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CSF Tau, Aβ_{42}, and MHPG Differentiate Dementia with Lewy Bodies from Alzheimer's Disease

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Abstract. Differentiating dementia with Lewy bodies (DLB) from Alzheimer's Disease (AD) can be difficult because of the substantial overlap in clinical features. Since deficits in serotonergic and dopaminergic pathways seem more pronounced in DLB patients, we investigated whether cerebrospinal fluid (CSF) analysis of neurotransmitter metabolites, in addition to brain-specific proteins, may improve the differentiation between DLB and AD. We retrospectively compared CSF concentrations of the neurotransmitter metabolites homovanillic acid (HVA), 5-hydroxyindolacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) and the brain-specific proteins total tau (t-tau), phosphorylated tau protein (p-tau), and amyloid-β_{42} (Aβ_{42}) in 45 patients with AD (mean age 71.6 years; 34 (76%) men; 44 probable AD, 1 definite) and 23 patients with DLB (mean age 71.6 years; 18 (78%) men; 6 possible DLB, 16 probable, 1 definite). The concentrations of all neurotransmitter metabolites, as well as those for t-tau and p-tau protein, were significantly lower in DLB compared to AD, irrespective of the diagnostic certainty (i.e., possible or probable). The currently used combination of Aβ_{42}, p-tau, and t-tau yielded a sensitivity of 92.9% and a specificity of 90%. The addition of MHPG resulted in an increased sensitivity of 97.6% and a specificity of 95% for the discrimination between DLB and AD. In conclusion, the combination of MHPG and the brain specific proteins t-tau, p-tau, and Aβ_{42} in CSF were associated with the clinical diagnosis of DLB and discriminated between AD and DLB with high diagnostic accuracy, suggesting this combination as a potential biomarker for DLB.

Keywords: Alzheimer's disease, amyloid-β, cerebrospinal fluid, dementia with Lewy bodies, diagnosis, MHPG, neurotransmitter metabolites, tau

INTRODUCTION

Dementia with Lewy bodies (DLB) is a common cause of dementia, accounting for up to 20% of the dementia population [1]. Core features include fluctuating cognition, visual hallucinations, autonomic disturbances, and parkinsonism. The neuropathological hallmark is the 'Lewy body', an intraneuronal inclusion body consisting of, among others, ubiquitin and α-synuclein, present in the substantia nigra and neocortex as well as limbic and forebrain structures [2, 3].

Differentiation between DLB and Alzheimer's disease (AD) on clinical grounds alone can be difficult

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due to substantial overlap in clinical presentation, as reflected by low sensitivity of the clinical criteria for DLB [2, 4, 5]. However, early recognition is important because of the therapeutic consequences. DLB patients show great sensitivity to neuroleptics, which may cause physical and cognitive deterioration, and even increased mortality [6–8]. Hence, biomarkers that improve the early recognition of DLB are urgently needed.

Currently the cerebrospinal fluid (CSF) concentrations of amyloid-β_{42} ($A\beta_{42}$), total tau protein (t-tau), and tau protein phosphorylated at Thr181 (p-tau) are employed to identify (incipient) AD patients among patients with dementia syndromes or MCI [9]. However, the differentiation between the different dementia syndromes based on CSF analysis is limited, e.g., because of considerable overlap between AD and DLB [10–16].

Deficits in serotonergic and dopaminergic pathways, associated with symptoms of autonomic dysfunction or parkinsonism, are more pronounced in DLB patients compared to AD patients [17–20]. We anticipated that CSF concentrations of the neurotransmitter metabolites homovanillic acid (HVA), 5-hydroxyindolacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), the catabolic end-products of dopamine and epinephrine degradation, are lower in DLB than in AD [21–24]. Therefore, we aimed to investigate the additional diagnostic value of CSF neurotransmitter metabolites compared to CSF brain-specific proteins in differentiating between DLB and AD.

