Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

Cognitive and Motor Decline in Dementia with Lewy Bodies and Parkinson's Disease Dementia

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ABSTRACT: Background: There is a need to better understand the rate of cognitive and motor decline of Dementia with Lewy bodies (DLB) and Parkinson's disease Dementia (PDD).

Objectives: To compare the rate of cognitive and motor decline in patients with DLB and PDD from the E-DLB Consortium and the Parkinson's Incidence Cohorts Collaboration (PICC) Cohorts.

Methods: The annual change in MMSE and MDS-UPDRS part III was estimated using linear mixed regression models in patients with at least one follow-up (DLB $n = 837$ and PDD $n = 157$).

Results: When adjusting for confounders, we found no difference in the annual change in MMSE between DLB and PDD (−1.8 [95% CI −2.3, −1.3] vs. −1.9 [95% CI −2.6, −1.2] [$P = 0.74$]). MDS-UPDRS part III showed nearly identical annual changes (DLB 4.8 [95% CI 2.1, 7.5]) (PDD 4.8 [95% CI 2.7, 6.9], [$P = 0.98$]).

Conclusions: DLB and PDD showed similar rates of cognitive and motor decline. This is relevant for future clinical trial designs.

Dementia with Lewy bodies (DLB) and Parkinson's Disease (PD) Dementia (PDD) are common age-related neurodegenerative disorders associated with abnormal deposits of alpha-synuclein in the brain. They share a wide range of clinical and neurobiological features, and cannot be distinguished neuropathologically.[1] The distinction between these two conditions

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is based on clinical grounds and centered on the 1-year rule, with patients developing dementia before or within 1 year of motor onset classified as DLB and those developing dementia at least 1 year after motor symptoms as PDD.

Although some differences have been described between DLB and PDD, including differences in neuropsychiatric symptoms, cognitive profiles, and co-existing Alzheimer's disease pathology,[2–6] there is a need to better understand their rate of cognitive and motor decline. Unlike numerous cross-sectional findings, evidence on the rate of cognitive impairment in DLB compared with PDD is limited and derived mainly from small samples or cohorts with limited years of follow-up.[5,7–13] Studies comparing the severity of motor symptoms and their rate of decline are even fewer.[11,12] Given the development of promising disease-modifying treatments targeting shared biological pathways, such information is highly relevant for clinical trial design as it is debated whether trials could combine PDD and DLB, which would facilitate recruitment.[5,14]

Against this background, we aimed to compare the rate of cognitive and motor decline in DLB and PDD using two large international multicenter cohorts from the European-DLB (E-DLB) Consortium and the Parkinson's Incidence Cohorts Collaboration (PICC).

Methods

A total of 20 centers (Table S1) recruited patients with DLB or PD. Probable DLB[15] ($n = 983$) subjects were mostly referrals from outpatient clinics, including memory, movement disorders, geriatric medicine, psychiatric, and neurology clinics with cross-center harmonization of diagnostic procedures from E-DLB.[16] PD ($n = 1104$) cases were identified from the six population-based PD studies that form PICC.[17] Of 1104 patients with incident PD originally included, 299 developed PDD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth Edition[18] or Movement Disorder Society criteria.[19] Detailed descriptions of the cohorts' procedures have been described previously.[16,20–25] All participants who had at least one follow-up visit after the first recorded visit for DLB ($n = 837$) or PDD onset ($n = 157$) were included in this study. The local ethics committee at each center approved each study and all participants signed written informed consent.

We harmonized demographics and medical history information at baseline and follow-up. Global cognition was evaluated using the Mini-Mental State Examination (MMSE).[26] Motor severity was evaluated using the Unified PD Rating Scale (UPDRS) part III or the Movement Disorder Society-UPDRS (MDS-UPDRS) part III.[27] We used the simplified conversion method from UPDRS to MDS-UPDRS part III.[28] For modeling, time-zero was defined as the first recorded visit for DLB and the first visit with dementia for PDD. We performed descriptive analyses by estimating means and standard deviations for quantitative variables and percentages for categorical variables. The median and interquartile range (IQR) was calculated when applicable. Differences between groups were compared using t tests, Mann–Whitney and χ^2 tests, as appropriate.

