LETTER

CSF tau proteins correlate with an atypical clinical presentation in dementia with Lewy bodies

A cerebrospinal fluid (CSF) Alzheimer's disease (AD) profile, that is, decreased amyloid-β1-42 ($A\beta_{42}$) and increased total tau protein (t-tau) and/or phosphorylated tau at threonine-181 (p-tau),[1] has been identified in a substantial number of dementia with Lewy bodies (DLB) patients, and it has been related to a more rapid cognitive decline.[1] We investigated the association between AD CSF biomarkers and DLB core clinical features to better understand in vivo how AD pathology influences DLB clinical presentation.

We included 171 subjects with a clinical diagnosis of probable DLB[2 3] from the European DLB consortium (E-DLB). The centres involved are summarised in online supplementary table 1. Clinical examination was performed as previously reported.[1] Dopamine transporter (DAT) single-photon emission CT scans (123I-FP-CIT-SPECT) were performed in 80 patients.

CSF samples were collected at each centre according to the procedures detailed in online supplementary table 1. An AD CSF profile was defined as low $A\beta_{42}$ combined with high t-tau or p-tau.[1] Information about pharmacological treatments of patients were not available at each centre. Statistical analyses were performed using SPSS V.24. Association between CSF biomarkers (normal or abnormal), and each core features (present or absent), were tested with χ^2 test. Associations between single CSF biomarkers and groups of subjects with different core clinical features' number (1–4) were tested with Armitage test for trend.

Local ethics committees approved the study. All patients gave their written consent for the use of their clinical, instrumental and laboratory data for research purposes.

The overall characteristics of the 171 patients are shown in the table.

An AD CSF profile occurred in 17% (n=29). Compared with the non-AD profile group, the AD profile group was significantly older (age mean±SD of AD-profile group 72.8±10, non-AD profile group 68.6±9.1, p value=0.027) and had a lower Mini Mental State Examination (MMSE) score (mean±SD of AD-profile group 20±5.7, non-AD profile group 23.7±4.3, p value <0.001).

Table 1 Demographic, clinical and CSF data

Total subjects=171	
Male n (%)	60 (59.4)
Age (in years, mean±SD)	70.8±10
Disease duration (in years, mean±SD)	4.5±4
MMSE (mean±SD)	23.4±5.1
UPDRS III (mean±SD)	16.8±7.1
1 FEATURE n (% within total)	7 (4.1)
PA n=2	
VH n=4	
CF n=1	
2 FEATURES n (% within total)	40 (23.4)
PA+VH n=2	
PA+CF n=14	
PA+RBD n=10	
VH+CF n=6	
CF+RBD n=8	
3 FEATURES n (% within total)	72 (42.1)
PA+VH+ CF n=31	
PA+CF+ RBD n=23	
VH+CF+ RBD n=14	
PA+VH+ RBD n=4	
4 FEATURES n (% within total) PA+VH+CF+RBD	52 (30.4)
Abnormal $A\beta_{42}$	58 (33.9)
Abnormal t-tau	44 (25.7)
Abnormal p-tau	54 (31.6)
AD CSF profile	29 (17)

Clinical core features were assessed at the time of lumbar puncture.
AF, Alzheimer'sdisease; CF, cognitive fluctuations; PA, Parkinsonism; RBD, REM sleep behaviour disorder; REM, sleep behaviour disorder; UPDRS, Unified Parkinson's Disease Rating Scale; VH, visual hallucinations.

Only Parkinsonism showed association with CSF tau biomarkers, being the distribution of visual hallucinations, fluctuations and REM sleep behaviour disorder similar between normal and abnormal CSF t-tau and p-tau groups. Parkinsonism was present in 63.6% of those patients with abnormal levels of CSF t-tau, compared with 86.6% of those with normal CSF t-tau (Pearson χ^2 test p value=0.001). For CSF p-tau the values were 63% and 88.9% (χ^2 test p value <0.001). No association was found between clinical core features and $A\beta_{42}$ values or the presence of an AD CSF profile (table 1).

A lower number of concurrent core features was associated with a higher percentage of subjects with abnormal t-tau (p value=0.014) and p-tau (p value=0.01). This association was not found for $A\beta_{42}$ and the AD CSF profile.

123I-FP-CIT-SPECT resulted to be pathological in 72 out of 80 patients (90%).

For validation purposes of our findings, we separately analysed those 72 patients with positive 123I-FP-CIT-SPECT and the analysis showed results in accordance to those in the full dataset.

The main findings of this DLB multicentre cohort study, in concordance with previous pathological studies,[4] are the association of abnormal CSF t-tau and p-tau levels with a lower frequency of Parkinsonism and the association between a lower number of concurrent core features and abnormal CSF t-tau and p-tau values.

A previous CSF study reported higher occurrence of visual hallucinations in DLB patients with an AD CSF profile.[5] This effect disappeared in our study even if 59 patients of that study (Amsterdam cohort, online supplementary table)[5] are part of our cohort. We could hypothesise that the lack of the effect was due to a larger population sample and a different description in the previous study of the AD CSF profile as the ratio between tau and $A\beta_{42}$>0.52.[5] We could also speculate that in the Amsterdam cohort[5] there was more cortical Lewy body pathology, which may have contributed to the genesis of visual hallucinations. Our E-DLB multicentre cohort may contain a more Parkinson's Disease with Dementia (PDD) like phenotype, with more Parkinsonism and less cortical Lewy bodies. This may account

also for the low percentage of patients with AD CSF profile (17%), as compared with amyloid PET positive scan in DLB reported in literature (around 60%). It should be underlined that while positive amyloid positron emission tomography (PET) correlates with low $A\beta_{42}$ in the CSF, no correlation has been demonstrated between positive amyloid PET and AD CSF profile which is a composite parameter including $A\beta_{42}$ and tau proteins.

With our study we aimed to explore the relationship between single CSF biomarkers and DLB core features in a large cohort of DLB patients. However, because of the multicentric and retrospective nature of this study, we could not analyse raw values of CSF biomarkers neither consequently the ratio t-tau/ $A\beta_{42}$, as each centre used different pre-analytical sampling procedures and locally established AD cut-off values of CSF biomarkers. Furthermore, it is unknown which are the pathological thresholds of AD CSF biomarkers in DLB. This probably had an influence on our results, leading to a decrease in the likelihood to find associations between CSF biomarkers and core features. Nonetheless, the recruitment of DLB patients from different centres across Europe and the large sample size improved the generalisability of the findings.

Even though our study lacks neuropathological confirmation of DLB diagnosis, almost half of our cases underwent 123I-FP-CIT-SPECT and the results in this subsample coincided with those of the complete dataset, strengthening our findings.

In conclusion, we observed that in clinically diagnosed DLB patients, tau pathology is associated with less typical clinical DLB presentation, with lower occurrence of Parkinsonism and lower number of concurrent core features. This could be explained by the complexity of the molecular relationship between Lewy body and AD-type pathology, which is still unclear. In some individuals, the two pathologies overlap, resulting in a less characteristic clinical profile. The presence of tau pathology (increased t-tau and p-tau in CSF) may conceal the clinical characteristics of DLB, making its clinical presentation atypical.

It would be interesting in the future to assess alpha-synuclein levels, which based on a recent hypothesis may interfere with Aβ clearance, and to understand whether the AD CSF profile is associated with more memory dysfunction in DLB.

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