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Original Research Article

Clinical and Neuropsychological Differences between Mild Parkinson's Disease Dementia and Dementia with Lewy Bodies

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Key Words

Parkinson's disease · Mild dementia · Dementia with Lewy bodies · Clinical presentation

Abstract

Background: The specific profile of dementia in Parkinson's disease (PDD) and dementia with Lewy bodies (DLB) in the earliest stages of dementia is still unclear and subject of considerable controversy. ***Methods:*** We investigated 27 PDD patients and 24 DLB patients with parkinsonism in the early stage of dementia, i.e. with a Mini-Mental State Examination score of ≥24. ***Results:*** Compared to PDD, patients with DLB demonstrated significantly lower scores when testing attention and executive functions [modified card sorting test ($p < 0.001$) and digit span backward ($p < 0.02$)], as well as when testing constructive abilities [copy of complex designs ($p = 0.001$) and pentagon ($p < 0.001$)]. Using logistic regression analysis, diagnosis was predicted from the cognitive profile, with an overall accuracy of 88.2%. In addition, PDD patients showed a significantly higher Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore ($p < 0.001$) as well as higher UPDRS motor item scores [tremor at rest ($p = 0.01$) and bradykinesia ($p = 0.001$)]. ***Conclusions:*** The cognitive profile in PDD differs from that in DLB in the early stage of dementia, with worse performance on tests of attention and executive functions and constructive abilities in DLB compared to PDD patients. In contrast, motor symptoms are more severe in PDD than in DLB.

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Introduction

The prevalence of dementia in Parkinson's disease (PDD) is close to 30%, and at least 75% of Parkinson's disease (PD) patients who survive for more than 10 years will develop dementia [1, 2].

The dementia of PD often closely resembles dementia with Lewy bodies (DLB), with fluctuating cognition and visual hallucinations. Current consensus criteria suggest that a differentiation should be made between DLB and PDD on the basis of the duration of extrapyramidal signs prior to the onset of dementia [3]. The diagnostic label of PDD is reserved for patients who have had motor symptoms only for at least 12 months before the onset of dementia. The cognitive profile and parkinsonism in DLB and PDD are similar, although some differences have been noticed [4–7].

Recently, the Movement Disorder Society Task Force has proposed to revise criteria for PD, such that patients who present with motor signs should be diagnosed with PD even in the presence of dementia [8]. The Task Force raises the question whether the diagnosis of PD should or should not depend on the presence (or timing) of dementia. If the diagnosis of PD did not depend on the presence of dementia, similar profiles of PDD and DLB could be expected, especially in the early stage of dementia. However, such changes should be underpinned by solid evidence.

Therefore, we compared the clinical and neuropsychological profiles of patients with DLB and PDD. In contrast to most previous studies, which were based on patients with moderately severe dementia [5, 6, 9–12], we included patients with mild or very mild dementia, which is relevant given the increased focus on the early stages of neurodegenerative diseases.

Methods

Participants

Patients were selected from subjects who sought consultation at the Department of Neurology, University Hospital 'Alexandrovska', Sofia, Bulgaria. Patients presented with cognitive and/or motor complaints or were in the advanced stage of PD requiring hospitalization. The research was approved by the local ethics committee, and all subjects signed informed consent. The evaluation process comprised a detailed medical history (from patients, family members and medical records), physical and neurological examinations, cognitive evaluations, appropriate laboratory tests and neuroimaging. Psychiatric evaluation included a semistructured interview and the Geriatric Depression Scale [13]. Exclusion criteria were clinically relevant cerebrovascular disease, uncorrected visual deficit as well as evidence of causes for dementia such as vitamin B_{12} deficiency, folic acid deficiency, thyroid dysfunction or head trauma. None of the patients were tested during a period of episodic confusion. We also excluded patients if the time of onset of dementia relative to parkinsonism was unclear.

For the diagnosis and staging of dementia in both groups, we used the following neuropsychological tests: Mini-Mental State Examination (MMSE) [14], Mini-Mental Parkinson (MMP) [15] and Dementia Rating Scale [16]. We used an MMSE score of ≥24 to categorize mild PDD and DLB, as is often used in Alzheimer's disease [17, 18], PD [19, 20] and DLB [21].

The evaluation of activities of daily living, including the abilities to manage personal finances, use the telephone, take care of all shopping needs, use public transportation, take medications and cope in social situations, was based on the interview with the patients and their caregivers. The relative contribution of motor versus cognitive impairment to activities of daily living performance was determined by the clinicians at the time of the interview. The

impact of cognitive impairment on daily living was considered significant when the patient showed deterioration in more than one daily activity, i.e. dementia, which was a requirement for inclusion. All DLB patients examined in this study had parkinsonism at the time of examination, which was also required for inclusion and was based on the judgment of a neurologist with experience in movement disorders.