For the longitudinal analysis, we used a linear mixed regression model with time, DLB/PDD grouping variable (as a dummy), and the interaction between them as fixed effects; the random effects included a nested random intercept and slope for time (patients nested in centers) with an unstructured covariance matrix for each level. During data exploration, based on the Akaike information criterion of our models and the decreasing frequency of observations during follow-up (supplementary Fig. S1A), the analyses were truncated at 5 years of follow-up. The models were adjusted by sex and age; additionally, we included years of education as a confounder for the cognitive model and the levodopa equivalent daily dose (LEDD)[29] for the motor symptoms model. Patients were right-censored due to death, loss to follow-up, or last recorded visit, and considered missing at random (MAR). The final models were fitted by restricted maximum likelihood (REML). Hypotheses were rejected in each model on an alpha level of 0.05. IBM SPSS Statistics 26 was used for data management, STATA 15 for data manipulation and R version 4.0.5 for modeling and graphics.

TABLE 1 *Cohort overview at time-zero*

	DLB	PDD	Total	*P* value
Total (%)	837 (84.2)	157 (15.8)	994 (100.0)	
Age	76.9 ± 8.7	75.8 ± 7.1	76.8 ± 8.5	0.11
Sex (%)				**0.02**
Male	416 (49.7)	94 (59.9)	510 (51.3)	
Year of education	8.8 ± 4.9	11.2 ± 3.5	9.2 ± 4.7	**<.001**
MMSE	21.4 ± 5.2	22.0 ± 5.3	21.5 ± 5.2	0.19
MDS-UPDRS part III	27.2 ± 14.3	45.6 ± 12.5	32.1 ± 16.0	**<.001**
Levodopa equivalent daily dose (mg)	98.0 ± 182.8	498.0 ± 330.9	341.7 ± 343.3	**<.001**

Note: Values are mean ± SD and *N* (%) if not otherwise indicated. Bold values are statistically significant $P < 0.05$.
Abbreviations: DLB, Dementia with Lewy Bodies; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified PD Rating Scale; MMSE, Mini-Mental State Examination; PDD, Parkinson's Disease Dementia.

Results

A total of 157 patients with newly diagnosed PDD and 837 DLB were eligible for this study. The mean number of follow up visits were 4.1 (±2.2) for DLB and 3.7 (±1.9) for PDD patients (Fig. 1B). The median follow-up time was 2.8 (IQR 2.4) for DLB and 2.4 (IQR 2.9) for PDD patients. As expected, at time zero, MDS-UPDRS part III scores were higher in PDD compared to DLB, while MMSE scores were similar in both groups (Table 1). These results remained unchanged after adjusting for age and sex for both comparisons, and in addition for LEDD for motor symptoms and years of education for global cognition at the intercept of the longitudinal models.

Both groups experienced cognitive decline during follow-up. The DLB group experienced an annual decline of −1.8 (95% CI −2.3, −1.3) points in MMSE compared to an annual decline of −1.9 points (95% CI −2.6, −1.2) in the PDD group. The rate of decline was comparable in both unadjusted and adjusted models ($P = 0.74$; Fig. 1A and Table S3).

Both groups experienced motor progression during the follow-up period. A difference in the rate of motor decline was seen in the unadjusted model but not maintained once age, sex and LEDD were included as confounders ($P = 0.98$). After adjustment, the DLB group showed an annual progression rate of 4.8 (95% CI 2.1, 7.5) MDS-UPDRS part III units. A nearly identical annual progression rate of 4.8 (95% CI 2.7, 6.9) MDS-UPDRS part III units was observed in the PDD group (Fig. 1B and Table S4).

Discussion

Our findings suggest that once dementia is reached, the rate of cognitive and motor decline in DLB and PDD is similar. These findings support the hypothesis that PDD and DLB may be different phenotypic expressions of the same underlying process[30] and are relevant for patient management and the design of future clinical trials.

Comparing the clinical course of PD/PDD and DLB is challenging for several reasons, including inherent between group differences in demographics such as age at disease onset, differences in the treatment of motor symptoms, and a substantial heterogeneity in the clinical presentation within and across these diagnostic groups. For these reasons, sufficiently large and clinically well-characterized cohorts are needed to provide reliable data on the rate of cognitive and motor decline in these two diagnostics groups.

In our study comprising nearly a 1000 patients, we observed similar global cognitive impairment, as measured by MMSE, in DLB and PDD at time of dementia diagnosis, and subsequently a similar rate of cognitive decline of −1.8 and −1.9 MMSE points in DLB and PDD patients, respectively. Our results are in line with previous studies with shorter follow-up periods, which reported annual rates of MMSE decline between −1.1 and −2.1 points in DLB and −1.2 and −1.8 points in PDD.[31,32] Similarly, the rate of decline in several domains of cognitive function does not differ across groups when analyzed longitudinally,[5] despite cross-sectional differences being widely reported in the literature.[5,7–9,11,33]

