ARCHIVAL REPORT

Cerebrospinal Fluid Biomarkers in Parkinson's Disease with Dementia and Dementia with Lewy Bodies

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Background: Clinical criteria for differentiating Parkinson's disease (PD) with dementia (PDD) from dementia with Lewy bodies (DLB) are unsatisfactory. Their existence as distinct clinicopathologic entities is still debated, although the burden of Alzheimer's disease (AD) pathology seems higher in DLB. Thus, analysis of cerebrospinal fluid (CSF) biomarkers (β-amyloid$_{1-42}$ [Aβ42], total tau, and hyperphosphorylated tau [p-tau]) in living subjects might provide significant pathophysiological information on these diseases.

Methods: Cerebrospinal fluid biomarkers were measured in DLB ($n = 19$), PDD ($n = 18$), and AD ($n = 23$) subjects matched for age, sex, and dementia severity, as well as in PD ($n = 20$) and normal control subjects ($n = 20$).

Results: DLB showed the lowest mean CSF Aβ42 levels, with a negative association to dementia duration ($\rho = -.42$, $p = .07$). In DLB patients, mean CSF total tau levels were significantly lower than in AD patients (508 ± 387 vs. 960 ± 619, respectively) but twofold to threefold higher than in PDD (286 ± 184), PD (160 ± 64), or normal control subjects (177 ± 76), with a positive association to dementia severity (Mini-Mental State Examination: $\rho = -.54$, $p = .02$; Milan Overall Dementia Assessment: $\rho = -.66$, $p = .002$). PDD patients had mean CSF Aβ42 and total tau levels similar to those seen in PD patients. Hyperphosphorylated tau was significantly increased in the AD group only.

Conclusions: Cerebrospinal fluid Aβ42 and total tau have a different behavior in DLB and PDD, being related to duration and severity of dementia in DLB alone. Hyperphosphorylated tau is not significantly altered in these conditions.

Key Words: CSF biomarkers, dementia, dementia with Lewy bodies, parkinsonisms, Parkinson's disease, Parkinson's disease with dementia

It is well known that approximately 40% of patients with Parkinson's disease (PD) develop cognitive impairment severe enough to fulfill diagnostic criteria for dementia (1). More recent estimates suggest that 25% to 30% of PD patients have dementia (PDD), which accounts for 3% to 4% of degenerative dementias (2). Parkinson's disease with dementia is characterized by PD with later occurring dementia, while in dementia with Lewy bodies (DLB), dementia precedes or coincides with parkinsonism. However, extrapyramidal signs (EPS) may be lacking in up to 50% of DLB cases (3).

Whether PDD and DLB are distinct clinicopathologic entities is still debated (4–6). A matter of controversy is the actual impact of the overlap of underlying pathologies, i.e., Lewy bodies (LBs), β-amyloid plaques, and neurofibrillary tangles (NFT), on the clinical picture of PDD and DLB (3,7,8) and whether DLB patients with and without concurrent Alzheimer's disease (AD) pathology should be considered as a distinct group (6,9). According to studies using α-synuclein immunostaining, the cumulative effects of progressive PD pathology seem to be the main causative factor of cognitive impairment in these entities (4,10–12). However, the close interaction between α-synuclein and tau, as well as their co-localization in LBs (13), support the view that synucleinopathies and tauopathies cannot be rigidly regarded as separated entities (14).

Although pathology is considered to be the gold standard for establishing the etiology of dementia in PD, pathological studies mostly give the terminal picture of a disease process developing over decades (15). Cerebrospinal fluid (CSF) analysis might represent the best way to evaluate how relevant is the contribution of AD pathology throughout the clinical course of these diseases. Previous studies have shown that 1) CSF levels of β-amyloid$_{1-42}$ (Aβ42) are inversely related to brain density of senile plaques (16), a typical neuropathological feature of both AD and DLB; 2) CSF levels of total tau reflect the intensity of neuronal damage and degeneration; and 3) CSF hyperphosphorylated tau (p-tau), a putative marker of NFT presence (17), is exclusively derived from the brain and is particularly sensitive to the early Braak stage of tau pathology targeting the hippocampal formation (18). These CSF biomarkers have consistently been shown to be useful for diagnosing incipient AD, with a sensitivity and specificity of approximately 90% (19–21); p-tau has also been shown to be useful in clinical discrimination between AD and DLB (22).

