.

Diagnostic and clinical procedures

The diagnosis of probable DLB was made according to the consensus diagnostic criteria [2], the diagnosis of PD was made according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD [17], and the diagnosis of PDD was made according to the diagnostic criteria by the MDS task force for dementia associated with PD [18]. In 92 DLB patients, a [^{123}I]FP-CIT SPECT scan was performed (25%) and of those 85 DLB patients had an abnormal [^{123}I]FP-CIT SPECT scan (92%) to support the clinical diagnosis. For all centers, the assessment procedures included a detailed history, and physical, neurological, and neuropsychological examinations. Disease duration was defined as time between onset of first symptom and lumbar puncture. Global cognition was assessed with the Mini-Mental State Examination (MMSE) at most centers. For a subset of patients from two centers (Karolinska Institute, Stockholm and University of Pennsylvania, Philadelphia) the Montreal Cognitive Assessment (MoCA) was used. To be able to compare cognitive data the MoCA score for these 60 patients was converted to an equivalent MMSE score using a published formula [19].

Ethics

Local ethics committees at the individual centers approved the study. The patients gave their written consent to use the unidentified results of their clinical and biomaterial for research purposes.

CSF procedures

The procedures to obtain and store CSF at the different centers are summarized in Supplementary Table 2. In all centers, CSF (1) was obtained by lumbar puncture in the L3-4 or L4-5 interspace; (2) collected in polypropylene tubes and centrifuged for 10 min at 4°C; and (3) stored in aliquots of 0.5 mL at −80°C or −70°C until further analysis [20].

Three different assays were used to analyze the concentrations of CSF $A\beta_{42}$, t-tau, and p-tau in the samples: (1) Sandwich enzyme-linked immuosorbent assays [ELISA] INNOTEST®, formely Innogenetics N.V., Ghent, Belgium, now Fujirebio (8 centers); (2) Luminex xMap technology using the Inno-Bia AlzBio3 kit, formerly Innogenetics, now Fujirebio (1 center); and (3) ELISA kit from Biosource Europe S.A (1 center). CSF biomarkers were dichotomized according to locally available cut-off values. An AD CSF profile was defined as abnormal (low) $A\beta_{42}$ combined with abnormal (high) t-tau and/or p-tau [21, 22]. Based on this profile, DLB, PDD and PD patients were categorized in an AD CSF profile positive group (AD+) and an AD CSF profile negative group (AD−).

Statistical analysis

All statistical analyses were performed using IBM SPSS software for Mac, version 22.0. Differences between groups were assessed with ANOVA followed by Bonferroni *post-hoc* tests for continuous variables, or with Pearson Chi-Square tests for categorical variables, where appropriate. Multivariate logistic regression analysis was used to correct for age and gender in the between diagnostic group analyses. Differences between DLB AD+ and DLB AD-were determined with center adjusted (entered as dummies) ANOVAs for continuous variables or with logistic regression analyses for categorical variables. A value of $p < 0.05$ was considered significant.

RESULTS

Patient characteristics

We included 594 patients of whom 375 were diagnosed with probable DLB, 55 were diagnosed with PDD, and 164 were diagnosed with PD. Patient characteristics according to diagnosis are shown in Table 1. There were no differences in age, gender, education, MMSE score, and duration of dementia diagnosis between DLB and PDD patients. PD patients were younger ($p < 0.001$), and had higher level of education ($p < 0.001$) and MMSE score ($p < 0.001$) compared with DLB and PDD patients.

CSF biomarkers by diagnosis

The percentages of patients with abnormal AD CSF biomarkers are shown in Table 2 and Fig. 1. A large proportion of DLB patients had abnormal values of $A\beta_{42}$ (49%), t-tau (28%), and p-tau (32%), and proportions were far lower in PD ($A\beta_{42}$: 12%; t-tau: 4%, p-tau: 7%, all

$p < 0.001$). The prevalence of abnormal AD biomarkers in PDD was in between ($A\beta_{42}$: 42%, PDD versus DLB $p = 0.31$, PDD versus PD $p < 0.001$; t-tau: 17%, PDD versus DLB $p = 0.11$, PDD versus PD $p < 0.05$; p-tau: 6%, PDD versus DLB $p < 0.05$, PDD versus PD $p = 0.81$). When adjusted for age and gender using logistic regression, results remained essentially unchanged, with the exception of the difference between PDD and PD for t-tau, which lost significance.

