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Tau Protein, Aβ42 and S-100B Protein in Cerebrospinal Fluid of Patients with Dementia with Lewy Bodies

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Key Words

Dementia with Lewy bodies · Alzheimer's disease · Cerebrospinal fluid · Tau protein · Aβ42 · S-100B protein · Parkinson's disease · Laboratory marker

Abstract

The intra vitam diagnosis of dementia with Lewy bodies (DLB) is still based on clinical grounds. So far no technical investigations have been available to support this diagnosis. As for tau protein and β-amyloid$_{(1–42)}$ (Aβ42), promising results for the diagnosis of Alzheimer's disease (AD) have been reported; we evaluated these markers and S-100B protein in cerebrospinal fluid (CSF), using a set of commercially available assays, of 71 patients with DLB, 67 patients with AD and 41 nondemented controls (NDC) for their differential diagnostic relevance. Patients with DLB showed significantly lower tau protein values compared to AD but with a high overlap of values. More prominent differences were observed in the comparison of DLB patients with all three clinical core features and AD patients. Aβ42 levels were decreased in the DLB and AD groups versus NDC, without significant subgroup differences. S-100B levels were not significantly different between the groups. Tau protein levels in CSF may contribute to the clinical distinction between DLB and AD, but the value of the markers is still limited especially due to mixed pathology. We conclude that more specific markers have to be established for the differentiation of these diseases.

Introduction

Dementia with Lewy bodies (DLB) is the second most common type of dementia. A definite diagnosis of DLB can only be made on the basis of neuropathology [1].

As DLB patients often suffer from neuroleptic sensitivity [2], there is a need to improve clinical diagnosis of DLB to prevent these patients from receiving the wrong

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medication. For Alzheimer's disease (AD), a typical cerebrospinal fluid (CSF) pattern of β-amyloid$_{(1–42)}$ (Aβ42) and tau protein was postulated. A decrease in Aβ42 and an increase in tau protein levels have been found in most of the studies [3–6]. Total tau protein, the main structural component of neurofibrillary pathology, is assumed to be a marker of neuronal damage in CSF [7, 8], whereas Aβ42 is the main component of AD plaques [3–5].

Elevated levels of the astroglial marker S-100B protein have been observed in acute neurological disease and possibly indicate damage to astroglial cells in these diseases [9]. Elevated levels of S-100B have also been reported in neurodegenerative diseases like AD [10], frontotemporal dementia [11, 12] and amyotrophic lateral sclerosis [13]. High levels were reported in Creutzfeldt-Jakob disease and could even be seen in serum samples [14]. In these cases raised levels are considered to represent astroglial activation. Up to now no data has been available for the differential diagnostic value of S-100B protein in DLB patients.

For DLB, decreased Aβ42 and normal tau levels were reported in small groups of clinically diagnosed patients [15, 16], but this could not be verified in selected patients diagnosed post mortem [17]. We have now evaluated tau protein, Aβ42 and S-100B protein in a larger group of patients with DLB, AD and in nondemented controls (NDC) to evaluate whether these markers will help to differentiate between AD and DLB.

Materials and Methods

Patients with DLB

The group of DLB patients comprised 2 'definite' cases, 63 'probable' cases and 6 cases with Parkinson's disease dementia (PDD). Clinical records from all patients were analyzed according to the clinical criteria of McKeith et al. [1]. At least two of the core symptoms (fluctuating cognitive decline, extrapyramidal signs, and visual hallucinations) are required for the diagnosis of 'probable' DLB. All cases included fulfilled the criteria for at least 'probable DLB'. Twenty-three patients presented with two (group DLB-II) and 48 patients with all three core features (group DLB-III). All patients were hospitalized at least several days for the documentation of fluctuating cognition. Dementia was supported either by Mini Mental Status Examination (MMSE) [18] or extensive neuropsychological testing and medical history given by relatives. In 22 patients with DLB, MMSE was performed at the time of lumbar puncture. Hallucinations and parkinsonism could not be attributed to medication in all patients that were included. If parkinsonism had been present for a long time (more than 1 year) before dementia was diagnosed, such patients were classified according the established criteria as PDD (n = 6). The other 65 cases were designated 'probable' DLB. All patients underwent brain imaging to exclude other diseases. Risk factors for vascular lesions were recorded.