MATERIALS AND METHODS

Patients

We included consecutive patients with a clinical diagnosis of DLB who were referred to either the movement disorder clinic of the Department of Neurology or the memory clinic of the Department of Geriatric Medicine at the Radboud University Nijmegen Medical Centre to cover the broad clinical spectrum of DLB, who underwent a lumbar puncture between December 2003 and June 2008 as part of the diagnostic work-up (Fig. 1). The concentration of MHPG in CSF is independent of the fraction, however, since the concentrations of the neurotransmitter metabolites HVA and 5-HIAA do depend on the CSF fraction [25], only patients with separate collection of the 8th–10th ($\pm$2) milliliter fraction were included for analysis. Diagnostic evaluation included a detailed medical history, systematic physical and neurological examination, routine laboratory testing, and a brain MRI scan. Cognitive function was assessed using the Mini Mental State Examination (MMSE) [26]. Additionally, 15 DLB patients underwent neuropsychological assessment. Symptoms of parkinsonism were assessed using the Hoehn and Yahr score. Heteroanamnesis was employed to assess the presence of visual hallucinations and fluctuations in cognition. The clinical diagnosis was established by either a specialized neurologist or geriatrician.

Out of 93 eligible AD patients from the memory clinic database, an age and gender matched group of 45 AD patients was randomly drawn. The clinical diagnosis of these patients was established by a multidisciplinary team consisting of a geriatrician, a neurologist, and a neuropsychologist.

In April 2010 a single rater (MBA) reassessed the final clinical diagnosis by clinical chart review in order to improve diagnostic certainty. Reassessment of the clinical diagnosis was performed after a follow-up period of 12 months or longer (Table 1) according to the international consensus criteria for DLB [27] and AD [28]. The use of medication (serotonergic as well as dopaminergic medication), the presence of white matter lesions and the presence of behavioral disorders, hallucinations, and symptoms of autonomic dysfunction were recorded to enable subgroup analysis. The IRB has approved of this study which was conducted according to the Helsinki Declaration.

CSF parameters

CSF samples were collected in polypropylene tubes, centrifuged, aliquoted, and stored at -80°C until analysis. We aimed for separate collection of the 8th–10th ml ($\pm$2) fraction for analysis of neurotransmitter metabolites. The following CSF variables were taken into account for the present study: $A\beta_{42}$, t-tau, p-tau, MHPG, 5-HIAA, and HVA; all parameters were analyzed within 4 weeks after CSF collection.

The methods of analysis of $A\beta_{42}$, t-tau, p-tau, MHPG, HVA, and 5-HIAA in CSF, their validation and reference values have been previously described [25, 29, 30].

Statistical analysis

Between-groups analysis was performed using the Student's *t*-test in case of normally distributed data.