Cerebrospinal fluid studies carried out in DLB have mostly compared DLB with AD patients (23–26), while only few data are available for PDD (27). To investigate whether CSF analysis may show different patterns in PDD and DLB, reflecting a different contribution of AD pathology to dementia in these diseases, we measured Aβ42, total tau, and p-tau in the CSF of patients with a clinical diagnosis of PD, PDD, DLB, and AD and of age-matched, cognitively normal subjects.

Methods and Materials

The PD, PDD, DLB, and AD patients were enrolled from a consecutive series of patients referred to the Neurology Section in the period January 2003 to December 2005 for diagnostic

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Table 1. Demographics

	Number (F/M)	Age (years, mean ± SD)	Education (years, mean ± SD)	Duration of Dementia (years, mean ± SD)	MMSE (mean± SD)
Control Subjects	20 (10/10)	60 ± 12	7.5 ± 3	–	27.5 ± 1.8
PD	20 (9/11)	62 ± 6	8.2 ± 4	–	27.4 ± 1.8
PDD	8 (8/10)	65 ± 5	7.4 ± 3	7.0 ± 4.2	16.8 ± 3.4
DLB	19 (9/10)	70 ± 7	8.8 ± 5	4.0 ± 1.0	13.9 ± 4.3
AD	23 (13/10)	70 ± 6	7.9 ± 6	4.9 ± 2	15.5 ± 4.5

There were no significant differences among PDD, DLB, and AD in age, education, and MMSE scores.

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; SD, standard deviation.

evaluation of cognitive impairment and/or movement disorder. All of them underwent a thorough clinical and neurological evaluation comprehensive of neuropsychological assessment (the Mini-Mental State Examination [MMSE] [28] and the cognitive section of the Milan Overall Dementia Assessment [MODA], a global measure of dementia standardized in the Italian population [29]), an evaluation of psychobehavioral disturbances (NeuroPsychiatric Inventory) (30) and cognitive fluctuations (31), brain magnetic resonance imaging (MRI) for excluding vascular damages or other lesions, and lumbar puncture for CSF analysis upon informed consent by patient and relatives/caregivers.

Diagnosis of PD was based on standard criteria (32) and diagnosis of probable DLB or PDD was according to McKeith *et al.* criteria (33). As contrast groups, 23 AD patients and 20 age-matched cognitively normal subjects were enrolled. The AD patients fulfilled the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for a clinical diagnosis of probable AD (34). They were matched for education and severity of cognitive impairment with the DLB and PDD patients. None of the AD patients had cognitive fluctuations, visual hallucinations, or parkinsonism. The control subjects underwent CSF tapping for diagnostic reasons (headache, suspected myelopathy). None of them were referred to our service because of cognitive complaint, and the absence of any cognitive deficit was confirmed by their relatives. Regardless of the clinical history, a MMSE score of at least 26 was required for inclusion in the study.

According to the standard protocol used routinely in our ward, lumbar puncture was performed early in the morning, to limit potential circadian fluctuation in CSF protein concentrations, after an overnight rest, in the lateral decubitus position at the L4–5 interspace with a 20-gauge spinal needle. After CSF collection, individuals remained at bed rest for at least 2 hours. Cerebrospinal fluid (10 mL) was collected in sterile polypropylene tubes, centrifuged for 10 minutes at 4000*g*, and .5 mL aliquots were immediately frozen at −80°C. Cerebrospinal fluid biomarkers—Aβ42, total tau, and p-tau—were measured with enzyme-linked immunosorbent assay (ELISA) method (Innotest β amyloid 1–42, hTAU-Ag, p-TAU 181 Ag, Innogenetics NV, Gent, Belgium).

According to standard cutoffs (19), we considered as pathological values of Aβ42 < 500 pg/mL, total tau > 400 pg/mL, and p-tau > 80 pg/mL.

The study was approved by our Institutional Review Board, and all subjects or their relatives/caregivers signed an informed written consent before undergoing lumbar puncture.