A CSF profile compatible with AD (AD+) was observed in almost 25% of DLB patients, compared with only 9% of the PDD patients ($p < 0.05$) and 3% of the PD patients ($p < 0.001$) (Table 2 and Fig. 1). When adjusted for age and gender using logistic regression, results remained essentially unchanged.

To further explore the validity of the findings we analyzed the percentages of abnormal AD CSF biomarkers and a CSF AD profile in only those 85 DLB patients with decreased dopamine transporter binding on a [^{123}I]FP-CIT SPECT scan. The percentages were similar to those in the full data set.

AD+ CSF profile versus AD− CSF profile in DLB

To investigate whether an AD biomarker profile was associated with demographic and clinical differences in DLB, we compared DLB patients with an AD+ CSF profile (DLB AD+) to those without an AD CSF profile (DLB AD−). All analyses were adjusted for center. We found that the DLB AD+ group was older (74 versus 70 years, $p < 0.001$), more often female (49.4% versus 29.1%, $p < 0.001$), performed worse on the MMSE (20±6 versus 23±5, $p < 0.05$) and had a shorter disease duration (2.8 ±1.6 versus 3.5±3.1 years, $p < 0.05$) compared with DLB patients in the CSF AD-group (Table 3). The level of education did not differ between groups.

DISCUSSION

In this large LBD CSF multicenter cohort, we demonstrated that a substantial proportion of DLB patients have abnormal values for of the AD CSF biomarkers $A\beta_{42}$, t-tau, and p-tau, while abnormal AD CSF biomarkers were quite uncommon in PD. Patients with PDD had values in between. Moreover, our findings showed that around 25% of the DLB patients have a CSF profile compatible with AD, as defined by pathological $A\beta_{42}$ combined with pathological t-tau or p-tau, and that a CSF AD profile was more common in DLB (almost 25%) than in PDD (9%) and PD (3%). Several studies have compared the levels of CSF $A\beta_{42}$, t-tau, and p-tau between DLB and PDD or between DLB and PD (see [23] for review), however only a few studies, with relatively small DLB sample sizes, have evaluated AD CSF biomarkers across the full spectrum of LBD [15, 16]. The aggregated data of these studies suggest that the CSF profiles of DLB, PDD, and PD differ in the sense that DLB patients have a more AD-like CSF profile. Similar conclusions were also drawn based on amyloid imaging studies using Pittsburgh compound B (PiB) positron emission tomography (PET) which reported that cortical amyloid deposition is common in DLB, while it is lower in PDD and PD [24–27]. Together, these findings may reflect a difference in the underlying nature of DLB and PD(D), as it seems that in DLB AD pathology is quite common, while in PD(D) this is far less so.

In line with our findings, clinicopathological studies have also observed concomitant AD pathology in patients with DLB [28, 29]. The proportion of DLB patients with a CSF AD profile (25%) reported in the present study is smaller than reported in neuropathological studies (65–90%) [7, 30–32]. Differences in the age of DLB patients may have been responsible for the discrepancy between the present CSF study (mean age 71 years) and neuropathological studies (age >80 years). Age is known to be the greatest risk factor for developing AD pathology. In our multicenter DLB cohort, a CSF AD biomarker profile is more frequent in the older patients (71% in the age group >85 years versus 17% in the age group <65 years). In addition, AD pathology might develop over time in DLB. A recent CSF study in autopsyverified DLB, in which a second lumbar punctures was performed in 4 cases, showed that in one DLB patient $A\beta_{42}$ levels decreased over time below the pathological cut off value [10]. Longitudinal CSF or PiB-PET studies could contribute to the understanding of the progression of AD pathology during the course of DLB. A recent amyloid PET meta-analysis reported a prevalence of amyloid positivity in 51% of DLB patients and showed that amyloid positivity increased with age [33]. These results are in accordance with the present CSF study in which we have shown that 49% of the DLB patients had abnormal values of CSF $A\beta_{42}$. A previous CSF study reported a CSF AD profile, defined by the Schoonenboom formula ($A\beta_{42}/152 + 8.25 \times$ p-tau <1), in 47% of the DLB patients [34]. This is higher than the prevalence observed in the present CSF study, however the definition of a CSF AD profile we used in the present study is more conservative.

