Cerebrospinal fluid biomarkers in dementia with Lewy bodies

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CHAPTER 4

Alzheimer's disease cerebrospinal fluid biomarkers predict cognitive decline in Lewy body dementia

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ABSTRACT

Introduction: Alzheimer's disease pathologies are common in dementia with Lewy bodies, but their clinical relevance is not clear. CSF biomarkers amyloid-β 1-42, t-tau protein, and Tau phosphorylated at threonine 181 reflect Alzheimer's disease neuropathology ante mortem. In PD, low CSF amyloid-β 1-42 predict long-term cognitive decline, but little is known about these biomarkers as predictors for cognitive decline in Lewy body dementia. The aim of this study was to assess whether Alzheimer's disease CSF biomarkers predict cognitive decline in Lewy body dementia.

Methods: From a large European dementia with Lewy bodies multicenter study, we analyzed baseline Alzheimer's disease CSF biomarkers and serial MMSE (base-line and 1- and 2-year follow-up) in 100 patients with Lewy body dementia. Linear mixed-effects analyses, adjusted for sex, age, baseline MMSE, and education, were performed to model the association between CSF biomarkers and rate of cognitive decline measured with MMSE. An Alzheimer's disease CSF profile was defined as pathological amyloid-β 1-42 plus pathological t-tau or phosphorylated Tau.

Results: An Alzheimer's disease CSF profile, and pathological levels of amyloid-β 1-42, were associated with a more rapid decline in MMSE (2.2 points difference, $p < 0.05$ and 2.9 points difference, $p < 0.01$, respectively). Higher t-tau values showed a trend toward association without statistical significance (2.0 points difference; $p = 0.064$), whereas phosphorylated tau was not associated with decline.

Conclusions: Reduced levels of CSF amyloid-β 1-42 were associated with more rapid cognitive decline in Lewy body dementia patients. Future prospective studies should include larger samples, centralized CSF analyses, longer follow-up, and biomarker-pathology correlation.

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second-most common cause of neurodegenerative dementia, causing 15% to 20% of the cases.[1] The diagnosis remains clinical, but there is an increased interest in the study of complementary tests that can support the clinical diagnostic criteria and predict the rate of decline. Cerebrospinal fluid (CSF) biomarkers are promising tools to optimize the diagnostic and prognostic accuracy because they are accessible and can be used in broader settings and can reflect the underlying neuropathology.[2]

α-synuclein-containing, intraneuronal Lewy bodies are the defining pathological hallmark of DLB, but most patients also have some degree of Alzheimer-type pathology, in particular, amyloid plaques.[3] Their clinical impact is not known in detail, but there is some evidence from postmortem studies that such Alzheimer changes lead to a more rapid cognitive decline in DLB.[4] Alzheimer's disease (AD) pathology is reflected in the CSF as elevated concentrations of total Tau protein (t-tau, a marker of axonal degeneration) and Tau phosphorylated at threonine 181 (p-tau; a marker of neurofibrillary tangle pathology) and reduced concentration of the 42-amino-acid-long amyloid-β protein (Aβ42; a marker of amyloid plaque pathology).[5] These markers have also been studied in DLB and Parkinson's disease (PD), another Lewy body disease with clinical and pathological similarities to DLB, and an AD CSF biomarker profile has been shown in 47% of DLB patients.[6] High CSF t-tau and p-tau and low CSF Aβ42 levels have also been demonstrated in PD dementia cases,[7] and low CSF Aβ42 levels have been found to predict future cognitive decline in PD.[8] AD CSF biomarkers have been linked to earlier death in DLB,[9] but their relationship with longitudinal cognitive decline in patients with DLB is not known. Therefore, the aim of this study was to test the hypothesis that an AD-type CSF profile predicts cognitive decline in longitudinally followed DLB patients.