In 2 cases, clinical diagnosis was confirmed by neuropathological examination using paraffin-embedded formalin-fixed brain tissue and immunochemistry. Distribution of Lewy bodies and frequency were evaluated on alpha-synuclein immunostains according to the consensus guidelines for the pathologic diagnosis of DLB [1].

Patients with AD

Additionally, we analyzed 67 AD patients and 41 nondemented controls. Diagnosis of AD was made according to the NINCDS-ADRDA work group criteria [19]. None of the AD patients suffered from hallucinations or extrapyramidal signs. All included patients were at least classified as 'probable' AD. Three cases of this group were neuropathologically verified using paraffin-embedded formalin-fixed brain tissue and immunochemistry.

Dementia was also diagnosed either with MMSE or extensive neuropsychological testing and history given by the relatives. In 45 patients with AD, MMSE was performed at the time of lumbar puncture. All patients underwent brain imaging to exclude other diseases. Risk factors for vascular lesions were recorded.

Patients without Dementia

The NDC group (n = 41) consisted of patients with depression (n = 14), acute psychosis (n = 5), old cerebral ischemic lesions (n = 5), radicular syndromes (n = 3), alcoholic delirium (n = 2), multiple sclerosis (n = 2) and 1 patient each with carpal tunnel syndrome, shoulder-hand syndrome, schizophrenia, diabetic neuropathy, myopathy, epileptic seizure, hydrocephalus, neuritis vestibularis, transient myelitis, and articular rheumatism.

Age at the time of lumbar puncture, sex distribution, duration of disease and MMSE scores of these groups are given in table 1.

Tau Protein, Aβ42 and S-100B Protein

Samples of all groups were obtained by lumbar puncture. Aliquots for Aβ42 and tau protein were stored at ±4°C and analyzed within 2 days. Aliquots for S-100B protein were stored at –80°C until measurement.

All samples were analyzed using commercially available assays [4, 14, 20–22] (tau protein and Aβ42: Innotest hTAU Antigen and Innotest β-Amyloid$_{(1–42)}$, Innogenetics, Ghent, Belgium; S-100B protein: Sangtec Medical, Bromma, Sweden). In most reports, normal levels for tau protein were below 450 pg/ml [4–7]. Aβ42 should be above 450 pg/ml in nondemented patients [3–6] and S-100B levels were below 2 ng/ml in control CSF samples [14, 22].

Tau protein was analyzed in 179 cases. Aβ42 levels were determined in 173 patients and S-100B protein was measured in 113 CSF samples (table 2).

Statistical Analysis

The distribution of CSF marker levels between subgroups of the study population was compared by nonparametric rank tests (for two groups: Wilcoxon-Mann-Whitney U test, for more than two groups: Kruskal-Wallis test).

Table 1. Epidemiological data, MMSE score and clinical classification

	DLB	AD	NDC
Age at the time of lumbar puncture[1], years	50–89 (median: 72)	45–86 (median: 66)	45–56 years (median: 51 years)
Sex (m:f)	40:31	23:44	15:26
Duration of disease[2], months	1–180 (median: 16.5)	6–80 (median: 24)	not applicable
MMSE score[2]	11–25 (median: 16.5)	1–26 (median: 17.5)	not applicable
Exact diagnosis	63 probable DLB 6 PDD 2 definite DLB	64 probable AD 3 definite AD	see text

[1] $p < 0.001$ between NDC and AD/DLB.
[2] Before lumbar puncture.

Table 2. Overview of analysis of markers and groups

	DLB			AD			NDC		
	median	range	n	median	range	n	median	range	n
Tau protein*, pg/ ml	333	97–1,579	71	543	133–1,200	67	130	59–486	41
Aβ42**, pg/ml	403	100–1,339	71	382	119–1,011	61	818	485–1,322	41
S-100B protein, ng/ml	2.28	0.83–6.76	59	2.33	0.71–5.18	32	1.87	108–2.82	22

* $p < 0.001$ between AD/DLB and NDC and $p < 0.05$ between AD and DLB; ** $p < 0.001$ between AD/DLB and NDC.