In the present study, we have shown that the proportion of patients with abnormal values of CSF $A\beta_{42}$ was the lowest in PD (12%). This is in line with previous PiB-PET studies [27, 35]. According to a recent meta-analysis of PiB-PET studies in LBD, the rate of amyloid positivity is 57%, 35%, 13%, and 21% in DLB, PDD, PD and healthy controls, respectively [27]. Important to mention is that PD patients are younger than PDD patients in most studies. It is possible that AD pathology develop over time in a subset of PD patients, which is probably associated with APOE $\varepsilon 4$ genotype [36, 37]. Noteworthy, it seems that amyloid positivity in PD patients is equally or even lower compared to healthy controls. Large studies of age-comparable healthy participants indicate an average of 20% Aβ positivity [38]. This might suggest that α-synucleinopathy is in some manner protective against Aβ pathology. Further studies should investigate this hypothesis.

Further analysis of the DLB patients with a CSF AD biomarker profile in the present study revealed that those patients were older, more often female, had a shorter disease duration, and had more cognitive impairment as assessed by the MMSE compared with DLB patients who had an AD−(i.e., normal) CSF biomarker profile. These findings correspond with previous studies showing that a CSF AD biomarker profile in DLB was associated with older age and worse cognitive performance on the MMSE [34, 39]. Findings from clinico-pathological studies suggest that multiple pathology (Aβ plaques, neurofibrillary tangles, and α-synuclein inclusions) in DLB have synergistic action and contribute to cognitive decline [5, 6, 40]. In addition, studies in animal models showing that mice that develop both DLB and AD pathologies (3xTg-AD mice crossed with $\alpha\text{-syn}_{A53T}$ transgenic mice (M83)) exhibit accelerated cognitive decline assessed with the Barnes circular maze [41]. The aggregated evidence supports the hypothesis that AD pathology in DLB is associated with

earlier and more rapid cognitive decline. However, more studies, preferably with a longitudinal design, are necessary to sustain this hypothesis.

One of the strengths of the present study was that we studied the presence of abnormal AD CSF biomarkers in patients across the spectrum of LBD. Furthermore, this multicenter collaboration avoids several of the risks of biases associated with single-center studies by having included substantially more patients than previous CSF studies. However, there are a number of limitations that need to be considered in interpreting this study. First, we used retrospective data from different cohorts, which may have introduced bias due to differences in study designs. For example, we noticed a considerable variability in the prevalence of DLB patients with abnormal values of CSF $A\beta_{42}$ across centers (Supplementary Table 1). The variation in prevalence between centers could be caused either by variations in pre-analytical sample handling and ELISA assays (Supplementary Table 2), by cohort characteristics or by diagnostic differences. However, careful comparison of the pre-analytical sample handling procedures did not reveal considerable differences between centers and all centers used the McKeith clinical diagnostic criteria for DLB. This study lacks autopsy confirmation of the diagnosis. Considering the low sensitivity of the current clinical diagnostic criteria for DLB, the clinical diagnosis may thus not be correct for all cases and the accuracy of the clinical diagnoses could differ between centers. However, the investigators involved in the present study have extensive clinical experience in diagnosing DLB and PD, and 23% of DLB patients had a [^{123}I]FP-CIT SPECT scan to support the clinical diagnosis. Nevertheless, the differences between centers emphasize the importance of accurately following harmonization protocols and guidelines for pre-analytic sample handling, biochemical procedures as well as the clinical assessments of the patients. The recent established DLB consortium has developed guidelines and protocol recommendations for future prospective cohort studies in DLB, which have been published on the website of the EU Joint Programme – Neurodegenerative Disease (JPND) Research [42].

In this study we only evaluated the presence of AD CSF biomarkers. As aggregates of α-synuclein protein are the main components of Lewy bodies, the pathologic hallmark of PD, PDD, and DLB, it will be interesting to evaluate α-synuclein in the CSF of patients with these diseases. To date, however, no robust CSF test for α-synuclein is clinically available. Future research is needed to evaluate whether α-synuclein species could be reliable biomarkers for the diagnosis and early detection of LBD.