METHODS

Study Population

From a European multicenter study of DLB (E-DLB), we selected 100 patients with diagnostic criteria for probable DLB, of whom we had baseline CSF results and Mini–Mental State Examination (MMSE) scores at baseline and at 1 or 2 years of follow-up, from four different centers (Memory Clinic, Karolinska University Hospital, Huddinge; Clinical Memory Research Unit, Department of Clinical Sciences, Lund University; Neuropsychology Unit and Geriatric Day Hospital, Strasbourg Resource and Research Memory Center, University Hospital of Strasbourg; and Center for Age-Related

Medicine, Stavanger University Hospital; see details in Supplementary Table 1). Eighty patients started treatment with a cholinesterase inhibitor after baseline assessment.

Diagnostic and Clinical Examination

The diagnosis of DLB was made according to the consensus criteria[10] by the treating physician, a group of at least two expert clinicians, or by a multidisciplinary team at a consensus diagnostic meeting on the basis of all available clinical and diagnostic test data.

Clinicians performed a clinical interview with patients and caregivers regarding demographics, previous diseases, and drug history. Per design, clinical procedures were not harmonized across centers, but at all centers the assessment procedures included a detailed history and physical, neurological, and psychiatric examinations using standardized scales, such as the motor subscale of the UPDRS and the Neuropsychiatric Inventory. Based on these scales and/or the clinical examination, the core diagnostic features, such as parkinsonism, visual hallucinations, and fluctuating cognition, were considered to be present or absent. Routine blood tests and brain imaging were performed and often also neuropsychological testing. Dopamine transporter (DAT) single-photon emission computed tomography scans (DAT-scans) were performed in 38 of the DLB patients (24 with a pathological scan). Cognition was evaluated using MMSE[11] at baseline and annually for up to 2 years.

Ethics

Local ethics committees at the individual centers approved the study. Patients gave their written consent to use the unidentified results of their clinical, instrumental, and laboratory investigations for research purposes.

CSF Procedures

CSF was obtained at all centers with the following procedures: (1) lumbar puncture in the L3 to L4 or L4 to L5 interspace; (2) collection in polypropylene tubes and centrifuged for 10 minutes at 4 °C; and (3) storage in aliquots of 0.5 mL at -80 °C or -70 °C until further analysis. Further details are summarized in Supporting Table 1. CSF analyses were performed locally according to standard routines. INNOTEST enzyme-linked immunosorbent assays [ELISA] were used to analyze t-tau (missing data for 2 patients) and p-tau (missing for 7 patients) in all samples and Aβ42 in 93 samples (Fujirebio, Ghent, Belgium), and the remaining 7 samples were analyzed for Aβ42 using ELISA kits from Biosource Europe S.A. (Nivelles, Belgium).

Accordingly, raw CSF values could not be pooled, and we used the locally available cut-off values for each biomarker to dichotomize in pathological and normal values (Supporting Table 1). An AD CSF profile was defined as pathological (low) Aβ42 combined with pathological (high) t-tau or p-tau.[12] Based on this profile, DLB patients were divided in an AD CSF profile pathological group and an AD CSF profile normal group.

Statistical Analysis

Statistical analyses were done using IBM SPSS soft-ware (version 20; IBM Corp, Armonk, NY) and R Project for Statistical Computing (Vienna, Austria). Results are shown as mean 6 standard deviation for normally distributed continuous variables, median (range) for non-normally distributed continuous variables, and number and percentage for categorical variables. Comparisons of baseline clinical and demographic data in the CSF profile groups were per-formed using parametric Student's t test and nonparametric Mann-Whitney U test, as appropriate. Analyses with linear mixed-effect (LME) models were used to determine whether the rate of cognitive decline measured by MMSE during the 2-year follow-up was predicted by the AD CSF profile, followed by the specific CSF measures (i.e., Aβ42, t-tau, and p-tau), all with pathological or normal values. Impact on decline is represented by the interaction term between factor and time (year of follow-up), adjusted for age, sex, and education. The LME analysis includes also the baseline value, which was therefore not adjusted for as a cofactor. There is considerable individual variation in both level and decline of MMSE, and therefore LME models with both random intercept and random slope were used. Thus, the statistical model underlying the LME analyses captures both these kinds of individual variation.