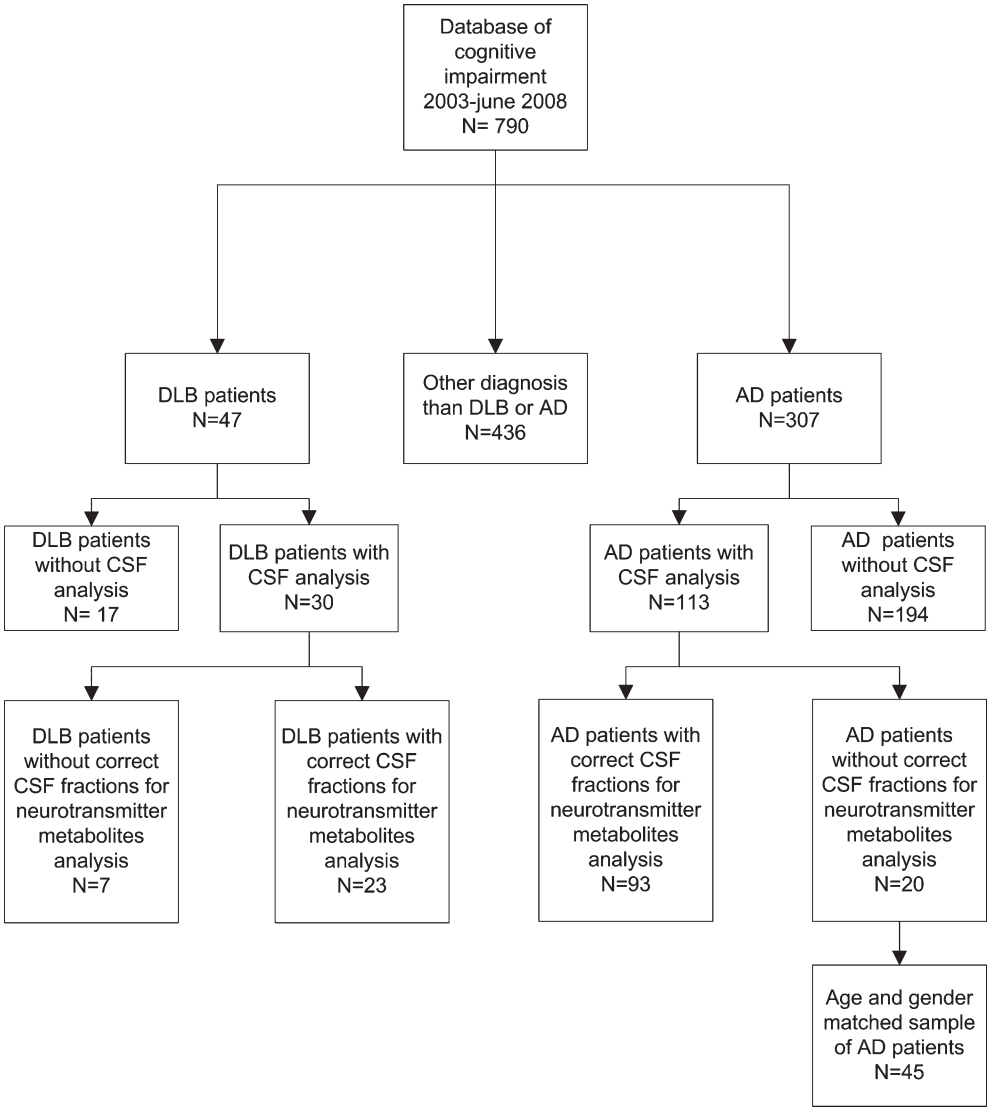

Fig. 1. Flowchart of patient inclusion in this study. AD: Alzheimer's disease, DLB: dementia with Lewy Bodies, CSF: cerebrospinal fluid, N: number. CSF was obtained during the initial diagnostic assessment upon presentation.

Non-Gaussian distributed data were analyzed using the Mann-Whitney test. Pearson correlation coefficient was used to analyze correlations. Prior to correlation analysis, non-Gaussian distributed data were log-transformed to meet assumptions of normality and homogeneity. Logistic regression analysis was used to analyze relations between categorical variables.

Multivariate logistic regression and receiver operator characteristic (ROC) analysis were used to evaluate the diagnostic value of CSF parameters. Statistical analysis was carried out using GraphPad Prism version 4 (San Diego, CA) and SPSS software version 16.0 (Chicago, IL).

RESULTS

Patients

At the time of the clinical chart review, 23 patients fulfilled the diagnostic criteria for DLB (6 possible DLB, 16 probable DLB, and 1 definite DLB) and 45 patients fulfilled the diagnostic criteria of AD (44 probable AD, and 1 definite AD). None of the patients complied with the criteria for mild cognitive impairment (MCI) [38]. Demographic characteristics are shown in Table 1. Six DLB patients and two AD patients had deceased at the time of the chart review.

Table 1
Characteristics of the diagnostic groups

Demographic characteristics	DLB	AD	*p*-value[b]
Number of patients	23	45	
Age, y[a]	71.6 (9.3)	71.6 (9.4)	NS ($p=0.89$)
Number of men (%)	18 (78)	34 (76)	NS ($p=0.88$)
Disease duration, months[a]	38.8 (26.4)	33.0 (28.1)	NS ($p=0.42$)
Cognitive function, MMSE[a]	23.0 (4.2)	19.5 (5.3)	<0.05
Duration of follow up, months	55.9 (30.3)	49.7 (32.4)	NS ($p=0.75$)
Vascular co-morbidity (%)[a]	5 (22)	12 (27)	NS ($p=0.73$)
Autonomic dysfunction (%)[a]	13 (76.5)	9 (20.5)	<0.001
Orthostatic hypotension (%)	2/(11.8)	1 (2.3)	<0.001
Urogenital dysfunction (%)	11 (64.7)	8 (18.2)	<0.001
Hallucinations (%)[a]	13 (57)	1 (2)	<0.001
Use of SSRI (%)[a]	4 (17)	3 (7)	NS ($p=0.15$)
Use of L-dopa (%)[a]	6 (26)	0 (0)	<0.001
Severity of parkinsonism, H&Y score[a]	2.5 (2.0–2.5)	NA	NA
CSF fraction analyzed, ml (lower margin)[c]	8.0 (7.0–9.0)	7.3 (6.8–8.0)	NS ($p=0.18$)
CSF fraction analyzed, ml (upper margin)[c]	11.0 (10.0–11.5)	10.0 (9.0–10.5)	<0.05