Statistical Analysis

Considering the nonnormal distribution of the data, nonparametric analyses were performed. Kruskal-Wallis test (nonparametric analysis of variance [ANOVA]) was applied to identify differences in neuropsychological scores and CSF biomarkers in the five groups considered; when significant, the Mann-Whitney test for comparison was used. For evaluating differences in the neuropsychological tests, we compared PDD, DLB, and AD patients, accepting $p < .05$ as statistically significant. Regarding CSF biomarkers, multiple comparisons were carried out among the five groups considered. Taking into account the number of comparisons, $p < .008$ was considered statistically significant after Bonferroni correction. Spearman correlation was used to evaluate the association between duration of disease and CSF biomarkers.

Results

Our sample (Table 1) was composed of 20 PD patients, 18 PDD patients, 19 DLB patients, 23 AD patients, and 20 control subjects. Despite variable duration of parkinsonism prior to dementia (range: 2–9 years), the PDD patients were clinically homogeneous in that all initially presented with what appeared to be typically levodopa-responsive PD. By contrast, not all DLB patients exhibited EPS; additionally, in those who displayed parkinsonism during the course of disease (12 of 19, 64%), dementia was invariably the presenting feature. Visual hallucinations were present in 15 of 19 DLB patients, and in 9 of them, the hallucinations represented an early feature of the disease. Cognitive fluctuations occurred in 14 of 19 DLB patients. Six of 19 DLB patients showed EPS, fluctuations, and visual hallucinations; 6 patients showed cognitive fluctuations and visual hallucinations; 4 patients had EPS and visual hallucinations; and 3 patients showed EPS and fluctuations.

The DLB, PDD, and AD groups did not show significant differences with regard to age and education. Although duration of dementia was longer in the PDD group, dementia severity, as expressed by mean MMSE scores, was similar in the PDD, the DLB, and the AD groups. In PDD patients, mean duration of motor disturbances prior to dementia onset was 5.3 ± 2.1 years (range: 2–9, median: 4.6 years). In Table 2, neuropsychological scores obtained by PD, PDD, DLB, and AD patients are reported. Nonparametric ANOVA (Kruskal-Wallis test) showed that all neuropsychological scores were significantly different among groups (Table 2). Multiple group comparisons (Mann-Whitney test) showed that DLB patients performed significantly worse than PDD patients on tests assessing attention (digit cancellation test), reversal learning, and semantic word fluency. Conversely, DLB patients performed better than AD patients on orientation

Table 2. Neuropsychological Scores Obtained in PD, PDD, DLB, and AD Groups

MODA Items	CTRL ($n = 20$)	PD ($n = 20$)	PDD ($n = 18$)	DLB ($n = 19$)	AD ($n = 23$)
Orientation	12.6 ± .6	12.5 ± .9	7.9 ± 2.6	7.6 ± 3.8	5.4 ± 3.2[e]
	13 (11–13)	*13 (10–13)*	*8 (3–12)*	*9 (1–13)*	*6 (0–10)*
Digit Cancellation Test	9.8 ± .4	8.5 ± 1	4.7 ± 1.7	2.6 ± 1.7[b]	4.6 ± 1.9
	10 (9–10)	*9 (7–10)*	*5 (0–7)*	*3 (0–5)*	*5 (1–8)*
Reversal Learning	4.9 ± .2	4.6 ± .6	4.2 ± 1.2	2.9 ± 1.7[c]	2.1 ± 1.1
	5 (4–5)	*5 (3–5)*	*4 (0–5)*	*3 (0–5)*	*2 (0–3)*
Logical Reasoning	6 ± 0	5.3 ± .5[a]	3.5 ± 1.4	3.2 ± 2	1 ± 1.1[e]
	6 (6–6)	*5 (5–6)*	*4 (0–5)*	*3 (0–6)*	*1 (0–4)*
Prose Memory	7.9 ± .4	5.8 ± 2.5[a]	2.2 ± 2	1.3 ± 1.3	1.3 ± 1.7
	8 (7–8)	*6.5 (0–8)*	*2 (0–5)*	*1 (0–4)*	*1 (0–4)*
Semantic Word Fluency	5 ± 0	4.1 ± 1[a]	2.5 ± .8	1.6 ± .6[c]	1.7 ± .9
	5 (5–5)	*4.5 (2–5)*	*3 (1–4)*	*2 (1–3)*	*2 (0–4)*
Token Test	5 ± 0	4.9 ± 0.4	3.9 ± 1	2.9 ± 1.7	1.7 ± .9
	5 (5–5)	*5 (4–5)*	*4 (2–5)*	*3 (0–5)*	*2 (0–3)*
Finger Agnosia	4.9 ± .4	4.1 ± 1.5	1.6 ± 1.5	.9 ± .8[d]	2 ± 1
	5 (4–5)	*5 (0–5)*	*1 (0–4)*	*1 (0–2)*	*2 (0–4)*
Construction Apraxia	2.9 ± .4	2.1 ± .5[a]	.7 ± .7	.7 ± .6[d]	1.4 ± .7
	3 (2–3)	*2 (1–3)*	*1 (0–2)*	*1 (0–2)*	*1 (0–3)*
Street's Completion Test	3 ± 0	2.8 ± .4	3 ± 0	.9 ± .7	1.1 ± 1.1
	3 (3–3)	*3 (2–3)*	*1 (0–3)*	*1 (0–2)*	*1*