In conclusion, in this large multicenter CSF study we showed that (1) a substantial proportion of DLB patients had abnormal values for AD CSF biomarkers $A\beta_{42}$, t-tau and p-tau, (2) approximately 25% of DLB patients have a CSF profile compatible with AD compared with only 9% of PDD patients and 3% of PD patients, and (3) a CSF AD profile in DLB patients is associated with a more severe disease course. AD biomarkers *in vivo* mirror the neuropathological substrate of cognitive impairment across LBD. Recognition of the presence of a CSF AD biomarker profile in DLB patients may advance patient guidance and individualization of treatment strategies. In addition, disease-modifying treatments directly targeting amyloid and tau aggregates, which are currently under development for AD, may have clinical value in DLB as well. CSF could be used to select DLB-patients for future trials and DLB patients with a CSF profile compatible with AD could be included in

future trials of AD disease-modifying treatments. The recognition of considerable variability of the presence of AD biomarkers between DLB, PDD, and PD is important for the identification of molecular mechanisms involved in the LBD. Future research is warranted to gain more insight into the molecular mechanisms underlying the pathophysiology and to further elucidate the contribution of concomitant AD pathology toward the clinical manifestation of LBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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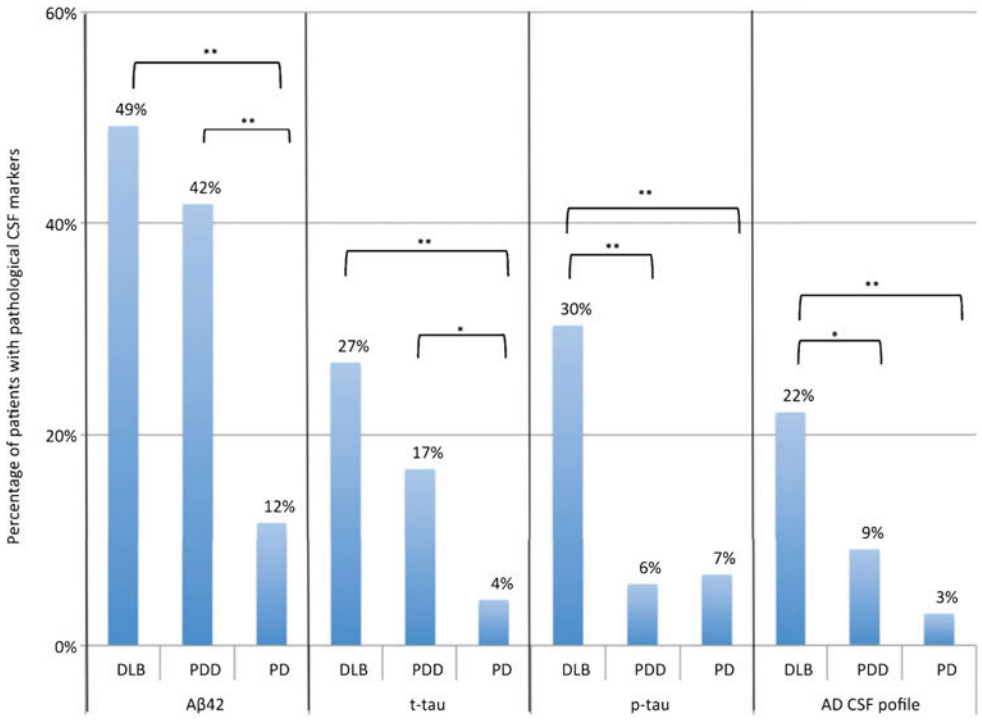

Fig. 1.

Percentage of patients with abnormal CSF biomarkers by diagnosis. Differences between groups were assessed with Pearson Chi-Square tests. Aβ42, Amyloid-β_{42}; DLB, Dementia with Lewy bodies; PD, Parkinson's disease; PDD, Parkinson's disease dementia; t-tau, total tau; p-tau, tau phosphorylated at threonine 181. *$p < 0.05$; **$p < 0.001$.

Table 1

Patient characteristics by diagnosis

	DLB (*n* = 375)	PDD (*n* = 55)	PD (*n* = 164)
Age, years Mean ± SD	71.1 ± 8.4[a]	71.1 ± 8.2[a]	65.7 ± 7.2
Gender			
Male	248 (66.5%)	41 (74.5%)	117 (71.3%)
Female	125 (33.5%)	14 (25.5%)	47 (28.7%)
Education, years [*]			
Mean±SD	10.8±3.7[a]	11.8 ± 3.9[a]	15.0±3.2
MMSE score [†]			
Mean±SD	22.0 ± 5.4[a]	22.6 ± 4.2[a]	28.4 ± 1.7
Disease Duration, years [§]			
Mean±SD	3.4 ± 2.9[a,c]	8.3 ± 5.8[b]	5.8 ± 4.7
Duration of dementia diagnosis, years			
Mean±SD	3.4 ± 2.9	2.8 ± 2.4	n/a

Data are expressed as Mean ± SD for continuous variables, and as *n* (%) for categorical variables. Differences between groups were assessed with ANOVA followed by Bonferroni *post-hoc* test for continuous variables or with Pearson Chi-Square test for categorical variables. DLB, Dementia with Lewy bodies; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; PDD, Parkinson's disease dementia.