Data represent mean and standard deviation (in case of Gaussian distribution), median and interquartile range (in case of non- Gaussian distribution) or number and percentage. [a] At the time of lumbar puncture. [b] *P* value for differences using student's T-test. Gender distribution, the presence of vascular comorbidity, autonomic dysfunction, hallucinations and the use of medication were analyzed using χ^2 test. [C] for neurotransmitter metabolite analysis DLB: dementia with Lewy bodies; AD: Alzheimer's disease; MMSE: mini mental state examination; SSRI: selective serotonine reuptake inhibitor; L-dopa: levodopa; H&Y score: Hoehn and Yahr score; NA: not applicable; CSF: cerebrospinal fluid.

The initial diagnoses, prior to CSF analysis were possible AD ($n=18$), probable AD ($n=19$), cognitive disorder not further specified ($n=6$), Creutzfeldt-Jakob disease ($n=1$) and possible DLB ($n=1$) for the AD patients; and for the DLB patients: possible DLB ($n=10$), possible AD ($n=3$), Parkinson's disease ($n=5$), corticobasal degeneration ($n=1$), multiple system atrophy ($n=1$), cerebral small vessel disease ($n=2$) and psychogenic complaints ($n=1$).

Disease duration, gender, and age at the time of lumbar puncture were similar in AD and DLB. MMSE score was lower in AD ($p<0.05$). Six DLB patients, and none of the AD patients, used dopaminergic therapy (median 375 mg; range 62.5–800 mg L-dopa/day).

CSF parameters

The results of the CSF analysis are presented in Fig. 2. The concentrations of 5-HIAA ($p<0.01$), HVA

