Clinical Neurology and Neurosurgery 194 (2020) 105832

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

# Neuropsychiatric feature profiles of patients with Lewy body dementia

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ARTICLE INFO

*Keywords:*
Cognitive disorders
Dementia
Lewy body dementia
Neurodegenerative diseases
Neuropsychiatry
Parkinson disease

ABSTRACT

*Objective:* Differential diagnosis between Parkinson's disease (PD) dementia and dementia with Lewy bodies (DLB) is difficult due to common features, whereas management decisions and research endpoints depend upon knowledge of dementia severity. We aimed to assess risk factors for age at dementia onset, as well as which neuropsychiatric features are associated with pharmacotherapy and signs and symptoms of Lewy body dementia.
*Patients and methods:* Patients with PD dementia or DLB were evaluated for age at disease onset, education, sanitation, anthropometric measures, alcohol use, smoking, history of infections or head trauma with unconsciousness, family history of neurodegenerative diseases, functional independence, cognition, behavior, motor features, caregiver burden and pharmacotherapy.
*Results:* Fifty-one patients were recruited (37 with DLB, 14 with PD dementia). Cumulative alcohol use and married status were associated with earlier dementia onset, whereas history of treated systemic infections and cumulative family history of primary neurodegenerative diseases led to later dementia onset. The length of dementia was shorter only for severely impaired patients who used anti-depressants, but not for users of cholinesterase inhibitors, while no behavioral symptom was associated with dopaminergic therapy. Night-time behavior disturbances were inversely associated with sleep satisfaction, while caregiver burden was more affected by depression and motor features. Non-motor symptoms were more burdensome for patients with DLB, while in PD dementia anxiety and dysphoria occurred when motor features were less burdensome.
*Conclusions:* PD dementia and DLB are two phenotypes of the same pathological entity, differing mostly by the occurrence of parkinsonian signs. Predictors of dementia onset differ from other neurodegenerative diseases.

## 1. Introduction

Lewy-type synucleinopathy [1] consists of pathological neuronal inclusions and aggregates accumulating in the neocortex, in basal nuclei, in the brainstem and in peripheral neurons [1,2], causing the typical neuropsychiatric manifestations of Lewy body dementia (LBD) when neurotransmitter deficits arise in cortical and subcortical structures [3]; amyloidogenesis and the presence of *APOE*-ε4 alleles are also represented [4], but less so than in Alzheimer's disease (AD) [3,5], though *APOE*-ε4 alleles have been associated with earlier onset of motor features in Parkinson's disease (PD) [6]. Nevertheless, the amyloid-β load does not affect sensitivity of clinical diagnosis of dementia with Lewy bodies (DLB) [7].

Differential diagnosis between LBD syndromes (essentially consisting of PD dementia and DLB) is still difficult due to common features between them [8]. The main criterion is still the "one year rule", with dementia occurring before or concurrently with parkinsonism in DLB, and parkinsonism preceding the onset of dementia for at least one year in PD dementia [9].

Clinical diagnosis of probable DLB requires a dementia syndrome with two of the following core features with or without indicative biomarkers: recurrent visual hallucinations, fluctuating cognition with pronounced variations in attention and alertness, at least one spontaneous cardinal feature of parkinsonism, and REM sleep behavior disorder [10]. These criteria are potentially applicable to patients with PD dementia [3,9], but it should be noted that up to half of all patients with DLB have no extrapyramidal signs [11].

Some clinical features might be useful for differential diagnoses. In

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https://doi.org/10.1016/j.clineuro.2020.105832
Received 5 August 2019; Received in revised form 22 February 2020; Accepted 2 April 2020
Available online 08 April 2020
0303-8467/ 

LBD, earlier onset of visual hallucinations is the best predictor of limbic pathology which, in addition to cortical pathology, associates with visual misperceptions and misidentification [12]. Contrariwise, absence of visuospatial impairment is the best negative predictor of Lewy-type synucleinopathy [13]. Paranoid delusions are the most frequent delusions in LBD, whereas Capgras delusions may occur in up to 10 % of patients with DLB, but have not been described in PD dementia [9]. Apathy, anxiety and depression support clinical diagnosis of DLB, but are not specific [10]. REM sleep behavior disorder is a parasomnia that increases risk of α-synucleinopathies and dementia whether occurring with or without narcolepsy, and is associated with more hallucinations and delusions [9,10]. Orthostatic hypotension presents with fluctuating cognition, confusion, drowsiness and dizziness [14]. Repeated falls and syncope result from dysautonomia, whereas urinary incontinence is more prevalent than in AD, usually due to detrusor hyperactivity secondary to lesions of nigrostriatal dopaminergic neurons [15]. Overall, extrapyramidal signs are not useful for differential diagnosis between DLB and AD [13].

Risk factors for DLB consist of AD and PD risk factors in combination, except for smoking and education (which cause opposing risks for AD and PD); nonetheless, depression and low caffeine intake are associated with both AD and PD, and have additive risks for DLB [5]. For PD dementia, age and severity of motor symptoms seem to have a combined effect on dementia risk [9], leading to higher mortality in comparison with cognitively unimpaired patients with PD [16]. Moreover, older age at PD onset has been associated with more sensory and autonomic symptoms, sleep disorders, dementia and psychosis [17], whereas the postural instability gait difficulty phenotype of PD is associated with faster cognitive decline and higher incidence of dementia, depression and apathy [18]. Nevertheless, risk factors for age at LBD onset have not been reported before.

Management decisions and research endpoints depend upon knowledge of dementia severity and its correlations with other neuropsychiatric features [19]. Our primary aim was to assess the risk factors for age at dementia onset, as well as which features were associated with the length of signs and symptoms of LBD. Secondarily, we sought to determine which neuropsychiatric features were associated with the length of dementia, pharmacological therapy and parkinsonian signs and symptoms for DLB and PD dementia in independent associations (considering that parkinsonism usually differs in onset and intensity for these dementia syndromes).

## 2. Patients and methods

### 2.1. Participants and clinical assessment

In this cross-sectional study, consecutive outpatients with LBD syndromes were recruited from the Department of Neurology and Neurosurgery at *Hospital São Paulo*, Federal University of São Paulo – UNIFESP, from January 2014 to June 2017. All patients who had either probable or possible PD dementia according to Movement Disorder Society Task Force clinical diagnostic criteria [9], or either probable or possible DLB [10], were invited to participate. Clinical diagnosis of PD followed traditional recommendations [20] derived from the Queen Square Brain Bank criteria. All patients had a magnetic resonance exam of the brain or, in cases of claustrophobia, a computed tomography scan to exclude vascular lesions, whereas cerebrospinal fluid biomarkers (total *tau*, phospho-*tau* $Thr_{181}$, and amyloid – $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-38}$) measured by way of enzyme-linked immunosorbent assays were employed for diagnostic confirmation when cognitive decline was slower than expected or atypical behavioral features were presented. Patients with prior history of stroke or intracranial mass lesions, such as tumors, would be excluded.