Results

Tau Protein

Tau protein levels ranged between 97 and 1,579 pg/ml (median: 333 pg/ml) in the DLB group, between 133 and 1,200 pg/ml (median: 543 pg/ml) in the AD group and between 59 and 486 pg/ml (median: 130 pg/ml) in the NDC group (fig. 1). 43 DLB patients showed tau levels below and 28 showed tau levels above 450 pg/ml.

There were significantly higher levels of tau protein in the AD and DLB groups compared to the NDC group ($p < 0.001$). Tau protein levels were higher in the AD group compared to the DLB group ($p = 0.003$).

β-Amyloid$_{(1–42)}$

Aβ42 levels ranged between 100 and 1,339 pg/ml (median: 403 pg/ml) in the DLB group, between 191 and 1,011 pg/ml (median: 382 pg/ml) in the AD patients and between 485 and 1,322 pg/ml (median: 818 pg/ml) in the NDC group (fig. 1).

Aβ42 levels were significantly decreased in AD and DLB compared to NDC ($p < 0.001$). There was no statistically significant discrimination between AD and DLB by Aβ42 ($p = 0.85$).

S-100B Protein

The levels of S-100B protein ranged between 0.83 and 6.76 ng/ml (median: 2.28 ng/ml) in the DLB patients, between 0.71 and 5.18 ng/ml (median: 2.33 ng/ml) in the AD patients and between 1.08 and 2.82 ng/ml (median: 1.87 ng/ml) in the control group (fig. 1). S100-B protein was analyzed in 22 patients of the NDC group: Four patients with depression showed levels between 1.26 and 2.51 ng/ml (median: 2.14 ng/ml). Five patients with isch-

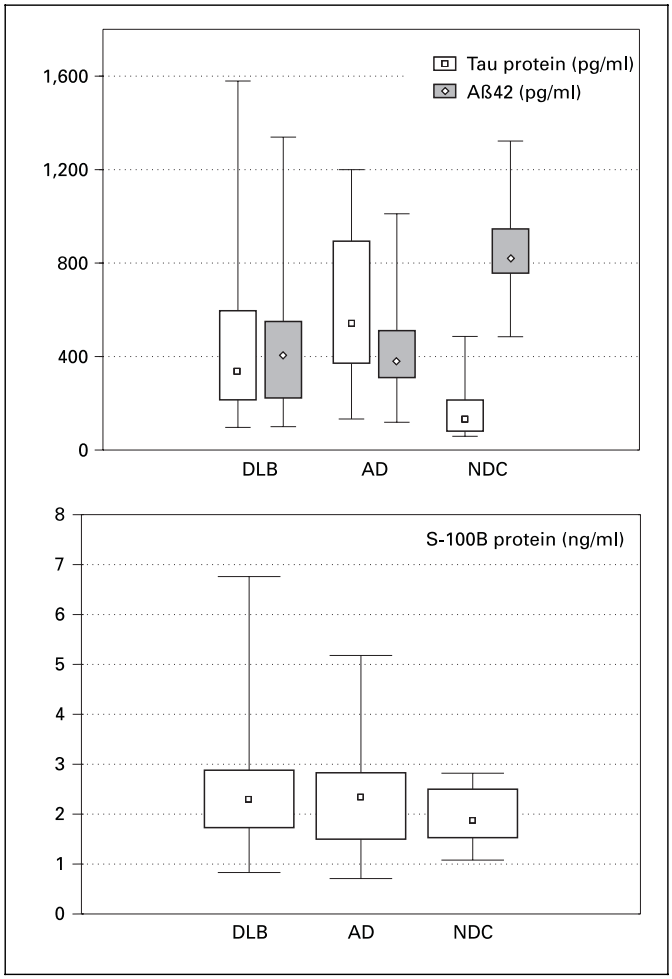

Fig. 1. Box plots of tau protein (ng/ml), Aβ42 (pg/ml), and S-100B protein (ng/ml) in CSF of patients suffering from DLB, AD and NDC (□ median, ☐ 25–75%, ⊥ min–max).

emia had levels between 1.53 and 2.82 ng/ml (median: 2.66 ng/ml). The levels of 5 patients with peripheral neurological disorder varied between 1.08 and 2.51 (median: 2.1 ng/ml). S100B level of the patient with acute psychosis was 1.37 ng/ml, with myopathy 2.55 ng/ml, with hydrocephalus 2.6 ng/ml, neuronitis vestibularis 2.35 ng/ml, epileptic seizures 1.53 ng/ml, articular rheumatism 1.82 ng/ml, transient myelitis 2.6 ng/ml, and the patient with alcoholic delirium showed an S100B level of 1.26 ng/ml.