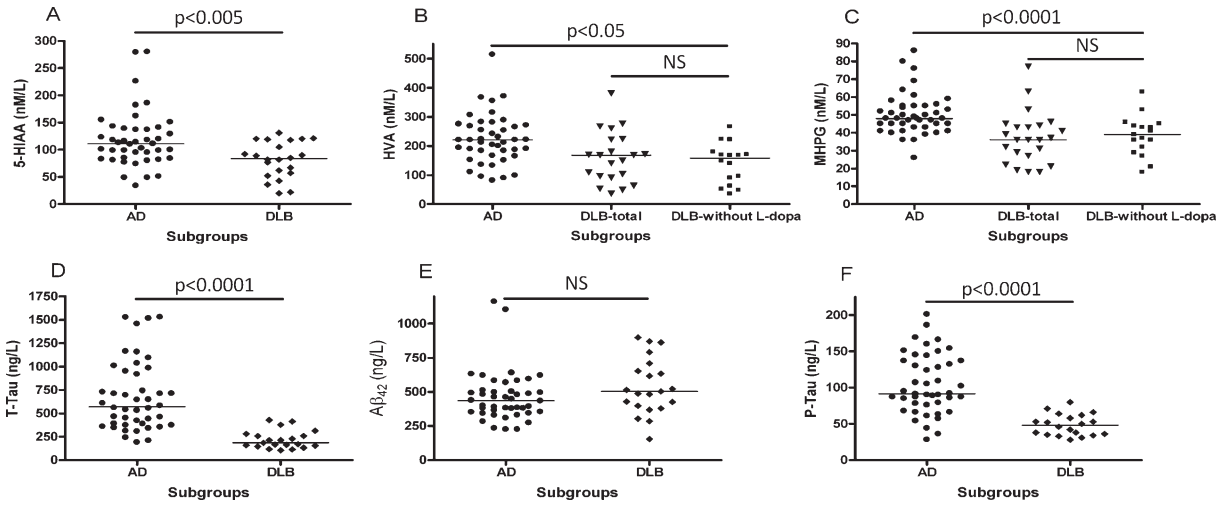

Fig. 2. Scatterplots of the CSF concentrations of (A) 5-HIAA (nM), (B) HVA (nM), (C) MHPG (nM), (D) T-Tau (ng/L), (E) $A\beta_{42}$ (ng/L) and (F) P-Tau (ng/L) in DLB and AD subgroups. Horizontal lines represent median levels.

Table 2
ROC-analysis of CSF parameters in DLB vs. AD

CSF variables	Number of patients[a]	Cut-off point	Sensitivity (%)	Specificity (%)	Area under the curve (95% CI)	Youden index[b]	Likelihood ratio[c]
Univariate analysis							
5-HIAA (nM)	DLB $n=22$, AD $n=43$	<92.5	72.1	68.2	0.72 (0.58–0.86)	0.39	2.10
MHPG (nM)	DLB $n=22$, AD $n=43$	<44.5	74.4	78.3	0.81 (0.68–0.92)	0.53	4.43
HVA (nM)	DLB $n=22$, AD $n=43$	<182.0	76.2	70.0	0.69 (0.54–0.85)	0.46	2.54
$A\beta_{42}$ (ng/L)	DLB $n=21$, AD $n=44$	>482.0	62.0	65.0	0.65 (0.49–0.81)	0.27	1.78
P-tau (ng/L)	DLB $n=21$, AD $n=44$	<67.0	81.0	95.0	0.92 (0.86–0.99)	0.76	16.19
T-tau (ng/L)	DLB $n=20$, AD $n=44$	<294	90.4	90.0	0.95 (0.91–1.0)	0.80	9.05
Multivariate analysis							
Model 1[d]	DLB $n=22$, AD $n=42$	>0.42	92.9	90.0	0.96 (0.92–1.0)	0.82	
Model 2[e]	DLB $n=22$, AD $n=44$	>−0.455	97.6	95.0	0.99 (0.97–1.0)	0.93	39.6

[a] Due to missing data points, not all CSF parameters were available in all patients. [b] Youden index: sensitivity + specificity – 1.0 [c]Likelihood ratio: sensitivity/(1-specificity) [d] $y=-5.098+0.005\times$ p-tau, $+0.020\times$ t-tau $-0.002\times A\beta_{42}$. AUC: 0.96 (0.92–1.0) [e] $y=-13.965+0.072\times$ p-tau, $+0.021\times$ t-tau $+0.143\times$ MHPG $-0.006\times A\beta_{42}$. AUC: 0.99 (0.97–1,0)ROC-: receiver operating characteristic; DLB: dementia with Lewy bodies; AD: Alzheimer's disease; CSF: cerebrospinal fluid; 5-HIAA: 5-hydroxyindolacetic acid; HVA: homovanillic acid; MHPG: 3-methoxy-4-hydroxyphenylethyleneglycol; $A\beta_{42}$: amyloid β42; p-tau: phospho-tau; t-tau: total tau protein; 95 CI: 95% confidence interval.