After diagnostic confirmation, patient assessment consisted of: sex, age, country of birth, estimated age at onset of dementia, education, marital status, lifetime urban living and sanitary conditions, history of head trauma with loss of consciousness, history of depression under pharmacotherapy before dementia onset, history of systemic infection treated with antibiotic, family history of primary neurodegenerative diseases, sleep satisfaction and estimated daily length of sleep [21], body mass index, waist circumference, quantification of alcohol use and smoking, daily amount of different medications (with particular attention to cholinesterase inhibitors, Memantine, Levodopa, anti-depressants and anti-psychotics), and scores on the Neuropsychiatric Inventory (NPI) [22], digit span (digits forward and digits backward), Mini-Mental State Examination (MMSE) [23], Severe MMSE [24], Clinical Dementia Rating (CDR) [25], a 15-item Clock Drawing Test (free drawing) [19], the Index of Independence in Activities of Daily Living (ADL) [26], Lawton's Scale for Instrumental Activities of Daily Living (IADL) [27], the Brazilian Version of the Zarit Caregiver Burden Interview [28], the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [29], and the Schwab & England scale [30]. Demographic data was provided by caregivers, as well as information on the length of time since the following neuropsychiatric features started: fluctuating cognition (including daytime drowsiness, behavioral inconsistency and incoherent speech), episodic complex visual hallucinations, spontaneous cardinal features of parkinsonism, REM sleep behavior disorder without atonia, episodic transient unconsciousness, systematized delusions, and depression. All cognitive and functional assessments, body mass index and waist circumference measurements were conducted on weekdays at morning time, by the same examiner (FFO), whereas clinical features based on interviews were assessed in a detailed self-report or proxy-report.

The ADL reflects behavioral levels of six sociobiological functions: bathing, dressing, toileting, transfer, continence, and feeding; after caregivers were queried, each function was scored as zero for dependency or one for independence, with an index total of zero to six. A trichotomous version (1 = unable; 2 = able with help; 3 = able without help) of IADL was employed [19]; caregivers provided all information, with a total score of 9–27.

Information concerning age at dementia onset was determined following a review of medical records, and confirmed after an interview with the caregiver, who should have frequent visits with the patient (preferably a family member). The time of subjective memory complaints or mild cognitive impairment was not taken into account, but rather only the time at dementia onset.

Retrospective information from patient files was also retrieved to estimate the time it took them to reach scores over 1.0 on the CDR, as well as a score of 15 on the MMSE. Only patients who had already reached these scores were taken into account for statistics on cognitive and functional outcomes.

### 2.2. Outcome measures

The main outcome measures were the risk factors for age at dementia onset, as well as features which were associated with the length of signs and symptoms of LBD. Secondarily, we measured which neuropsychiatric features were independently associated with the length of dementia, pharmacological therapy and parkinsonian signs and symptoms for DLB and PD dementia separately.

### 2.3. Statistical analyses

A multiple regression model considering all the assessed risk factors was employed, with age at dementia onset as the dependent variable. Linear regressions were used to compare clinical parameters with the length of signs and symptoms of LBD, as well as to compare neuropsychiatric features with the length of dementia, pharmacological therapy and scores on the MDS-UPDRS for each dementia syndrome. Statistical comparisons for continuous variables were conducted by way of the Kruskal-Wallis test (or Mann-Whitney test when only two unmatched groups were compared). Fisher's exact test was employed to

correlate categorical variables. Spearman correlations were estimated for items from the neuropsychiatric, functional and motor tests, with levels of significance corrected for false discovery rates to minimize the occurrence of type I errors. The threshold of significance was set at $p < 0.05$.

### 2.4. Ethical aspects

This study is part of the research project 064990/2013 (CAAE 21514813.0.0000.5505) approved by the Ethics Committee of *Hospital São Paulo*, Federal University of São Paulo – UNIFESP, in October 2013. All invited patients and their legal representatives agreed to participate on the research and signed the Informed Consent Form before the evaluation, with no exceptions.

## 3. Results

Overall, 51 patients with LBD syndromes were recruited, considering 37 patients with DLB (72.5 %) and 14 patients with PD dementia (27.5 %). Of all 51 patients, 18 were in the mild dementia stage (35.3 %), 21 were in the moderate dementia stage (41.2 %), and 12 were in the severe dementia stage (23.5 %). Cerebrospinal fluid biomarkers were required for diagnostic confirmation from 27 patients with DLB.

Table 1 shows clinical and demographic results for all patients, whereas Table 2 shows features of neuropharmacological therapy. Patients with DLB slept longer than patients with PD dementia (9.62 ± 1.8 h per day *versus* 8.07 ± 3.4 h per day, $p = 0.005$) and were more satisfied with their sleep (81.1 % *versus* 42.9 %, $p = 0.014$), but none of the anthropometric or demographic parameters from Table 1 were significantly different according to the dementia syndrome. All patients who used cholinesterase inhibitors (76.5 % of all patients) or Memantine (7.8 % of all patients) used these medications in the highest possible dosages. The mean number of cholinesterase inhibitors that had been used at any time was 0.98 ± 0.7; none of them (Donepezil, Galantamine, Rivastigmine, or no cholinesterase inhibitor therapy) affected the length of the disease in any of the dementia stages ($p > 0.28$). Regarding patients with severe dementia, depression under specific pharmacological therapy was associated with shorter length of the dementia syndrome (2.67 ± 1.5 years, $n = 6$) in comparison to patients who used no anti-depressant (7.08 ± 2.5 years, $n = 6$), $p = 0.01$; nevertheless, the difference was non-significant in the mild ($p = 0.53$) and moderate ($p = 0.12$) dementia stages.

Table 3 shows results of risk factors affecting age at LBD onset, while Table 4 shows associations between several clinical parameters and the length of the most notable signs and symptoms of LBD. The length of fluctuating cognition was associated with slower time to cognitive and functional outcomes, as well as with MDS-UPDRS scores, and inversely associated with Severe MMSE scores, with digit span – digits forward, and with the Schwab & England scale. The length of time since the first visual hallucination was associated with slower time to cognitive and functional outcomes, and inversely associated with the Schwab & England scale. The length of parkinsonism was associated with slower time to cognitive and functional outcomes, as well as with MDS-UPDRS scores, and inversely associated with Severe MMSE scores and functionality. The length of REM sleep behavior disorder was associated with slower time to reach a MMSE score of 15, as well as with scores on Part IV of the MDS-UPDRS. The length of time since the first episode of transient unconsciousness was associated with scores on Parts II and III of the MDS-UPDRS, and inversely associated with most cognitive and functional scores. The length of time since the first systematized delusion was associated with slower time to cognitive and functional outcomes, with the amount of different medications, and with MDS-UPDRS scores, and inversely associated with the Clock

**Table 1**
Clinical and demographic results for Lewy body dementia.

| Variables, $n = 51$ | | Mean | SD[a] | Range | $n$ (%) |
|---|---|---|---|---|---|
| Age at dementia onset (years-old) | | 73.50 | 8.3 | 50 – 88 | – |
| Current age (years-old) | | 77.76 | 7.8 | 55 – 90 | – |
| Length of dementia (years) | | 4.26 | 3.3 | 0 – 14 | – |
| Sex | Female | – | – | – | 20 (39.2 %) |
| | Male | – | – | – | 31 (60.8 %) |
| Marital status | Married | – | – | – | 23 (45.1 %) |
| | Single | – | – | – | 3 (5.9 %) |
| | Divorced | – | – | – | 1 (1.9 %) |
| | Widower | – | – | – | 24 (47.1 %) |
| Schooling (years) | | 4.02 | 4.0 | 0 – 15 | – |
| Country of birth | Brazil | – | – | – | 48 (94.1 %) |
| | Portugal | – | – | – | 3 (5.9 %) |
| Lifetime urban living (%) | | 74.61 % | 25.5 % | 5%-100 % | – |
| Lifetime living with sanitation (%) | | 74.80 % | 25.9 % | 5%-100 % | – |
| History of head trauma with loss of consciousness | | – | – | – | 7 (13.7 %) |
| History of depression under pharmacotherapy before dementia onset | | – | – | – | 33 (64.7 %) |
| History of systemic infection treated with antibiotic | | – | – | – | 24 (47.1 %) |
| Lifetime alcohol use (liters per year) | | 18.24 | 52.6 | 0 – 325 | 14 (27.5 %)[b] |
| Lifetime smoking (packs per year) | | 67.04 | 142.1 | 0 – 670 | 24 (47.1 %)[c] |
| Estimated daily length of sleep (hours per day) | | 9.20 | 2.4 | 4 – 18 | – |
| Sleep satisfaction | | – | – | – | 36 (70.6 %) |
| Body mass index (kg/m$^2$) | | 26.80 | 5.35 | 13.59 – 43.28 | 13 (25.5 %)[d] |
| Waist circumference (cm) | | 94.76 | 12.54 | 65 – 131 | – |
| Family history of primary neurodegenerative diseases | | – | – | 0 – 4[e] | 24 (47.1 %)[f] |