RESULTS

One hundred participants had MMSE scores at baseline and 1-year follow up, and 76 had MMSE score at 2-year follow-up. Of the 100 subjects, 32%showed an AD CSF profile, 69% had a pathological value for Aβ42, 31.6% for t-tau (2 missing), and 26.9% for p-tau (7 missing). Baseline clinical and demographic variables showed no statistically significant differences between groups by AD CSF profile (Table 1).

Table 1 | Demographics of DLB patients by AD CSF profile at baseline

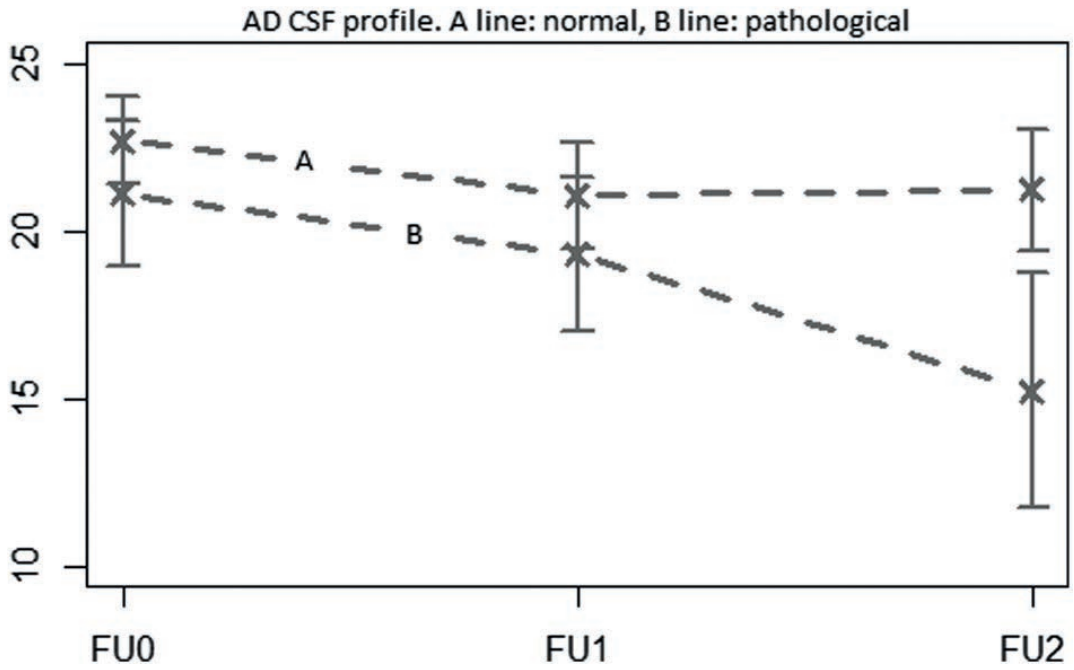
	AD CSF Profile		
	Pathological	**Normal**	***p* value**
N	32	68	
Age at baseline	74.22 ± 7.95	71.93 ± 7.79	0.176
Sex (% Male)	16 (26.2%)	45 (73.8%)	0.122
Education (years)	8.88 ± 3.34	10.63 ± 4.16	0.043
Disease duration (years)[b]	2.79 ± 1.94	3.01 ± 2.58	0.678
MMSE	21.09 [5-30]	22.68 [6-30]	0.200

Numbers represent mean and SD, if not otherwise stated. Missing data: [a] education 9 patients; [b] duration 1 patient.

CSF Profile and Cognitive Decline

The overall rate of decline was 1.9 points per year. The LME analyses showed that the group with AD CSF profile was significantly associated with a more rapid decline, with 2.2 points per year (standard error [SE]: 1.1) higher annual decline in the AD CSF pathological group than the AD CSF normal group (p = 0.04; Figure 1). Male sex and higher level of education were both associated with more rapid decline (p < 0.05).