Values are expressed as mean ± SD, *median (range)*. AD, Alzheimer's disease; CTRL, control subjects; DLB, dementia with Lewy bodies; MODA, Milan Overall Dementia Assessment; PD, Parkinson's disease; PDD, Parkinson's disease with dementia.

[a] $p < .01$ versus CTRL.
[b] $p < .01$ versus PDD and AD.
[c] $p < .01$ versus PDD.
[d] $p < .01$ versus AD.
[e] $p < .01$ versus DLB and PDD (Mann-Whitney test).

and logical reasoning but worse on tests assessing visual-spatial function (construction apraxia), digit cancellation test, and finger agnosia. Significant differences also emerged between PD patients and normal control subjects. In fact, PD patients had a worse performance on tests evaluating logical reasoning, verbal memory, semantic fluency, and visual-spatial function.

CSF Analysis

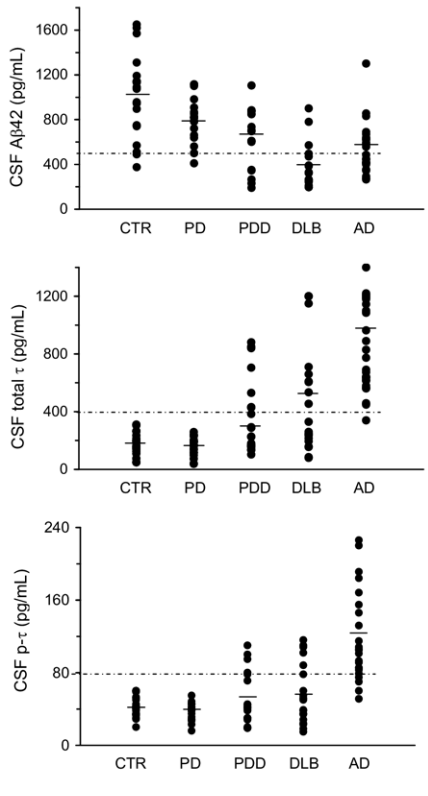
In Table 3, mean values of CSF biomarkers measured in all groups considered are reported. The scatter of the values is reported in Figure 1. Nonparametric ANOVA (Kruskal-Wallis test) showed that Aβ42 (χ^2: 42.051, $p < .0001$) and total tau (χ^2: 53.629, $p < 0.0001$) values were significantly different in the groups considered. Mann-Whitney test showed the lowest CSF Aβ42 levels in DLB patients ($p = .005$ vs. PDD) and significantly higher CSF total tau levels than in control subjects and PD patients. No significant difference was documented between the DLB and the PDD groups with respect to p-tau, whose levels were significantly increased in the AD group only. As expected, total tau and p-tau were pathologically high in the great majority of AD patients (96% and 78%, respectively), while Aβ42 was markedly reduced in half of the AD cases. Conversely, almost