[a] SD = standard deviation.
[b] Patients who had any history of alcohol use during their lifetimes.
[c] Patients who had any history of smoking during their lifetimes.
[d] Patients with obesity (body mass index > 30 kg/m$^2$).
[e] Range of the number of family members with primary neurodegenerative diseases (up to third degree) for each patient.
[f] Patients with family history.

**Table 2**
Features of neuropharmacological therapy for Lewy body dementia.

| Variables, $n = 51$ | | $n$ | Mean[a] | SD[a] | Range[a] |
|---|---|---|---|---|---|
| Use of a cholinesterase inhibitor | Donepezil | 15 | 10.00 mg/day | 0.0 mg/day | 10 – 10 mg/day |
| | Galantamine | 9 | 24.00 mg/day | 0.0 mg/day | 24 – 24 mg/day |
| | Rivastigmine | 15 | 12.00 mg/day | 0.0 mg/day | 12 – 12 mg/day |
| Use of Memantine | | 4 | 20.00 mg/day | 0.0 mg/day | 20 – 20 mg/day |
| Use of Levodopa | | 24 | 445.83 mg/day | 321.7 mg/day | 200 – 1500 mg/day |
| Use of an anti-psychotic[b] | Olanzapine | 3 | 8.33 mg/day | 2.9 mg/day | 5 – 10 mg/day |
| | Quetiapine | 20 | 107.50 mg/day | 137.0 mg/day | 25 – 600 mg/day |
| | Risperidone | 1 | 1.00 mg/day | 0.0 mg/day | 1 – 1 mg/day |
| Use of anti-depressants[b] | Amitriptyline | 1 | 25.00 mg/day | 0.0 mg/day | 25 – 25 mg/day |
| | Citalopram | 2 | 30.00 mg/day | 14.1 mg/day | 20 – 40 mg/day |
| | Duloxetine | 2 | 45.00 mg/day | 21.2 mg/day | 30 – 60 mg/day |
| | Escitalopram | 1 | 20.00 mg/day | 0.0 mg/day | 20 – 20 mg/day |
| | Fluvoxamine | 1 | 50.00 mg/day | 0.0 mg/day | 50 – 50 mg/day |
| | Mirtazapine | 2 | 30.00 mg/day | 0.0 mg/day | 30 – 30 mg/day |
| | Nortriptyline | 1 | 25.00 mg/day | 0.0 mg/day | 25 – 25 mg/day |
| | Sertraline | 14 | 96.43 mg/day | 36.5 mg/day | 50 – 150 mg/day |
| | Trazodone | 5 | 80.00 mg/day | 27.4 mg/day | 50 – 100 mg/day |
| | Venlafaxine | 2 | 75.00 mg/day | 0.0 mg/day | 75 – 75 mg/day |

[a] SD = standard deviation; the mean values, standard deviations, and ranges of doses for medications only consider patients who used them.
[b] Overall, 30 patients (58.82 %) used anti-depressants (but one patient used two anti-depressants at the same time: Duloxetine + Trazodone), and 24 patients (47.06 %) used an anti-psychotic during the evaluation, but nineteen of them used an anti-depressant and an anti-psychotic at the same time: eight used Sertraline + Quetiapine, three used Sertraline + Olanzapine, two used Duloxetine + Quetiapine, two used Mirtazapine + Quetiapine, two used Trazodone + Quetiapine, one used Citalopram + Quetiapine, one used Venlafaxine + Quetiapine, and one used Fluvoxamine + Risperidone.

**Table 3**
Multiple regression results for age at Lewy body dementia onset.

| Effects[a], $n = 51$ | β | t | p |
|---|---|---|---|
| Constant | 82.6125 | 8.1349 | < **0.0001** |
| Male sex | 7.1534 | 1.9976 | 0.0533 |
| Married status | −8.5653 | −2.9912 | **0.0050** |
| Years of schooling | −0.5765 | −1.5548 | 0.1287 |
| Born abroad | 4.4284 | 0.9133 | 0.3671 |
| Lifetime urban living (%) | −5.5877 | −0.6337 | 0.5303 |
| Lifetime living with sanitation (%) | 5.5672 | 0.6418 | 0.5250 |
| History of head trauma with loss of consciousness | −3.5837 | −1.1356 | 0.2636 |
| History of depression under pharmacotherapy before dementia onset | −2.3315 | −1.0994 | 0.2788 |
| History of systemic infection treated with antibiotic | 4.7842 | 2.1455 | **0.0387** |
| Lifetime alcohol use (liters per year) | −0.0681 | −3.0554 | **0.0042** |
| Lifetime smoking (packs per year) | −0.0020 | −0.2501 | 0.8039 |
| Body mass index (kg/m$^2$) | 0.1030 | 0.2241 | 0.8240 |
| Waist circumference (cm) | −0.1051 | −0.5575 | 0.5806 |
| Family history[b] of primary neurodegenerative diseases | 3.3890 | 2.8756 | **0.0067** |

[a] $n = 51$; F-ratio = 3.0067; p = 0.0041; Multiple R = 0.7342; Adjusted Squared Multiple R = 0.3597.
[b] Coefficient for the number of family members (up to third degree) with the condition.

Drawing Test and with functional scores. The length of time since the first episode of depression was associated with slower time to cognitive and functional outcomes, with caregiver burden, and with scores on Parts II, III and IV of the MDS-UPDRS, and inversely associated with Severe MMSE scores and functionality.

Overall, 36 patients with LBD (70.6 %) reported sleep satisfaction. Patients who were satisfied with their sleep slept longer (9.64 ± 2.4 h per day *versus* 8.13 ± 2.0 h per day, p = 0.026), and had higher scores on the CDR sum-of-boxes (12.11 ± 3.8 *versus* 9.90 ± 3.7, p = 0.044). Sex (p = 0.755), years of schooling (p = 0.959), age (p = 0.926), age at dementia onset (p = 0.385), length of dementia (p = 0.054), body mass index (p = 0.563), the daily amount of different medications (p = 0.154), and scores on the MMSE (p = 0.086), the Severe MMSE (p = 0.193), the Clock Drawing Test (p = 0.282), the Brazilian Version of the Zarit Caregiver Burden Interview (p = 0.176), the CDR (p = 0.107), the NPI (p = 0.612), ADL (p = 0.251) or IADL (p = 0.959) had no associations with sleep satisfaction.

Regarding behavioral domains of the NPI, only night-time behavior disturbances were inversely associated with sleep satisfaction: satisfied patients scored 2.69 ± 3.6 *versus* 8.93 ± 3.8, p < 0.0001. Agitation (p = 0.788), hallucinations (p = 0.061), anxiety (p = 0.260), apathy (p = 0.508), delusions (p = 0.072), disinhibition (p = 0.352), dysphoria (p = 0.311), euphoria (p = 0.756), irritability (p = 0.292), aberrant motor behavior (p = 0.057), and appetite and eating abnormalities (p = 0.926) had no associations with sleep satisfaction.