[*] DLB: *n* = 258; PDD: *n* = 49; PD: *n* = 150

[†] DLB: *n* = 365; PDD: *n* = 53; PD: *n* = 158.

[§] DLB: *n* = 352; PDD: *n* = 41; PD: *n* = 164.

[a] $p < 0.001$ compared with PD.

[b] $p < 0.05$ compared with PD.

[c] $p < 0.001$ compared with PDD.

Table 2

AD CSF biomarkers by diagnosis

	DLB(n = 375)	PDD(n = 55)	PD(n = 164)	Chi square DLB versus PDD	Chi square DLB versus PD	Chi square PDD versus PD	*p-adjusted DLB versus PDD	*p-adjusted DLB versus PD	*p-adjusted PDD versus PD
$A\beta_{42}$									
Normal	190 (50.8%)	32 (58.2%)	145 (88.4%)	$P = 0.306$	$p < 0.001$	$p < 0.001$	$p = 0.378$	$p < 0.001$	$p < 0.001$
Abnormal	184 (49.2%)	23 (41.8%)	19 (11.6%)						
T-tau									
Normal	273 (73.2%)	45 (83.3%)	156 (95.7%)	$p = 0.110$	$p < 0.001$	$p = 0.003$	$p = 0.171$	$p < 0.001$	$p = 0.059$
Abnormal	100 (26.8%)	9 (16.7%)	7 (4.3%)						
P-tau									
Normal	239 (69.7%)	49 (94.2%)	153 (93.3%)	$p < 0.001$	$p < 0.001$	$p = 0.811$	$p = 0.001$	$p < 0.001$	$p = 0.567$
Abnormal	104 (30.3%)	3 (5.8%)	11 (6.7%)						
CSF profile									
AD−	292 (77.9%)	50 (90.9%)	159 (97.0%)	$p = 0.025$	$p < 0.001$	$p = 0.063$	$p = 0.050$	$p < 0.001$	$p = 0.371$
AD+	83 (22.1%)	5 (9.1%)	5 (3.0%)						

Data are expressed as n (%) for categorical variables. Differences between groups were assessed with Pearson Chi-Square test for categorical variables.

*Multivariate logistic regression analysis was used to correct for age and gender. DLB, Dementia with Lewy bodies; PD, Parkinson's disease; PDD, Parkinson's disease dementia; $A\beta_{42}$, amyloid-β_{42}; t-tau, total tau; p-tau, tau phosphorylated at threonine 181.

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Table 3

Demographics of DLB AD+ CSF profile versus DLB AD-CSF profile

	DLB AD+ (*n* = 83)	DLB AD−(*n* = 292)	p
Age, years			
Mean±SD	73.8 ± 8.0	70.3 ± 8.3	$p < 0.001$
Gender			
Male	41 (50.6%)	207 (70.9%)	$p < 0.001$
Female	40 (49.4%)	85 (29.1%)	
Education, years [*]			
Mean ± SD	10.2 ± 3.5	11.0 ± 3.8	$p = 0.281$
MMSE score [†]			
Mean ± SD	20.3 ± 6.0	22.6 ± 5.1	$p < 0.001$
Disease duration, years [§]			
Mean ± SD	2.8 ± 1.6	3.5 ± 3.1	$p = 0.025$

Data are expressed as Mean ± SD and as *n* (%) for categorical variables. Differences between groups were assessed with center adjusted (entered as dummies) ANOVA's for continuous variables or with logistic regression analyses for categorical variables.

[*] DLB AD^+: $n = 59$; DLB AD^-: $n = 199$.

[†] DLB AD^+: $n = 79$; DLB AD^-: $n = 286$.

[§] DLB AD^+: $n = 77$; DLB AD^-: $n = 275$. DLB, Dementia with Lewy bodies; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; PDD, Parkinson's disease dementia.