Dementia with Lewy Bodies

Diagnosis was based on the modified DLB Consortium criteria for DLB [3]. DLB was diagnosed when dementia occurred before, concurrently or within 1 year after the onset of parkinsonism. Of the 24 DLB patients, 21 had probable DLB according to consensus criteria at the time of testing, i.e. had at least one core feature in addition to parkinsonism: visual hallucinations (2 patients), cognitive fluctuations (11 patients), visual hallucinations and cognitive fluctuations (5 patients) or parkinsonism and one suggestive feature (3 patients). The remaining 3 DLB patients had possible DLB (i.e. parkinsonism and mild dementia) at initial evaluation but developed visual hallucinations and cognitive fluctuations during the first year after the baseline evaluation. Fluctuating cognition was rated as present when the caregiver gave positive answers to one or both questions about 'fluctuating confusion' or 'impaired consciousness' using the Clinical Assessment of Fluctuation Scale [22].

Dementia in Parkinson's Disease

The diagnosis of PDD was made based on the Movement Disorder Society Task Force criteria for dementia [23]. The onset of established PD (UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD [24]) preceded the development of dementia by at least 12 months. In this study, the time of onset of dementia in PDD patients was at least 4 years after the diagnosis of PD. To ensure that any differences in group test profiles could be attributed to differences in the underlying nature of the disorders rather than to differences in age, educational level and/or global level of dementia, we selected 27 patients from a large cohort of 86 PDD patients, who matched a DLB patient with regard to age, education and Mini Mental Parkinson.

Neuropsychological Assessment

Detailed cognitive evaluation of both groups included a neuropsychological battery. *Episodic memory* was assessed with the Buschke Free and Cued Selective Reminding Test [25]. *Attention and executive functions* were tested by the Trail Making Test part A and B [26], the Modified Card Sorting Test (MCST) [27], digit span backward of the Wechsler Adult Intelligence Scale [28] and the Stroop Test [29]. *Language abilities* were determined by the 15-item subset of the Boston Naming Test [30], the semantic verbal fluency and the phonemic verbal fluency [31]. *Visuospatial abilities* and constructional praxis were evaluated by the Clock Drawing Test [32], the ability to copy 5 complex designs [33] and the interlocking pentagon copying item within the MMSE [34].

Parkinsonism

The severity of parkinsonism in both patient groups was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) part III and IV [35], the Hoehn and Yahr staging [36] and the PD motor subtype according to the method suggested by Jankovic et al. [37]. All patients were evaluated in the off state.

Statistical Analysis

Not normally distributed data were analyzed using the Mann-Whitney test, normally distributed data were analyzed using Student's t test, and categorical data were analyzed

Table 1. Demographic and clinical characteristics of the DLB and PDD groups

	DLB (n = 24)	PDD (n = 27)	p value
Age, years	68.9 (7.0)	69.2 (8.8)	0.905
Sex, female/male	8/16	5/22	0.374
Education, years	14.2 (3.7)	13.6 (3.3)	0.536
Disease duration, years	2.4 (1.5)	12.4 (4.3)	0.000
Hallucination, n (%)	10 (41.7)	6 (22.2)	0.232
Delusions, n (%)	3 (12.5)	3 (11.1)	0.779
GDS	5.8 (4.1)	7.6 (3.5)	0.081
MMSE	25.7 (1.5)	26.2 (1.3)	0.228
MMP	22.5 (2.5)	22.3 (1.8)	0.681
L-dopa medications, n (%)	18 (75)	27 (100)	0.02
Dopamine agonist, n (%)	4 (17)	10 (37)	0.200
Cholinesterase inhibitors	3 (12.5)	0 (0)	0.195
Anxiolytic/antidepressive drugs	3 (12.5)	4 (14.8)	0.866
Antipsychotic drugs	2 (8)	0 (0)	0.446
UPRDS III (motor) total	29.6 (12.9)	42. 3(8.8)	0.000
Hoehn and Yahr stage	2.52 (0.6)	3.3 (0.5)	0.000
Motor subtype, PIGD/TD	16/5	16/7	0.877
Tremor at rest (mean score)	0.75 (1.0)	1.6 (1.3)	0.012
Postural tremor (mean score)	0.64 (0.7)	0.78 (0.9)	0.539
Intentional tremor (mean score)	0.39 (0.5)	0.3 (0.5)	0.525
Rigidity	2.6 (0.7)	3.1 (0.6)	0.053
Hand and feet bradykinesia	2.0 (0.8)	2.7 (0.6)	0.001
Postural stability	1.4 (0.8)	1.9 (0.7)	0.100
UPDRS IV: motor fluctuations	0.5 (1.6)	2.8 (1.9)	0.000
Dyskinesia	0.0 (0.0)	0.7 (1.2)	0.006