Table 5 shows associations of each functional, cognitive or behavioral test, as well as of caregiver burden with length of dementia, daily amount of different medications, and scores on the MDS-UPDRS for patients with DLB. Table 6 shows the same associations for patients with PD dementia. Length of dementia was associated with higher scores on the CDR sum-of-boxes, and lower scores on the digit span – digits forward and on the Schwab & England scale only for patients with DLB, as well as with higher caregiver burden and lower scores on the Clock Drawing Test for patients with PD dementia. The amount of different medications was associated with higher scores on the digit span – digits backward, more anxiety and more night-time behavior disturbances only for patients with PD dementia. Scores on Parts II and III of the MDS-UPDRS were associated with more cognitive and functional impairments, as well as with higher caregiver burden for all patients. Non-motor aspects of experiences of daily living were associated with higher caregiver burden, dysphoria, euphoria, night-time behavior disturbances, and appetite and eating abnormalities only in patients with DLB, and with apathy, delusions and irritability only in patients with PD dementia. Motor complications were associated with less basic independence and lower scores on the Severe MMSE, the digit span – digits backward, and the Schwab & England scale, as well as with more apathy only in patients with DLB.

The Supplementary tables show distinct correlations among specific items of the NPI (including caregiver distress scores), ADL, IADL, of the Brazilian Version of the Zarit Caregiver Burden Interview, of the MMSE, of the CDR sum-of-boxes, and of MDS-UPDRS Parts I, II, III and IV for patients with DLB and PD dementia. Most significant correlations were found for patients with DLB, though patients with PD dementia had

**Table 4**
Associations between clinical parameters and length of signs and symptoms of Lewy body dementia syndromes.

| Variable, $n = 51$ (except where noted[a]) | Mean ± SD[b] (range) | Length of time since fluctuating cognition started | Length of time since the first complex visual hallucination | Length of spontaneous cardinal features of parkinsonism | Length of time since REM sleep behavior disorder started | Length of time since the first episodic transient unconsciousness | Length of time since the first systematized delusion | Length of time since the first episode of depression |
|---|---|---|---|---|---|---|---|---|
| Mean ± SD[b] (range in years) | – | 3.33 ± 3.3 (0.0−11.5) | 3.31 ± 3.1 (0.0−12.0) | 3.87 ± 4.6 (0.0−19.0) | 2.74 ± 3.8 (0.0−19.0) | 0.35 ± 1.4 (0.0−9.5) | 2.25 ± 3.3 (0.0−14.0) | 3.23 ± 3.5 (0.0−16.0) |
| *n* (%) of patients who presented the clinical feature | – | 38 (74.51 %) | 41 (80.39 %) | 37 (72.55 %) | 33 (64.71 %) | 06 (11.76 %) | 28 (54.90 %) | 37 (72.55 %) |
| Time since dementia onset to Clinical Dementia Rating > 1.0 (years, $n = 33$[a]) | 3.61 ± 2.7 (0.5−11.0) | 0.7362 (**p = 0.001**) | 0.4377 (**p = 0.047**) | 0.6827 (**p = 0.007**) | 0.3353 (p = 0.122) | 0.1436 (p = 0.221) | 0.6708 (**p = 0.003**) | 0.8152 (**p < 0.001**) |
| Time since dementia onset to Mini-Mental State Examination = 15 (years, $n = 25$[a]) | 4.16 ± 2.8 (1.0−11.5) | 0.8682 (**p < 0.001**) | 0.8357 (**p < 0.001**) | 0.8497 (**p = 0.006**) | 0.4863 (**p = 0.021**) | 0.2043 (p = 0.165) | 0.4660 (**p = 0.034**) | 0.9931 (**p < 0.001**) |
| Daily amount of different medications | 5.29 ± 2.7 (0−13) | 0.0465 (p = 0.791) | −0.1493 (p = 0.354) | 0.1299 (p = 0.590) | 0.1234 (p = 0.538) | −0.1017 (p = 0.166) | 0.3643 (**p = 0.029**) | 0.3110 (p = 0.088) |
| Clinical Dementia Rating Sum-of-Boxes (0.0−18.0 points) | 11.46 ± 3.8 (5−18) | 0.1738 (p = 0.161) | 0.2087 (p = 0.066) | 0.2037 (p = 0.234) | −0.0675 (p = 0.637) | 0.1027 (**p = 0.048**) | 0.1695 (p = 0.162) | 0.0704 (p = 0.593) |
| Mini-Mental State Examination (0−30 points) | 15.82 ± 5.8 (3−28) | −0.1367 (p = 0.091) | −0.1129 (p = 0.132) | −0.0743 (p = 0.511) | 0.0585 (p = 0.533) | −0.0761 (**p = 0.025**) | −0.0510 (p = 0.525) | 0.0021 (p = 0.981) |
| Severe Mini-Mental State Examination (0−30 points) | 25.61 ± 5.7 (5−30) | −0.2156 (**p = 0.008**) | −0.0372 (p = 0.633) | −0.2571 (**p = 0.023**) | 0.0007 (p = 0.994) | −0.1206 (**p < 0.001**) | −0.0845 (p = 0.304) | −0.1849 (**p = 0.034**) |
| Clock Drawing Test (0−15 points) | 4.37 ± 4.4 (0-15) | −0.1091 (p = 0.318) | −0.0962 (p = 0.341) | −0.2234 (p = 0.136) | −0.1391 (p = 0.266) | −0.0400 (p = 0.389) | −0.2451 (**p = 0.019**) | −0.1180 (p = 0.307) |
| Digit Span – digits forward | 4.53 ± 1.3 (0−8) | −0.7271 (**p = 0.039**) | −0.5351 (p = 0.103) | 0.1628 (p = 0.743) | 0.4469 (p = 0.277) | −0.4738 (**p = 0.001**) | −0.0945 (p = 0.789) | −0.2152 (p = 0.572) |
| Digit Span – digits backward | 1.84 ± 1.1 (0−4) | −0.5249 (p = 0.233) | −0.1786 (p = 0.662) | 0.0337 (p = 0.956) | 0.1086 (p = 0.831) | −0.3605 (p = 0.051) | −0.1781 (p = 0.681) | −0.2757 (p = 0.555) |
| Index of Independence in Activities of Daily Living (0−6 points) | 3.96 ± 2.1 (0−6) | −0.4099 (p = 0.070) | −0.1646 (p = 0.437) | −0.9373 (**p = 0.002**) | −0.1011 (p = 0.701) | −0.2813 (**p = 0.002**) | −0.4497 (**p = 0.041**) | −0.4912 (**p = 0.039**) |
| Lawton's Scale for Instrumental Activities of Daily Living (9−27 points) | 12.12 ± 3.6 (9−22) | −0.1749 (p = 0.188) | −0.2478 (**p = 0.041**) | −0.0447 (p = 0.809) | 0.0678 (p = 0.659) | −0.0841 (p = 0.134) | −0.2659 (**p = 0.038**) | −0.1614 (p = 0.251) |
| Schwab & England Scale (0 %–100 %) | 52.75 ± 24.5 (0 %–90 %) | −3.9202 (**p = 0.041**) | −1.8454 (p = 0.305) | −8.5361 (**p < 0.001**) | −1.2925 (p = 0.564) | −2.5800 (**p = 0.001**) | −4.3667 (**p = 0.019**) | −5.2025 (**p = 0.009**) |
| Brazilian version of the Zarit Caregiver Burden Interview (0−56 points) | 19.14 ± 9.1 (3−38) | 0.0858 (p = 0.101) | 0.0793 (p = 0.100) | 0.0529 (p = 0.467) | 0.0619 (p = 0.305) | 0.0181 (p = 0.418) | 0.0653 (p = 0.204) | 0.1154 (**p = 0.035**) |
| MDS-UPDRS[c] Part I | 18.45 ± 7.2 (5−33) | 0.1518 (**p = 0.020**) | 0.1033 (p = 0.090) | 0.1981 (**p = 0.028**) | 0.1201 (p = 0.113) | 0.0149 (p = 0.598) | 0.1657 (**p = 0.009**) | 0.1008 (p = 0.150) |
| MDS-UPDRS[c] Part II | 19.84 ± 11.9 (1−47) | 0.1076 (**p = 0.005**) | 0.0280 (p = 0.450) | 0.2058 (**p < 0.001**) | 0.0804 (p = 0.077) | 0.0521 (**p = 0.001**) | 0.1008 (**p = 0.008**) | 0.1011 (**p = 0.014**) |
| MDS-UPDRS[c] Part III | 33.67 ± 26.0 (0−99) | 0.0559 (**p = 0.001**) | 0.0020 (p = 0.907) | 0.1160 (**p < 0.001**) | 0.0359 (p = 0.085) | 0.0214 (**p = 0.004**) | 0.0534 (**p = 0.002**) | 0.0494 (**p = 0.009**) |
| MDS-UPDRS[c] Part IV | 2.82 ± 4.6 (0−17) | 0.3059 (**p = 0.002**) | −0.0147 (p = 0.878) | 0.6542 (**p < 0.001**) | 0.3861 (**p < 0.001**) | 0.0414 (p = 0.346) | 0.1483 (p = 0.141) | 0.2652 (**p = 0.013**) |