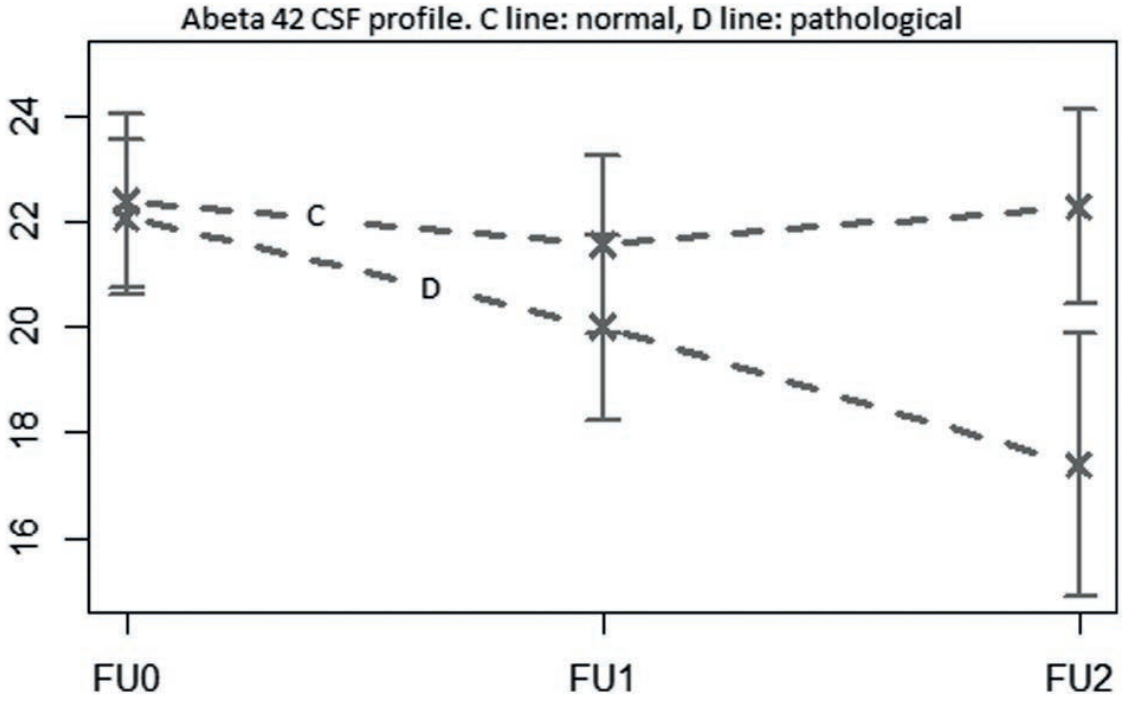
Figure 1 | Decline over time on MMSE according to AD CSF profile



Change in MMSE from baseline (FU0) to one (FU1) and two (FU2) years follow-up in those with (n = 32, Line B) and without (n = 68, Line A) a CSF AD profile. The difference was statistically significant (LME, P = 0.04).

Specifically, having a CSF Aβ42 value below the cutoff was associated with a more rapid decline; 2.9 (SE: 1.1) points difference per year, compared to those with a normal CSF Aβ42 value (p = 0.0079; Figure 2). The Aβ42-positive group was older (74.09 years) than those with normal Aβ42 values (69.48 years; p = 0.006), but this difference was adjusted for in the LME analysis. Having a CSF t-tau value above the cutoff was associated with a 2.0 (SE: 1.1) points difference/year more rapid decline compared to those with normal t-tau (p = 0.06). p-tau did not show any association with rate of decline. Table 2 summarizes these results. We conducted these analyses in the sub-group of patients who started cholinesterase inhibitor treatment after baseline and found the same results (data not shown), which indicates that difference in medication status did not influence the data. To further explore the validity of the findings, we analyzed only those 24 patients with decreased DAT on DAT-scan. Again, the findings were similar to those in the full data set.