Table 3. CSF Biomarkers (pg/mL) in the Groups Studied

	CSF Aβ42				CSF Total Tau				CSF P-Tau			
Control Subjects ($n = 20$)	1014 ± 368				177 ± 76				42 ± 11			
	1082 (374–1650)				*176 (49–311)*				*42 (20–60)*			
PD ($n = 20$)	788 ± 203				160 ± 64				37 ± 9			
	817 (409–1115)				*168 (38–259)*				*39 (16–55)*			
PDD ($n = 18$)	647 ± 269				286 ± 184				52 ± 29			
	700 (190–1104)				*227 (103–840)*				*42 (19–110)*			
DLB ($n = 19$)	373 ± 195				508 ± 387				55 ± 32			
	320 (195–900)				*455 (80–1200)*				*50 (15–116)*			
AD ($n = 23$)	544 ± 233				960 ± 619				119 ± 50			
	485 (265–950)				*829 (340–1500)*				*105 (61–226)*			
Mann-Whitney Test	PD	PDD	DLB	AD	PD	PDD	DLB	AD	PD	PDD	DLB	AD
Control Subjects	.03	.002	.000	.000	.50	.07	.002	.000	.26	.75	.47	.000
PD	–	.19	.000	.001	–	.03	.001	.000	–	.31	.21	.000
PDD		–	.005	.13		–	.08	.000		–	.77	.000
DLB			–	.002			–	.004				.000

Values are expressed as mean ± SD, *median (range)*.

Aβ42, β-amyloid$_{1-42}$; AD, Alzheimer's disease; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; p-tau, hyperphosphorylated tau.



	PDD (no.18)	DLB (no. 19)	AD (no. 23)
Aβ42 <500 pg/mL	6 (33%)	17 (89%)*	11 (49%)
total τ > 400 pg/mL	4 (22%)	10 (53%)	22 (96%)#
p-τ > 80 pg/mL	3 (17%)	5 (26%)	18 (78%)¶

* p < 0.01 vs. AD, < 0.001 vs. PDD; # p < 0.01 vs. DLB, < 0.0001 vs. PDD; ¶ p < 0.01 vs. DLB, < 0.001 vs. PDD (Fisher's exact test)

Figure 1. Scatterplot of CSF biomarker values in the four groups studied. The table at the bottom shows the different behaviors shown by the three dementia groups, according to the cutoff values. AD, Alzheimer's disease; CSF, cerebrospinal fluid; CTR, control subjects; DLB, dementia with Lewy bodies; PD, Parkinson's disease; PDD: Parkinson's disease with dementia.

90% of DLB cases had low Aβ42 and half of them showed high total tau. Only one third of PDD patients showed low Aβ42, and only one quarter had increased total tau (Figure 1). Two of the 18 PDD patients and 4 of the 19 DLB patients showed a CSF pattern similar to that typically reported for AD with pathological values in all the three biomarkers. Of the 23 AD patients, 4 had a CSF profile analogous to that seen in the DLB group, with decreased Aβ42 and increased total tau but normal p-tau.

The correlation analysis between duration of dementia and CSF biomarkers disclosed different patterns in these diseases. In DLB, CSF Aβ42 was negatively associated with dementia duration ($\rho = -.42$, $p = .07$), while total tau and p-tau did not show any relationship with dementia duration in any of the groups.

We also looked at the correlations between dementia severity, as expressed by patients' scores on cognitive tests, and CSF biomarkers. Interestingly, significant results were found exclusively in the DLB group, with inverse associations of total tau with both the MMSE ($\rho = -.54$, $p = .02$) and the MODA ($\rho = -.66$, $p = .002$) scores; the relation of Aβ42 to these indices of dementia severity was less strong ($\rho = .27$ and .35, respectively) and did not reach statistical significance.

Discussion

Our data indicate that CSF biomarkers behave differently in DLB and PDD.

In fact, Aβ42—a marker inversely related to senile plaque density—was remarkably reduced, and total tau—a marker of axonal damage—was increased in DLB alone. Although p-tau, a CSF biomarker more specific than total tau for NFT pathology, did not significantly differ between DLB and PDD, our results remain consistent with recent observations from autopsy specimens (35) that the burden of AD pathology, namely amyloid deposition, is greater in DLB than PDD.

There is significant biological and clinical overlap between DLB and PDD, which are considered Lewy body diseases (LBD) sharing a pathological substrate (5,36). In light of available clinical and neuropathological data, it has been unclear whether DLB and PDD are distinct conditions or part of a spectrum of diseases with variable combinations of Lewy body and AD pathology (14). The majority of studies suggest that Lewy body pathology is the main substrate driving the progression of cognitive impairment in PD, while this has been more controversial in DLB (4,36).