[a] There were 51 patients with Lewy body dementia in the study, but only 33 reached Clinical Dementia Rating scores > 1.0, and only 25 had reached a Mini-Mental State Examination score of 15 or lower.
[b] SD, standard deviation.
[c] MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

**Table 5**
Linear regressions for major test results regarding patients with dementia with Lewy bodies.

| Variable, $n$ = 37 | Mean ± SD[a] (range) | Coefficient for length of dementia (years) | Coefficient for daily amount of different medications | Coefficient for scores on the MDS-UPDRS[b] Part I | Coefficient for scores on the MDS-UPDRS[b] Part II | Coefficient for scores on the MDS-UPDRS[b] Part III | Coefficient for scores on the MDS-UPDRS[b] Part IV |
|---|---|---|---|---|---|---|---|
| Mean ± SD[a] (range) | – | 4.04 ± 3.0 (0.0−14.0) | 5.24 ± 2.9 (1−13) | 17.68 ± 7.3 (5−33) | 16.86 ± 10.6 (1−44) | 25.54 ± 21.4 (0−87) | 1.73 ± 3.6 (0−14) |
| Clinical Dementia Rating Sum-of-Boxes (0.0−18.0 points) | 11.49 ± 3.7 (5.0−18.0) | 0.3361 (**p = 0.011**) | −0.1614 (p = 0.220) | 1.0043 (**p = 0.001**) | 1.8679 (**p < 0.001**) | 3.3602 (**p < 0.001**) | 0.2473 (p = 0.135) |
| Mini-Mental State Examination (0−30 points) | 15.46 ± 5.2 (3−28) | −0.1005 (p = 0.298) | −0.0143 (p = 0.879) | −0.5698 (**p = 0.012**) | −1.0694 (**p < 0.001**) | −2.0089 (**p = 0.002**) | −0.1645 (p = 0.159) |
| Severe Mini-Mental State Examination (0−30 points) | 25.97 ± 5.2 (11−30) | −0.1108 (p = 0.251) | −0.0211 (p = 0.822) | −0.6789 (**p = 0.002**) | −1.2565 (**p < 0.001**) | −2.5051 (**p < 0.001**) | −0.2699 (**p = 0.018**) |
| Clock Drawing Test (0−15 points) | 4.00 ± 4.0 (0−15) | −0.0239 (p = 0.850) | −0.0307 (p = 0.800) | −0.7628 (**p = 0.009**) | −1.4369 (**p < 0.001**) | −1.9420 (**p = 0.026**) | −0.1007 (p = 0.511) |
| Digit Span – digits forward | 4.43 ± 1.1 (2−7) | −1.0625 (**p = 0.021**) | −0.0217 (p = 0.962) | −2.3079 (**p = 0.042**) | −2.9171 (p = 0.077) | −5.1763 (p = 0.122) | −0.5520 (p = 0.338) |
| Digit Span – digits backward | 1.76 ± 1.1 (0−3) | −0.1316 (p = 0.778) | −0.6730 (p = 0.128) | −2.8946 (**p = 0.008**) | −3.9760 (**p = 0.012**) | −8.0619 (**p = 0.011**) | −1.4116 (**p = 0.009**) |
| Index of Independence in Activities of Daily Living (0−6 points) | 4.43 ± 1.8 (0−6) | −0.4881 (p = 0.077) | −0.0162 (p = 0.953) | −2.2105 (**p < 0.001**) | −4.3631 (**p < 0.001**) | −6.3430 (**p < 0.001**) | −0.6976 (**p = 0.036**) |
| Lawton's Scale for Instrumental Activities of Daily Living (9−27 points) | 11.86 ± 2.9 (9−20) | −0.3200 (p = 0.058) | 0.0490 (p = 0.769) | −1.3812 (**p < 0.001**) | −2.0484 (**p < 0.001**) | −2.5596 (**p = 0.033**) | −0.0656 (p = 0.756) |
| Schwab & England Scale (0 %–100 %) | 58.11 ± 21.3 (10 %–90 %) | −6.1839 (**p = 0.006**) | −0.9346 (p = 0.684) | −22.3778 (**p < 0.001**) | −40.3203 (**p < 0.001**) | −63.6757 (**p < 0.001**) | −6.4696 (**p = 0.021**) |
| Brazilian version of the Zarit Caregiver Burden Interview (0−56 points) | 20.35 ± 9.3 (3−38) | 0.0535 (p = 0.326) | −0.0055 (p = 0.917) | 0.4107 (**p = 0.001**) | 0.4899 (**p = 0.008**) | 0.5435 (p = 0.160) | 0.0798 (p = 0.227) |
| Neuropsychiatric Inventory (0−144 points) | 43.05 ± 21.3 (7−84) | 0.0138 (p = 0.563) | −0.0039 (p = 0.866) | 0.2102 (**p < 0.001**) | 0.1695 (**p = 0.039**) | −0.0155 (p = 0.928) | 0.0059 (p = 0.839) |
| Agitation | 3.38 ± 4.2 (0−12) | 0.1370 (p = 0.254) | 0.0135 (p = 0.908) | 0.3648 (p = 0.215) | 0.3937 (p = 0.356) | −0.6406 (p = 0.458) | −0.0665 (p = 0.652) |
| Hallucinations | 5.70 ± 4.0 (0−12) | −0.0290 (p = 0.818) | −0.1707 (p = 0.154) | 0.4329 (p = 0.155) | 0.2255 (p = 0.613) | −0.2485 (p = 0.783) | −0.1344 (p = 0.378) |
| Anxiety | 5.54 ± 5.3 (0−12) | −0.0106 (p = 0.912) | 0.0612 (p = 0.506) | 0.2743 (p = 0.239) | 0.1780 (p = 0.599) | 0.0376 (p = 0.956) | −0.0360 (p = 0.757) |
| Apathy | 7.35 ± 4.7 (0−12) | 0.0050 (p = 0.963) | −0.0392 (p = 0.707) | 0.3238 (p = 0.218) | 0.2477 (p = 0.517) | 0.2630 (p = 0.734) | 0.2524 (**p = 0.049**) |
| Delusions | 3.68 ± 4.5 (0−12) | 0.0342 (p = 0.765) | −0.0532 (p = 0.628) | 0.4470 (p = 0.104) | 0.3566 (p = 0.375) | 0.6626 (p = 0.415) | 0.0374 (p = 0.788) |
| Disinhibition | 0.89 ± 2.5 (0−12) | −0.1389 (p = 0.493) | 0.0841 (p = 0.667) | −0.0723 (p = 0.885) | −0.0246 (p = 0.973) | −1.3337 (p = 0.356) | −0.0935 (p = 0.706) |
| Dysphoria | 3.43 ± 3.5 (0−12) | 0.0173 (p = 0.904) | −0.0152 (p = 0.912) | 1.1305 (**p < 0.001**) | 1.0333 (**p = 0.036**) | 0.8329 (p = 0.415) | 0.0272 (p = 0.876) |
| Euphoria | 1.27 ± 2.8 (0−12) | −0.0177 (p = 0.923) | −0.0448 (p = 0.800) | 1.0900 (**p = 0.011**) | 0.7586 (p = 0.238) | −0.3080 (p = 0.814) | −0.1706 (p = 0.443) |
| Irritability | 2.62 ± 3.9 (0−12) | 0.1711 (p = 0.185) | 0.0867 (p = 0.489) | 0.2844 (p = 0.373) | 0.1612 (p = 0.727) | −0.8513 (p = 0.359) | −0.0819 (p = 0.606) |
| Aberrant Motor Behavior | 3.05 ± 4.2 (0−12) | 0.1261 (p = 0.289) | −0.1408 (p = 0.218) | 0.1733 (p = 0.555) | 0.2358 (p = 0.578) | 0.1799 (p = 0.834) | −0.0099 (p = 0.946) |
| Night-Time Behavior disturbances | 3.81 ± 4.5 (0−12) | 0.0692 (p = 0.543) | 0.1080 (p = 0.322) | 0.8347 (**p = 0.001**) | 0.7185 (p = 0.068) | −0.2921 (p = 0.720) | −0.0054 (p = 0.969) |
| Appetite and Eating abnormalities | 2.32 ± 3.8 (0−12) | −0.1118 (p = 0.396) | 0.0039 (p = 0.976) | 0.7872 (**p = 0.011**) | 0.5950 (p = 0.199) | 0.2753 (p = 0.771) | 0.2598 (p = 0.100) |