While we found no difference in the severity of cognitive impairment between the two diagnostic groups, motor symptoms were more severe in PDD than DLB at the time of dementia diagnosis. Given that PD is characterized by progressive parkinsonism prior to dementia, this initial difference was expected and has also been reported in a previous cross-sectional study.[33] Similarly, during follow-up we observed more rapid motor decline in PPD than DLB in models that did not adjust for the differences in age and gender between the two groups in our study. However, age and sex are known sources of variation for motor progression.[34] Correspondingly, the difference was not

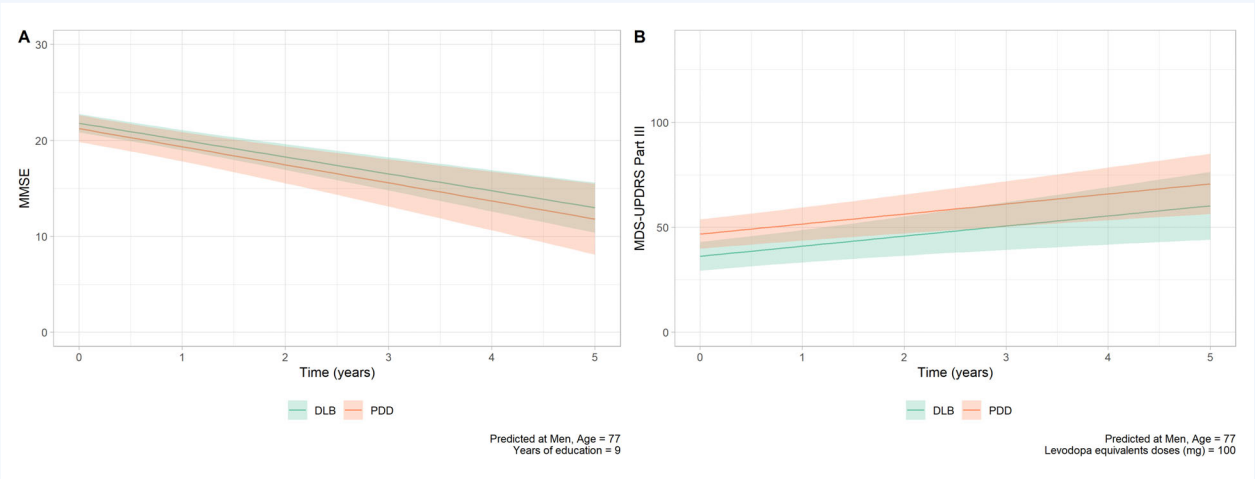

FIG 1. Prediction of cognitive and motor impairment over time. Estimated predicted rate of (A) cognitive decline measured by mini-mental state examination (MMSE) and (B) motor symptoms worsening measured by the Movement Disorder Society-Sponsored Revision of the Unified PD Rating Scale part III (MDS-UPDRS), in patients with dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).

maintained once age and sex were included as confounders, and with further adjustment for dopaminergic treatment. Indeed, the annual progression rates in the adjusted models were nearly identical, with annual slopes of 4.8 points in the MDS-UPDRS part III in both DLB and PDD. This is in agreement with other studies that reported estimated changes in UPDRS-III scores without finding differences associated with the effect of diagnosis (DLB vs. PDD)[11] even after adjusting for age and LEDD.[12] It is noteworthy that DLB and PDD patients might have been evaluated in different ON/OFF states during their motor assessment due to the different study protocols. Although our motor models were adjusted by LEDD to capture any residual response in these systems, motor symptoms frequently become less responsive to levodopa in the advanced stages of these disorders.

Some methodological limitations must be considered. We acknowledge the recruitment differences between the PD population-based cohorts and the DLB clinical-based studies. However, DLB population-based cohorts are incredibly scarce due to the difficulty of accurately differentiating between dementias in community studies. Also, the MMSE might not have picked up differences in the decline of the executive or visuospatial functioning between DLB and PDD. Nevertheless, it is the most often used screening tool for the overall measure of cognitive impairment in clinical, research, and community settings and is similarly sensitive when measuring the rate of cognitive change as the Montreal Cognitive Assessment.[13]

Our study has several significant strengths, including the large international multicenter approach, the use of standardized assessments, and lengthy follow-up. Finally, our results showing a similar rate of motor and global cognitive decline in DLB and PDD support the approach of combining these two related diseases to increase the statistical power in longitudinal research studies and randomized clinical trials evaluating motor and cognitive outcomes.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. writing of the First Draft, B. Review and Critique.

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Disclosures

Ethical Compliance Statement: The local ethics committee at each center approved each study. All participants signed written informed consent and regional ethical committees approved each study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Data S1. Supporting information.