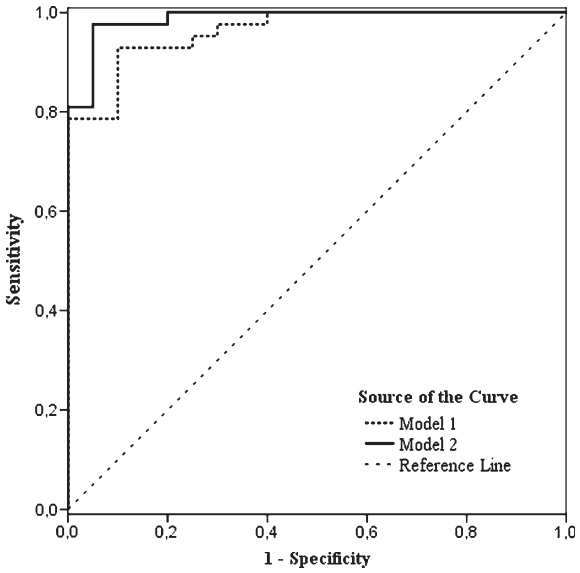

Fig. 3. ROC curves of the models 1 and 2 Model 1: $y=-5.098+0.005\times$p-tau, $+0.020\times$t-tau $-\ 0.002\times A\beta_{42}$. AUC: 0.96 (0.92–1.0) Model 2: $y=-13.965+0.072\times$p-tau, $+0.021\times$t-tau $+0.143\times$MHPG $-\ 0.006\times A\beta_{42}$. AUC: 0.99 (0.97–1.0).

($p<0.05$), and especially MHPG, t-tau, and p-tau (all $p<0.0001$) were lower in DLB as compared to AD whereas the $A\beta_{42}$ concentrations tended to be higher in DLB than in AD ($p=0.06$). We did not find an increase in median MHPG ($p=0.53$) or HVA concentrations ($p=0.43$) in DLB patients using dopaminergic medication relative to naïve DLB patients, hence these patients were not excluded from further data analysis.

Compared to our reference values, 72.7% of AD patients had a decreased CSF $A\beta_{42}$ (≤500 ng/l) as opposed to 45.5% of DLB patients ($p<0.05$). CSF t-tau was increased (≥350 ng/l) in 13.6% of DLB patients, compared to 84.1% of AD patients, whereas p-tau was increased (≥85 ng/l) in 0% of the DLB patients as opposed to 70.5% of the AD patients (all $p<0.0001$).

The above described differences in CSF parameters were present in AD and DLB patients irrespective of the certainty of diagnosis (i.e., possible or probable).

We demonstrated no association between the occurrence of behavioral problems, use of serotonergic medication, presence of white matter lesions on MRI or symptoms of autonomic dysfunction on one hand, and levels of the three neurotransmitter metabolites and brain-specific proteins t-tau, p-tau, or $A\beta_{42}$ on the other hand, neither in the entire group, nor in the DLB and AD patient groups separately. However, hallucinations were associated with lower MHPG (odds ratio (OR) 4.8, 95% CI 1.3–17.2, $p<0.001$) and HVA (OR 6.6, 95% CI 1.5–28.6, $p<0.001$) in DLB patients.

Repeating the analyses while adjusting for age, disease duration, and cognitive function did not markedly change our results.

Diagnostic accuracy

Univariate logistic regression analysis (carried out to discriminate DLB from AD) revealed that the sensitivity and specificity exceeded 80% for both t-tau and p-tau (Table 2). To assess the diagnostic value of neurotransmitter metabolites over the currently used combination of t-tau, p-tau, and $A\beta_{42}$, we performed multivariate logistic regression analysis using block entry regression.

The first block consisted of the the currently used brain specific proteins resulting in a Nagelkerke R^2 of 0.77 ($p < 0.001$, model $\chi^2(3) = 49.8$). In the second block MHPG, HVA, and 5-HIAA were added. Only MHPG showed significant added value to the constructed model based on block 1, improving Nagelkerke R^2 from 0.77 to 0.87 ($p < 0.001$, model $\chi^2(4) = 59.4$). ROC-curve analysis of the first model (based on t-tau, p-tau, and $A\beta_{42}$ demonstrated a sensitivity of 92.9% and a specificity of 90% (AUC 0.96). The subsequent addition of MHPG resulted in further improvement of the diagnostic accuracy with a sensitivity of 97.6% and a specificity of 95% (AUC 0.99).

DISCUSSION

We found that CSF concentrations of 5-HIAA, HVA, MHPG, t-tau, and p-tau were significantly lower in DLB than in AD, whereas CSF $A\beta_{42}$ tended to be higher in DLB. Most important, the combination of MHPG, p-tau, t-tau, and $A\beta_{42}$ analysis discriminated between AD and DLB with high diagnostic accuracy.