[a] SD, standard deviation.
[b] MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

more night-time behavior disturbances affecting NPI total scores. Whereas registration, naming and repetition did not affect MMSE total scores for any patient groups, hobbies were the only item not to affect CDR sum-of-boxes final scores only for patients with PD dementia.

Fig. 1 shows direct associations of dysphoria with non-motor (A) and motor (B) aspects of experiences of daily living in DLB, as well as inverse associations of dysphoria with subjective (C) and objective (D) motor features in PD dementia, similar to associations with anxiety scores (E and F).

## 4. Discussion

In this study, the only risk factors for earlier dementia onset were cumulative alcohol use and married status, whereas history of systemic infection treated with antibiotic or cumulative family history of primary neurodegenerative diseases were associated with later onset of dementia. Moreover, the length of dementia was shorter only for severely impaired patients with depression who used anti-depressants, but not for users of cholinesterase inhibitors in any dementia stage, unlike what is usually seen in AD [31]. In line with these findings,

**Table 6**
Linear regressions for major test results regarding patients with Parkinson's disease dementia.

| Variable, $n = 14$ | Mean ± SD[a] (range) | Coefficient for length of dementia (years) | Coefficient for daily amount of different medications | Coefficient for scores on the MDS-UPDRS[b] Part I | Coefficient for scores on the MDS-UPDRS[b] Part II | Coefficient for scores on the MDS-UPDRS[b] Part III | Coefficient for scores on the MDS-UPDRS[b] Part IV |
|---|---|---|---|---|---|---|---|
| Mean ± SD[a] (range) | – | 4.86 ± 4.0 (0.0 − 11.0) | 5.43 ± 2.4 (0 − 8) | 20.50 ± 6.5 (8 − 30) | 27.71 ± 12.0 (9 − 47) | 55.14 ± 25.3 (18 − 99) | 5.71 ± 5.7 (0 − 17) |
| Clinical Dementia Rating Sum-of-Boxes (0.0 − 18.0 points) | 11.39 ± 4.4 (5.5 − 18.0) | 0.1419 (p = 0.596) | −0.1563 (p = 0.332) | 0.8719 (**p = 0.027**) | 2.2832 (**p < 0.001**) | 4.2086 (**p = 0.003**) | −0.1807 (p = 0.639) |
| Mini-Mental State Examination (0 − 30 points) | 16.79 ± 7.4 (3 − 28) | −0.1280 (p = 0.416) | 0.1137 (p = 0.229) | −0.5755 (**p = 0.011**) | −0.9597 (**p = 0.026**) | −1.6827 (p = 0.075) | 0.0455 (p = 0.843) |
| Severe Mini-Mental State Examination (0 − 30 points) | 24.64 ± 6.9 (5 − 30) | −0.2757 (p = 0.085) | 0.0632 (p = 0.541) | −0.3755 (p = 0.157) | −1.0779 (**p = 0.018**) | −2.0143 (**p = 0.041**) | −0.1622 (p = 0.504) |
| Clock Drawing Test (0 − 15 points) | 5.36 ± 5.2 (0 − 15) | −0.4877 (**p = 0.015**) | −0.0517 (p = 0.708) | −0.6534 (p = 0.055) | −1.5448 (**p = 0.009**) | −3.1340 (**p = 0.013**) | −0.3718 (p = 0.239) |
| Digit Span – digits forward | 4.79 ± 1.9 (0 − 8) | 0.0123 (p = 0.984) | 0.5455 (p = 0.133) | −1.2619 (p = 0.196) | −2.1757 (p = 0.231) | −3.6364 (p = 0.347) | 0.9091 (p = 0.299) |
| Digit Span – digits backward | 2.07 ± 1.1 (0 − 4) | −0.7273 (p = 0.504) | 1.2440 (**p = 0.043**) | −0.5024 (p = 0.778) | −7.9522 (**p = 0.004**) | −11.8660 (p = 0.067) | −0.3158 (p = 0.841) |
| Index of Independence in Activities of Daily Living (0 − 6 points) | 2.71 ± 2.3 (0 − 6) | −0.5726 (p = 0.243) | 0.3770 (p = 0.205) | −0.1552 (p = 0.850) | −4.6452 (**p < 0.001**) | −8.7843 (**p < 0.001**) | −0.0726 (p = 0.920) |
| Lawton's Scale for Instrumental Activities of Daily Living (9 − 27 points) | 12.79 ± 5.0 (9 − 22) | −0.2665 (p = 0.245) | 0.1304 (p = 0.356) | −0.4208 (p = 0.259) | −1.9326 (**p < 0.001**) | −3.4270 (**p = 0.008**) | −0.0057 (p = 0.986) |
| Schwab & England Scale (0 %–100 %) | 38.57 ± 27.4 (0 %–90 %) | −5.8626 (p = 0.154) | 2.6462 (p = 0.302) | 0.1023 (p = 0.988) | −39.8684 (**p < 0.001**) | −74.3713 (**p < 0.001**) | −0.6725 (p = 0.913) |
| Brazilian version of the Zarit Caregiver Burden Interview (0 − 56 points) | 15.93 ± 7.9 (6 − 28) | 0.3169 (**p = 0.016**) | −0.0166 (p = 0.855) | 0.1047 (p = 0.663) | 0.9924 (**p = 0.011**) | 2.0750 (**p = 0.012**) | 0.2077 (p = 0.320) |
| Neuropsychiatric Inventory (0 − 144 points) | 42.29 ± 19.1 (8 − 78) | −0.0102 (p = 0.869) | 0.0435 (p = 0.234) | 0.2437 (**p = 0.004**) | −0.1040 (p = 0.572) | −0.2365 (p = 0.541) | −0.0303 (p = 0.732) |
| Agitation | 1.86 ± 3.7 (0 − 12) | −0.2909 (p = 0.349) | −0.2289 (p = 0.222) | −0.7734 (p = 0.112) | −0.6709 (p = 0.476) | −0.6995 (p = 0.726) | −0.1033 (p = 0.820) |
| Hallucinations | 3.07 ± 4.4 (0 − 12) | −0.0864 (p = 0.746) | 0.0813 (p = 0.616) | 0.7374 (p = 0.068) | 0.9619 (p = 0.215) | 1.0748 (p = 0.521) | −0.2756 (p = 0.468) |
| Anxiety | 6.21 ± 4.7 (0 − 12) | −0.1976 (p = 0.425) | 0.3203 (**p = 0.019**) | 0.2252 (p = 0.578) | −1.4323 (**p = 0.037**) | −3.0606 (**p = 0.034**) | −0.2624 (p = 0.462) |
| Apathy | 8.21 ± 3.9 (0 − 12) | −0.0078 (p = 0.979) | −0.2610 (p = 0.135) | 0.8909 (**p = 0.047**) | 0.6930 (p = 0.436) | 1.6299 (p = 0.382) | −0.0706 (p = 0.870) |
| Delusions | 3.21 ± 5.0 (0 − 12) | 0.0779 (p = 0.740) | 0.1554 (p = 0.266) | 0.8963 (**p = 0.006**) | 0.3642 (p = 0.604) | 0.8720 (p = 0.555) | 0.0363 (p = 0.914) |
| Disinhibition | 1.00 ± 2.2 (0 − 6) | −0.0323 (p = 0.952) | −0.2581 (p = 0.427) | −0.0484 (p = 0.956) | −1.6452 (p = 0.298) | −2.6452 (p = 0.432) | 0.0645 (p = 0.934) |
| Dysphoria | 4.79 ± 4.2 (0 − 12) | −0.1802 (p = 0.521) | 0.1216 (p = 0.478) | 0.4925 (p = 0.272) | −1.8134 (**p = 0.016**) | −3.8313 (**p = 0.016**) | −0.1554 (p = 0.702) |
| Euphoria | 0.57 ± 1.7 (0 − 6) | 0.0887 (p = 0.901) | 0.1290 (p = 0.767) | 1.9758 (p = 0.067) | 2.3790 (p = 0.253) | 5.1613 (p = 0.238) | −0.1048 (p = 0.919) |
| Irritability | 1.93 ± 2.9 (0 − 9) | 0.1050 (p = 0.793) | 0.3137 (p = 0.182) | 1.2176 (**p = 0.040**) | −0.9412 (p = 0.427) | −1.6369 (p = 0.513) | 0.2897 (p = 0.612) |
| Aberrant Motor Behavior | 0.57 ± 2.1 (0 − 8) | 0.1538 (p = 0.780) | 0.0769 (p = 0.819) | 1.2788 (p = 0.133) | 1.2500 (p = 0.444) | 2.1346 (p = 0.537) | −0.0962 (p = 0.903) |
| Night-Time Behavior disturbances | 6.43 ± 4.6 (0 − 12) | −0.1276 (p = 0.616) | 0.3537 (**p = 0.009**) | 0.5954 (p = 0.132) | −1.2972 (p = 0.070) | −2.6136 (p = 0.085) | −0.0010 (p = 0.998) |
| Appetite and Eating abnormalities | 4.43 ± 5.1 (0 − 12) | 0.3276 (p = 0.135) | −0.0485 (p = 0.729) | 0.0556 (p = 0.881) | 1.0243 (p = 0.118) | 1.8017 (p = 0.199) | 0.0870 (p = 0.792) |

[a] SD, standard deviation.
[b] MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