Figure 2 | CSF Aβ42 and decline over time on MMSE



Change in MMSE from baseline (FU0) to one (FU1) and two (FU2) years follow-up in those with (n = 69, Line D) and without an abnormally low (n = 31, Line C) CSF Aβ42 value. The difference was statistically significant (LME, P = 0.0079).

Table 2 | Annual rate of decline on MMSE in patients bases on abnormal or normal values on the CSF markers

		Mean Rate of Decline	*p* value
AD CSF profile	Pathological	3.6	0.04
	Normal	1.4	
CSF Aβ42	Pathological	3.2	0.0079
	Normal	0.2	
CSF t-tau	Pathological	3.5	0.06
	Normal	1.5	
CSF p-tau	Pathological	2.2	0.85
	Normal	2.5	

The *p* value represents significance of the rate being different from the rate in the normal group. Abbreviations: Aβ42, Amyloid-β 1-42; p-tau, Tau phosphorylated at threonine 181; t-tau, total Tau protein.

DISCUSSION

This study demonstrates that having a value below the cutoff of CSF Aβ42, a marker of amyloid pathology, is associated with a faster cognitive decline during 2-year follow-up in patients with DLB. We are not aware of previous longitudinal studies of CSF markers in DLB, but our findings are consistent with similar findings in PD.[8] These results have immediate clinical implications by suggesting that CSF Aβ42 values, although of little diagnostic value, might have prognostic significance in patients with DLB.

Several cross-sectional studies have demonstrated low CSF Aβ42 concentrations in DLB, whereas the t-tau and p-tau findings have been inconsistent.[13] Similarly, amyloid imaging studies have supported the role of amyloid deposition for cognitive impairment in DLB.[14] In addition, clinicopathological studies suggest that the presence of amyloid plaques in DLB patients are associated with lower concentrations of CSF Aβ42,[15] and with cognitive decline, in addition to Tau and Lewy body pathologies.[4] Recent studies have reported increased CSF α-synuclein levels in patients with DLB,[16] but the variation of total α-synuclein levels is large, and although an association with dementia has been shown in PD,[17] this has not yet been demonstrated in DLB.

The role of Tau pathology in DLB is not well known. We observed a non-significant trend suggesting that high CSF t-tau, considered to be a marker of neurodegeneration in general, may also be associated with a more rapid decline. In contrast, p-tau was not associated with cognitive decline, suggesting that tau pathology is not a major driver of cognitive decline in DLB. Inconsistent results have been reported in previous

studies of p-tau and t-tau, although associations between cognitive impairment and high p-tau have been reported in PD in some,[18, 19] but not all,[7, 20-22] studies. In DLB, an association between high CSF t-tau and increased mortality has been reported.[23] In the largest study of CSF markers in DLB to date,[24] CSF t-tau and p-tau were only marginally higher in 60 DLB patients compared to healthy subjects, and significantly lower than in AD, and p-tau was a significant discriminator between AD and DLB. Taken together, there is evidence that pathological processing of Aβ, Tau, and α-synuclein contribute to cognitive decline in DLB, possibly with a synergistic effect, which is in line with studies in animal models.[25] However, more studies are needed to clarify this, and it will be interesting to see whether the recently available tau imaging can increase our understanding of the role of tau pathology in DLB.