Values are presented as mean (SD) unless otherwise indicated. GDS = Geriatric Depression Scale; PIGD = postural instability and gait difficulty subtype; TD = tremor dominant subtype.

using the χ^2 test. A statistical significance level of 0.05 was chosen for all analyses. Since this was an exploratory analysis, no formal attempt was made to adjust for multiple testing. Cognitive variables that were significantly associated with diagnosis in bivariate analysis were included as independent variables in a subsequent multivariate logistic regression model, using diagnosis as the dependent variable. Logistic regression analysis was used to investigate whether the diagnosis could be accurately predicted from the cognitive profile.

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of both groups are presented in table 1. There were no significant intergroup differences regarding age, education, MMSE and MMP scores, and gender, as expected due to the matching procedure, but PDD patients showed a significantly longer disease duration than DLB patients.

Of the PDD patients, 6 had hallucinations at the time of testing (6 had visual hallucinations and 3 of them had additional auditory hallucinations), compared to 10 of the DLB patients (7 had visual hallucinations, 2 had auditory hallucinations, and 1 had other hallucinations).

Table 2. Neuropsychological performance of both groups

	DLB	PDD	p value
Memory (FCSRT)			
Immediate recall	12.0 (3.0)	12.2 (2.9)	0.859
Free recall	17.1 (6.6)	14.7 (5.8)	0.170
Total recall	39.3 (5.8)	37.5 (7.3)	0.357
Recognition	15.7 (0.8)	15.4 (0.8)	0.242
Free delayed recall	5.8 (3.0)	5.7 (3.0)	0.879
Total delayed recall	13.8 (2.1)	13.5 (2.5)	0.626
Language (BNT)	12.8 (1.8)	13.4 (1.3)	0.226
Semantic fluency (animals), n	12.7 (3.7)	14.3 (3.3)	0.109
Phonemic fluency (letter M), n	6.5 (3.4)	6.2 (2.5)	0.636
Attention/executive function			
Digit span forward	5.1 (1.1)	5.2 (0.7)	0.815
Digit span backward	2.8 (1.1)	3.4 (0.8)	0.023
TMT-A (correct lines)	22.3 (4.5)	23.8 (0.6)	0.122
TMT-B (correct lines)	11.1 (10.3)	12.4 (8.9)	0.629
MCST (categories)	2.2 (1.6)	3.0 (1.7)	0.093
Perseverative errors (P%)	63.0 (20.2)	38.1 (21.7)	0.000
Stroop Test part 3	15.1 (10.4)	20.3 (9.2)	0.066
Visuospatial and constructive abilities			
Copy designs	6.8 (2.2)	8.7 (2.2)	0.001
Pentagon	3.7 (1.4)	5.2 (0.6)	0.000
Clock Drawing Test	5.9 (2.2)	6.7 (2.2)	0.227

FCSRT = Free and Cued Selective Reminding Test; BNT = Boston Naming Test; TMT = Trail Making Test.

Comparison of Motor Symptoms

On the Hoehn and Yahr scale as well as on UPDRS III (motor scale) and IV (motor fluctuations and dyskinesia), the PDD group had significantly higher scores than the DLB group, but there was no significant difference in predominant motor subtype between both groups. The tremor severity was higher in the PDD group, but only regarding the tremor at rest, which was marginally significant ($p = 0.012$). Compared to DLB patients, PDD patients also demonstrated a significantly higher score on hand and feet bradykinesia as well as a tendency towards increased rigidity.

Comparison of Neuropsychological Tests

The neuropsychological performances of both groups are demonstrated in table 2. There were no significant group differences for the memory or language test scores.

The DLB group performed poorer than the PDD group on two of the three visuoconstructive tests. Among the attention/executive tests, the only difference was that DLB patients showed more perseverative errors on the MCST and a more significant impairment in digit span backward, although the latter was only marginally significant. On the Stroop Test, part 2 ($p = 0.054$) and 3, there were also trends towards poorer performance in the DLB group.

A binary logistic regression analysis showed that the full model with the four scores that differed between the groups was statistically significant ($\chi^2 = 0.994$; d.f. 8; $p = 0.000$), indicating that the cognitive profile distinguished between DLB and PDD patients. The correct prediction of PDD and DLB was 88.9 and 87.5%, respectively, yielding an overall success rate of 88.2%. The strongest predictor of diagnostic category was the variable 'pentagon drawing' [B –1,503; Wald 5,907; d.f. 1; $p = 0.015$; OR 0.223 (95% CI 0.066–0.748)].