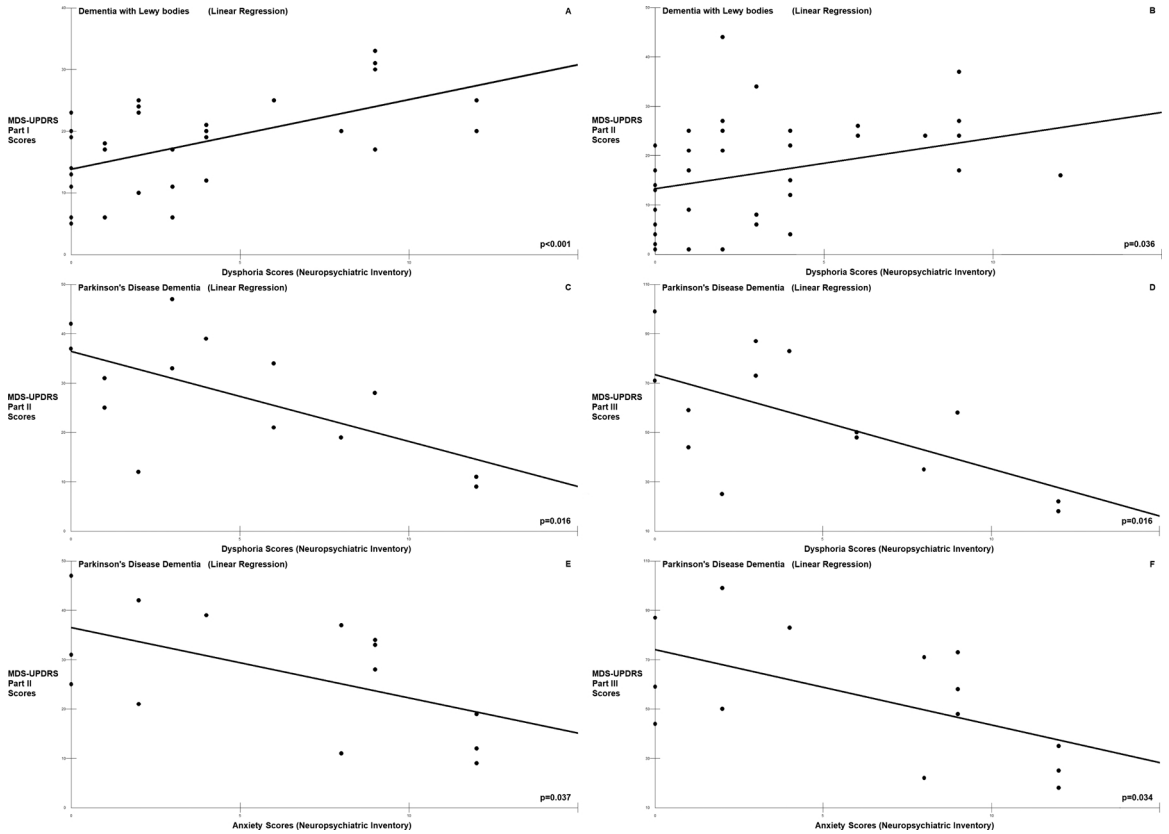


**Fig. 1.** A – Associations of dysphoria with scores on Part I of the MDS-UPDRS (non-motor aspects of experiences of daily living) in patients with dementia with Lewy bodies, $p < 0.001$. B – Associations of dysphoria with scores on Part II of the MDS-UPDRS (motor aspects of experiences of daily living) in patients with dementia with Lewy bodies, $p = 0.036$. C – Associations of dysphoria with scores on Part II of the MDS-UPDRS (motor aspects of experiences of daily living) in patients with Parkinson's disease dementia, $p = 0.016$. D – Associations of dysphoria with scores on Part III of the MDS-UPDRS (motor examination) in patients with Parkinson's disease dementia, $p = 0.016$. E – Associations of anxiety with scores on Part II of the MDS-UPDRS (motor aspects of experiences of daily living) in patients with Parkinson's disease dementia, $p = 0.037$. F – Associations of anxiety with scores on Part III of the MDS-UPDRS (motor examination) in patients with Parkinson's disease dementia, $p = 0.034$.

patients with LBD are more likely to have depression than patients with AD [32], and more likely to have family history of PD or cerebrovascular pathology than cognitively healthy people [5,9], possibly translating into a survival bias in our sample – our patients survived longer without dementia when they had family history of primary neurodegenerative diseases. Systemic bacterial infections and deficient sanitary conditions have been associated with LBD [8], but not with AD onset [33], suggesting involvement of environmental factors in development of LBD syndromes, though antibiotic use might delay dementia onset.

The association of alcohol use with earlier onset of LBD may be explained by several different mechanisms, such as the modulation of dopamine transmission by α-synuclein leading to alcohol craving, or *SNCA* overexpression associated with alcohol dependence [34]. Furthermore, married patients probably had earlier dementia onset because of earlier detection of functional impairment by their partners.

The length of fluctuating cognition and parkinsonism, as well as the length of time since the first systematized delusion, the first visual hallucination and the first episode of depression, were associated with slower time to cognitive and functional outcomes, probably reflecting less aggressive disease course. However, only the length of fluctuating cognition and parkinsonism, the length of time since the first systematized delusion, the first episode of transient unconsciousness and the first episode of depression, were associated with motor and non-motor experiences of daily living. The length of time since the first systematized delusion was the only feature to be associated with the amount of different medications, whereas the length of fluctuating cognition was the only feature to be inversely associated with attention. It should be noted that delusional jealousy [35] and visual hallucinations [36] have been associated with dopaminergic therapy, though less than half of our patients received such therapy at evaluation time.

The length of REM sleep behavior disorder was associated with motor complications and with slower time to cognitive outcomes, while the length of time since the first episode of depression was the only feature associated with caregiver burden. Whereas autonomic symptoms have been reported to interact with REM sleep behavior disorder increasing risk of α-synucleinopathies [37], depression may be caused by atrophy or dysfunction of the pontomesencephalic-limbic emotional circuitry [5], thus being associated with more functional impairment and caregiver burden.

More than 70 % of the patients with LBD reported sleep satisfaction, sleeping longer, but with higher scores on the CDR sum-of-boxes. Length of sleep has been correlated with sleep satisfaction in AD [21], while overall prolonged sleep duration has been associated with smaller brain volumes, poorer executive function, and higher risk of dementia [38]. Regarding behavioral domains of the NPI, only night-time behavior disturbances were inversely associated with sleep satisfaction, but it should be noted that patients with PD dementia had more night-time behavior disturbances affecting NPI total scores, and were less satisfied with their sleep.