S-100B neither discriminated between NDC and the two dementia groups (p = 0.36: AD vs. NDC; p = 0.11: DLB vs. NDC) nor between AD and DLB (p = 0.699).

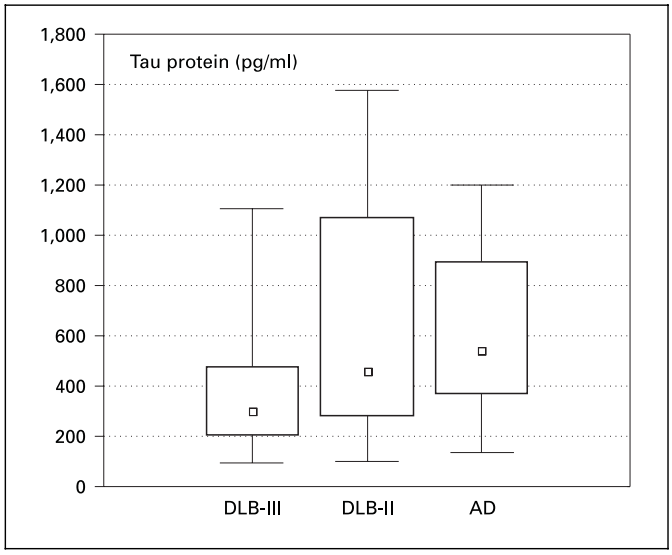

Fig. 2. Tau protein (ng/ml) in patients suffering from AD and DLB with two core features [1] (DLB-II, n = 23) and with three core features (DLB-III, n = 48) (□ median, ☐ 25–75%, ⊥ min–max).

Analysis of the Groups according to Clinical Presentation

Variation of MMSE and duration of disease between AD and DLB groups was not significant ($p > 0.05$), nor was the variation of age at the time of lumbar puncture between AD and DLB ($p > 0.05$). Age at the time of lumbar puncture was significantly different between the demented groups (AD and DLB) and the NDC group ($p < 0.001$).

In the group of DLB patients presenting with two core features (DLB-II, n = 23), tau protein ranged between 99 and 1,579 pg/ml (median: 448 pg/ml). Tau protein levels in the DLB-III group (patients fulfilling all three main criteria, n = 48) ranged between 97 and 1,104 pg/ml (median: 324 pg/ml) (fig. 2). Tau protein levels of the DLB-III group were significantly lower compared to the AD group ($p < 0.001$) but not between DLB-II and AD ($p = 0.89$). S-100B and Aβ42 levels did not show subgroup-specific alterations.

In the group of 6 patients with PDD values, tau protein levels ranged between 195 and 377 pg/ml (median: 235 pg/ml). In comparison, tau protein levels in the group of 63 patients with 'probable' DLB ranged between 97 and 1,579 pg/ml (median: 356 pg/ml). Again S-100B and Aβ42 levels did not show subgroup-specific alterations.

We found slightly higher S-100B levels in the DLB group with MMSE >18 (mean: 2.4 ng/ml) compared to the group with MMSE <18 (mean: 2.0 ng/ml).

Analysis of Neuropathologically Verified Cases

In the CSF of the 2 'definite' DLB cases, tau protein was 466 and 289 pg/ml, respectively and Aβ42 was 542 and 333 pg/ml, respectively. S-100B protein was measured only in 1 definite DLB case, at 1.62 ng/ml. Both patients were clinically classified as 'probable' DLB and fulfilled all three core criteria. The 3 'definite' AD cases presented with tau protein levels between 332 and 1,200 pg/ml and S-100B protein levels between 3.4 ng/ml and 2.5 ng/ml (Aβ42 was not done).