Discussion

The relationship between DLB and PDD is still unresolved, and there are both similarities and differences. Recently, it was suggested to classify DLB with parkinsonism as a subtype of PD [8]. However, more studies are needed to clarify this, and this is particularly true for the early disease stages.

Major Findings of Present Work

In this study, we compared cognitive and motor symptoms of patients with mild DLB and PDD. The main finding was that DLB patients showed more attention/executive and visuoconstructive deficits as compared to PDD patients. The logistic regression analysis was able to correctly classify 88.2% of the patients with DLB or PDD, based on the cognitive profile. The strongest predictor of diagnostic category was the variable 'pentagon drawing'. Additionally, PDD patients demonstrated more significant motor deterioration based mostly on dopaminergic symptoms (tremor at rest and bradykinesia) compared to DLB patients.

Deficits in Attention/Executive Functions

In the domain of attention/executive functions, DLB patients performed significantly worse on digit span backward and MCST (perseverative errors) than PDD patients. In 2014, Yoon et al. [38] also found that the attention/executive domain is more affected in DLB compared to PD even in the mild cognitive impairment stage. A recent neuroimaging study showed that numbers of categories achieved and perseverative errors in the Wisconsin Card Sorting Test should be differentially estimated, because they reflect the function of different brain regions in patients with early dementia [39], i.e. categories achieved mainly reflect the function of the precentral segments, whereas perseverative error scores correlate with metabolic activity in the right thalamus.

Deficits in Constructive Abilities

We also found that even patients with mild DLB are unable to cope with tasks which involve constructive abilities compared to patients with mild PDD. Cormack et al. [9] found a strong correlation between total MMSE and Cambridge Cognition Examination scores and pentagon copying in PDD patients, but not in patients with DLB. The authors suggested that in PDD, constructional disability appears to develop proportionately to a global cognitive impairment, whereas in DLB there is a selective impairment of constructional ability, above and beyond the global impairment. Several other authors also notice that the level of visuospatial impairment found in patients with DLB is disproportionately severe relative to the deficits that they exhibit in other cognitive domains [4, 40]. A recent neuroimaging study showed that DLB patients exhibit more severe atrophy in parietal and occipital areas relative to those with PDD [41]. These data could explain the poorer visuospatial performance of DLB patients compared to PDD patients.

Severity of Parkinsonism

We found that patients with mild PDD have more significant motor deficit than DLB patients, which was mostly due to higher dopaminergic symptoms (tremor at rest and bradykinesia). Furthermore, resting tremor was more characteristic for PDD than for DLB patients, whereas the severity of postural and intention tremor was similar in both patient groups. Onofrj et al. [42] also concluded that tremor is common in DLB, and that the tremor in DLB patients presented a complex pattern of mixed tremors, characterized by rest and postural/action tremor. In vivo studies demonstrate that cell loss in the substantia nigra is less pronounced in DLB than in PD [11]. The underlying pathophysiology of impaired postural

control in PD is complex, although the role of the pedunculopontine nucleus is the most emphasized in recent years [43]. In the present study, we did not find any significant difference in postural instabilities between the two groups; we could suggest that the cholinergic changes in the pedunculopontine nucleus are rather similar in PDD and DLB.

Study Limitations

Firstly, the lack of pathological confirmation of the clinical diagnosis represents a potential limitation in this study. However, we have employed the most recent clinical consensus criteria available at the time of the study for both disorders which were found to be more sensitive than previous criteria [12]. In addition, all PD patients and most of the DLB patients have been followed for at least 4 years without evidence of diagnoses other than PD and DLB. Secondly, the sample size was relatively small, and thus the statistical power to detect small effect sizes was low, with a risk for type 2 error. Finally, a number of comparisons were performed without adjusting for multiple testing. Thus, our findings should be interpreted with caution.

Conclusions

In conclusion, the results of the current study indicate that patients with mild DLB and those with PDD exhibit a different cognitive symptom profile. In addition, at the mild dementia stage, motor symptoms are more advanced in PDD than in DLB. These differences likely reflect the heterogeneity of the underlying lesions in PD and DLB patients with mild dementia, i.e. more nigrostriatal pathological changes in PD and more cortical changes in DLB (Lewy bodies, amyloid plaques, vascular disease). Although the changes in motor profile could be related to different disease durations of the DLB and PD groups, it could not completely reflect differences in pathophysiology or pathology.

Future larger studies are needed, which take into account accompanying brain changes as well as the longitudinal course of the symptoms.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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