We are the first to rigorously investigate CSF MHPG in a large group of DLB patients. Only one earlier study examined CSF MHPG concentrations in DLB and, although the sample size was small ($n = 8$ subjects), findings are consistent with ours [22]. Moreover, our findings of lower concentrations of CSF MHPG are consistent with previous neuropathological studies, demonstrating degeneration of the locus coeruleus [31] and decreased concentrations of norepinephrine in putamen and neocortex, as compared to controls and AD patients [32]. Moreover, these findings are also compatible with the neuropathologically observed degeneration of nigrostriatal dopaminergic neurons in DLB [33], because reduced availability of dopamine results in a decrease of dopamine-derived neurotransmitter metabolites.

Interestingly, even though 5-HIAA and HVA were significantly lower in DLB as compared to AD, both did not contribute significantly to the constructed model, possibly because the direction of the effects were similar to MHPG and the strong correlation between CSF HVA and MHPG r 0.618, $p < 0.001$.

The brain specific proteins t-tau, p-tau, and $A\beta_{42}$ have been studied abundantly in both AD and DLB. We confirmed previous results that CSF $A\beta_{42}$ concentrations are low in DLB and close to the levels observed in AD patients [10–16], possibly reflecting the AD-like pathology observed in a proportion of the DLB patient upon postmortem examination, substantially limiting its discriminating properties. We also found increased t-tau levels in AD, but generally normal levels in DLB. Previous studies demonstrated conflicting results; some studies found elevated t-tau concentrations in DLB patients [14, 15], whereas other studies showed normal t-tau concentrations [10, 16, 37], as we did. In our study, as in two other reports [34, 37], p-tau concentrations were normal in DLB, although conflicting results were also reported [35]. These discrepancies underscore the importance of additional CSF parameters, in order to compose a more comprehensive and robust CSF profile.

Our results imply that the addition of CSF MHPG to the currently used analysis of brain-specific proteins can further improve the diagnostic differentiation between DLB and AD. The recent observation that up to 18% of patients suffering from dementia are treated with neuroleptics [36] further stresses the importance of diagnostic accuracy in early disease stages, because the use of neuroleptics in DLB patients is contraindicated for fear of increased physical and cognitive deterioration, as well as increased mortality [39].

Assessment of cognitive dysfunction is often performed by using the MMSE score. This score, however, has certain disadvantages, as it is an inaccurad method of cognitive assessment. For example, it is known that, as cognition is known to fluctuate in DLB, test–re-test variability is substantial. However, the MMSE is easy to perform and still the most commonly used cognitive screening assessment in daily practice, and therefore used in this study as well. The slightly lower MMSE scores in the AD subgroup might reflect the often more pronounced amnestic and orientation problems observed in AD.

This difference in MMSE likely does not affect the results for CSF t-tau, p-tau and $A\beta_{42}$, since it is known that CSF biomarker levels are hardly dependent on disease state and severity, especially in AD. It is, however, unknown whether this also applies to DLB and to CSF neurotransmitter metabolite levels. Therefore, to acknowledge these differences in MMSE score, but also in age and gender, between AD and DLB we included these parameters in our models, but this modification did not resulted in an altered AUC.

This study has several potential drawbacks. First, the retrospective design may have introduced selection bias. Only DLB and AD patients who underwent a lumbar puncture as part of their diagnostic workup were included in this study, possibly leading to selection of more atypical phenotypes. However, we included a substantial number of probable and even definite DLB patients, who showed similar CSF patterns.

Second, the clinical diagnosis was not confirmed neuropathologically in most patients. Misclassification may therefore have occurred. However, accuracy of the final clinical diagnosis was optimized using the following approach: thorough clinical and ancillary investigations at baseline; extensive follow-up (53 months for DLB and 50 months for AD patients) to monitor disease progression and development of new diagnostic signs; and establishing the diagnosis according to international consensus criteria in a specialized clinic. Third, the proposed model based on CSF biomarkers warrants validation in an independent and larger cohort. Despite these drawbacks, our results underline the importance of CSF analysis for the differentiation between dementia syndromes, specifically between AD and DLB. Moreover the addition of CSF MHPG to the currently used analysis of the brain-specific proteins t-tau, p-tau, and $A\beta_{42}$ may further improve this diagnostic differentiation. These results warrant validation in a prospective study with preferably neuropathological confirmation of the diagnosis and inclusion of patients with other types of dementia.

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