Analysis according to Insulin Medication

Twelve patients in the DLB group were known to have diabetes mellitus. Two of these used insulin medication. Tau protein values for these patients were 259 and 300 pg/ml, and S-100B protein levels were 2.17 and 2.85 ng/ml. Aβ42 levels were 704 and 698 pg/ml in the 2 DLB patients with insulin-dependent diabetes mellitus and ranged between 191 and 795 pg/ml (median: 519 pg/ml) in the DLB group with non-insulin-dependent diabetes mellitus. There were 2 patients with AD and diabetes mellitus. One was insulin-dependent. This patient showed a tau protein value of 667 pg/ml, Aβ42 level was 847 pg/ml and S-100B protein was 2.05 ng/ml.

Discussion

This is the first study in which CSF levels of tau protein, Aβ42 and S-100B protein were analyzed in a larger group of patients with DLB in comparison with AD patients. In smaller studies, discrepant laboratory findings for tau protein and Aβ42 were found [15–17, 23–26]. In two studies, it was suggested that DLB might be differentiated from AD by tau protein and Aβ42 [15, 16]. However, in both studies no analysis according to clinical core features was made and, surprisingly, decreases in Aβ42 were found in the clinical control group [16]. In our population of clinically well-defined DLB and AD patients, the CSF levels of tau protein discriminated significantly between AD and DLB and NDC. Aβ42 and S-100B protein in DLB did not differ significantly from the AD group.

We are aware that our study group is mainly based on clinical diagnoses. Molecular genetic studies have revealed that both AD and DLB share an elevated ApoE4 allele frequency [27]. The analysis of further laboratory markers might be stratified according to genetic markers. However, because of the homogeneity of our results, this might not be necessary for tau protein, Aβ42 and S-100B protein. We included solely patients with enough clinical information and detailed medical history given by the relatives to classify them as 'probable' DLB according to established criteria.

Up to now, no data have been available on S-100B levels in DLB. In a case report of neurodegenerative dementia, it was shown that S-100B levels correlate positively with disease progression, possibly due to gliosis, while tau protein can decrease due to neuronal loss [28].

It has recently been shown that insulin can increase Aβ42 levels in CSF [29], and in fact 3 of our patients who suffered from insulin-dependent diabetes mellitus had higher levels of Aβ42.

DLB patients often present with extrapyramidal signs at onset, not only in PDD. The onset of dementia represents the onset of cortical neuronal damage, which may apparently lead to the elevation of markers indicating neurodegeneration (e.g. tau protein). Our findings support this hypothesis. Massive neuronal loss occurs in many of the DLB cortical regions to a similar extent to that seen in AD, in addition to the classical sites of neuronal death in the brainstem, as in PD [30]. Patients with PD alone without dementia showed tau protein and Aβ42 levels comparable to NDC [15, 23]. Our patients with PDD presented with lower tau-protein levels than DLB patients. Our group with PDD is certainly too small for a valid comparison. However, our observation supports the idea that patients with parkinsonism, visual hallucinations (which may reflect a medication effect) and elevated CSF levels of tau protein are more likely to be DLB patients than patients with PD.

All patients of our DLB group exhibited at least two core features and were classified as having 'probable' DLB, but the majority of our patients exhibited all three core features with fluctuating cognition, spontaneous extrapyramidal signs and visual hallucinations. These DLB patients showed significantly lower tau protein levels compared to the AD patients of our group. Reciprocally 74% of our DLB patients with tau protein levels below 450 pg/ml showed all three core features. According to the literature, in autopsy-proven DLB patients 73% showed concomitant AD pathology with higher Braak stages (3–6) and only 27% with lower Braak stages (0–2). The clinical diagnostic accuracy for these autopsy-proven DLB cases was higher for patients with low (75%) compared to high (39%) Braak stage [30–32]. Our patients, fulfilling all three core criteria (DLB-III), have lower tau levels, whereas patients with only two or less core features may represent a group with AD mixed pathology, pronounced neuronal cell loss and therefore higher tau levels. The fact that tau protein discriminates between our DLB-III group,

showing all three core features, and AD patients is of low clinical relevance since e.g. patients with mixed pathology may also show neuroleptic sensitivity. CSF of DLB patients with mild tau pathology and with mild neuron loss will further need to be examined.

Whether or not other markers like phospho-tau and the analysis of the spectrum of amyloid peptides will help in this differentiation must be seen in separate studies [26, 33, 34]. We conclude from our results that the value of the markers measured here for the differentiation of DLB from AD is limited, but seems to be of differential diagnostic relevance for PDD and DLB.

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