The possible pathological differences between DLB and PDD remain to be better elucidated. Compared with PDD brains, DLB cases show quantitative rather than qualitative differences, with less severe neuronal loss in the substantia nigra, more frequent involvement of the C2-3 hippocampal area and of the amygdala, and more severe involvement of the neocortex by LBs (6,37). Although a minority of DLB cases show only a negligible cortical deposition of senile plaques (diffuse or pure Lewy body disease), most of them can be differentiated from PDD cases by more substantial deposition of cortical β-amyloid (Aβ) (38,39) and from AD cases by the absence of significant NFT accumulation in the neocortex (40). Compared with AD patients, most DLB cases also have fewer neuritic plaques but more Aβ positive diffuse plaques (40), which is consistent with our observation of lower Aβ42 levels in DLB than AD patients.

The amount of cortical Aβ deposition has been reported to correlate with dementia severity in DLB but not in PDD (6,41). Our CSF data are in agreement with these findings, since DLB patients showed the lowest Aβ42 levels and such a decrease was related to disease duration and, albeit insignificantly, to global severity of cognitive impairment. Dementia severity was also associated with increased total tau levels in DLB but not in PDD.

Cerebrospinal fluid total tau has been found to be increased in DLB compared with normal control subjects by some investigators (42) but not by others (24). Increased total tau levels have also been reported for PDD patients in one study (27). Kanemaru *et al.* (24) and Mollenhauer *et al.* (25) reported lower total tau levels for DLB compared with AD patients. In contrast, in an autopsy verified series, Tschampa *et al.* (42) found that CSF total tau levels in DLB were as increased as those observed in AD but were unrelated to NFT density, suggesting that CSF total tau is a nonspecific marker of axonal damage and/or degeneration. We cannot exclude, however, that its elevation and correlation with dementia severity may reflect more subtle forms of cytoskeletal pathology involving tau protein that has not yet resulted in overt NFT formation.

In the present study, decreased Aβ42 and increased total tau were found in both DLB and AD, but in the latter disease, they were unrelated to severity and duration of dementia. This indicates that plaque deposition and axonal damage continue to increase and are likely to significantly contribute to cognitive

impairment as the illness progresses in DLB alone. Conversely, in AD, these alterations are present even 6 years before clinical onset of dementia (20); therefore, these CSF biomarkers are considered state markers of AD, being not related to dementia progression once clinical AD is established.

In PD, the risk of developing dementia becomes greater along the path of disease progression in the brain, and dementia usually develops late. Alpha-synuclein induces fibrillization of tau, and at low concentrations, fibrillization of α-synuclein is promoted by tau protein (13). Both amyloid precursor protein and α-synuclein accelerate the formation of tau pathology in genetic animal models. Tau pathology may be part of a final common pathway for neurodegeneration, where different cofactors may induce tau fibrillization (43). This means that different pathologies may contribute to or exacerbate the progression and severity of cognitive decline. The increase in CSF total tau levels probably reflects such a neuronal damage (7,41). Reasonably, this process is more evident as the disease progresses, explaining the positive association of CSF tau levels with disease severity in DLB.

As expected, CSF p-tau was remarkably increased in AD, while it did not show any differential expression across the DLB, PDD, PD, and normal control groups, thus suggesting that NFT are unlikely to importantly contribute to dementia in DLB or PDD patients. These findings are in keeping with another CSF investigation (44) and also with neuropathologic data showing that widespread neocortical NFT accumulation occurs in AD alone, while in DLB and PDD (35), as well as in normal elderly subjects (45), NFT are considerably fewer in number and generally confined to allocortical areas.

Limits of this study are the lack of pathological verification of clinical diagnoses and the relative paucity of sample size. However, the notion of pathology as the gold standard is problematic in this context, since PDD and DLB are hardly distinguishable at autopsy and their differentiation is based exclusively on the time interval between the onset of cognitive relative to motor symptoms. The relatively small sample size is partially overcome by the homogeneity of the groups studied and availability of an abundance of clinical and neuropsychological data. Of note, there were quantitative rather than qualitative differences in the cognitive profile of DLB, PDD, and PD patients. In fact, in these groups, cognitive impairment was essentially restricted to executive and visual-spatial domains, although with noticeable variability in degree and severity (DLB > PDD > PD).

The neurochemical approach to the diagnosis of dementia in PD and parkinsonisms is an important and emerging issue. Cerebrospinal fluid biomarkers may be of help for adding pathophysiological information on the different conditions characterized by parkinsonism and dementia. In light of our data, DLB and PDD share some clinico-neuropsychological characteristics but seem to represent two different biological entities.

LP and PT contributed equally to this article.

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