This is the largest CSF study in DLB and one of the first using longitudinal cognitive data. However, some limitations need to be discussed. First, the observation period was relatively short, and thus these results should be validated in prospective studies of longer duration. This is also important because of the common fluctuating cognition in DLB, which may increase the variation in cognitive testing and might mask the association between CSF markers and rate of decline. Another limitation is that, per design, different assays were used at different centers, and thus measurements from the four centers could not be combined, and locally established cut points had to be applied to classify values as normal or abnormal. This likely reduced the likelihood of detecting associations between rate of decline and CSF markers. Furthermore, because this was a naturalistic study, treatment procedures were not standardized. Nearly all patients started treatment with a cholinesterase inhibitor after baseline, and these agents are effective in DLB[26] and thus variation in treatment status might have influenced the findings. However, analyses including only those without treatment showed similar findings as the overall analysis, indicating that treatment status is not a major confounder. MMSE was used as the measure of cognition, which is less sensitive to the early cognitive changes in PD and perhaps also DLB, than other scales such as the Montreal Cognitive Assessment (MoCA).[27] However, our recent analysis suggests that MMSE and MoCA are equally sensitive to the cognitive change in DLB,[28] as has been shown also in PD.[29] Still, we suggest that future studies should assess decline in the different cognitive domains separately to better understand how the course of the different cognitive domains are related to CSF biomarkers. In addition, progression of noncognitive symptoms, for example, parkinsonism and psychosis, may be even more clinically relevant than cognition, and thus their association with CSF markers should also be explored in future studies.

Only the three common CSF AD biomarkers were assessed, but there are many other CSF markers potentially associated with decline in DLB. In addition to α-synuclein and α-synuclein oligomers,[16, 30] it would be interesting to explore markers such as clusterin,[31] interleukin-6,[32]and Aβ species other than Aβ42,[33] and to correlate these biomarkers with the apolipoprotein E genotype, given their possible relationship to Aβ42 CSF levels[15] and cognitive decline.[34] Multimodal biomarker studies (i.e., combining different CSF markers as well as CSF and other techniques, including structural MRI[35]) might improve accuracy of the relationship of CSF biomarkers and cognitive decline in DLB patients. Finally, clinical diagnosis of DLB is not perfect, and autopsy validation was not available. However, the specificity of clinical criteria is high, suggesting that 80% to 90%of patients fulfilling clinical criteria for probable DLB also fulfill pathological criteria.[36] In addition, clinical diagnosis was made in centers with expertise and experience in DLB, patients were followed longitudinally, and the diagnosis was supported by DAT-scan in one third of cases. Thus, we believe that diagnostic accuracy is acceptable in this study. Of note, we observed the increased rate of decline associated with low CSF Aβ42 also when analyzing only patients with low DAT binding on DAT-scan. In conclusion, our findings indicate that having an AD-type CSF profile could be associated with a more rapid decline in people with DLB.

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SUPPLEMENTAL DATA

Supplementary Table 1 | Overview of CSF procedures

Center	Number of DLB patients	Centrifuging	Storage	Analysis Essay	Cut off values [ng/L]
Malmö/Lund	50	Centrifuged at 2000g for 10 minutes at 4°C	Stored at -80°C	INNOTEST Double sandwich ELISAs	Aβ42: <550 t-tau: >400 p-tau: >80
Strasbourg	32	Centrifuged at 1000g for 10 minutes at 4°C	Stored at -80°C	INNOTEST Double sandwich ELISAs	Aβ42: <500 t-tau: 50-70 years: >450 >70 years: >500 p-tau: >60
Stockholm	11	Centrifuged at 2000g for 10 minutes at 4°C	Aliquots of 0.5mL of 1mL stored in polypropylene tubes at -80°C	INNOTEST Double sandwich ELISAs	Aβ42: <550 t-tau: >400 p-tau: >80
Stavanger	7	Centrifuged at 2000g for 10 minutes at 4°C	Stored in polypropylene tubes at -80°C	Aβ42: Biosource Europe S.A. t-tau: INNOTEST hTau p-tau: INNOTEST Phos-pho-Tau (181)	Aβ42: <482 t-tau: >320 p-tau: >52

Abbreviations: Aβ42, Amyloid-β 1-42; DLB, dementia with Lewy bodies; ELISA, enzyme-linked immunosorbent assay; PD, Parkinson's disease; PDD, Parkinson's disease dementia; p-tau, Tau phosphorylated at threonine 181; t-tau, total Tau protein.