Length of dementia was associated with worse cognitive and functional scores, and particularly worse attentional scores only in patients with DLB. Significant associations of length of dementia with worsening functionality have been shown for AD [19], suggesting that progression of this dementia syndrome is more similar to DLB than to PD dementia. Anterior CA1 field atrophy in both hippocampi impairs processing and

execution of planned and context-appropriate behavioral responses, and has been described in patients with DLB, corresponding to attentional and executive impairment rather than the early memory dysfunction that is typical of posterior CA1 field atrophy in AD [39]. Moreover, length of dementia was associated with higher caregiver burden only in patients with PD dementia. Behavioral symptoms and severity of parkinsonism have been associated with higher caregiver burden in cognitively unimpaired patients with PD [40], but for patients with dementia it is likely that cognition and functionality assume a greater burden over caregivers depending upon the start time of behavioral and motor impairments relative to the dementia syndrome.

The amount of different medications was associated with more anxiety and more night-time behavior disturbances (probably reflecting the need of more diverse therapeutic options), but also with better working memory only in patients with PD dementia. Memory dysfunction in PD seems to involve mostly retrieval, rather than encoding and storage [9], possibly explaining why registration and repetition did not affect MMSE total scores as well.

Scores on Parts II and III of the MDS-UPDRS were associated with more cognitive and functional impairments, as well as with higher caregiver burden for all patients, as expected [40]. Non-motor symptoms had wider associations with functional, cognitive and behavioral outcomes for patients with DLB than for patients with PD dementia, but were associated with higher caregiver burden only in patients with DLB. Non-motor symptoms impact quality of life [41] and have been reported to predict caregiver burden more often than motor impairments, particularly when parkinsonism is not so intense [40].

Motor aspects of experiences of daily living were associated with dysphoria only in patients with DLB, whereas motor aspects of experiences of daily living and the motor examination were associated with less anxiety and less dysphoria only in patients with PD dementia. Motor complications were associated with less independence, worse working memory, and more apathy only in patients with DLB. Motor performance is known to affect self-maintenance in LBD [8] but, contrarily to DLB, in PD dementia anxiety and dysphoria usually occur when motor signs and symptoms are less burdensome.

Limitations of this study include the relatively small sample size, its cross-sectional nature precluding the assessment of causal relations, the lack of pathological confirmation, and the fact that all patients came from a single center. Nevertheless, misclassification bias was reduced by use of stringent diagnostic criteria. LBD syndromes are not as frequent as AD, and our original approach led to important conclusions regarding our analyses.

PD dementia and DLB seem to be two possible phenotypes of the same pathological entity [11], differing mostly by the length of parkinsonian signs. The fact that some neuropsychiatric features might help distinguish these two dementia syndromes should be considered in future biomarker research for elucidation of the pathophysiological processes that lead some patients to phenotypically develop DLB, while others develop PD dementia.

## Previous presentation of the information reported in the paper

Aspects of this study were previously presented (and published in the form of abstracts) at the following meetings:

1. 3rd Congress of the European Academy of Neurology

(European Academy of Neurology, Amsterdam/NETHERLANDS, June 2017)

https://doi.org/10.1111/ene.13367

Press Release (VJDEMENTIA): https://youtu.be/wtKMkshHT5c

2. AAIC > 16 – Alzheimer's Association International Conference 2016

(with an Alzheimer's Association Travel Fellowship to the first author)

(Alzheimer's Association, Toronto/CANADA, July 2016)

https://doi.org/10.1016/j.jalz.2016.06.2232

Finalist: Neuropsychiatric Syndromes Professional Interest Area Best Poster Award

3. NMDPD 2014 – The 10th International Congress on Non-Motor Dysfunctions in Parkinson's Disease and Related Disorders

(Kenes International, Nice/FRANCE, December 2014)

Oral Presentation at the Young Trainees Symposium

## CRediT authorship contribution statement

**Fabricio Ferreira de Oliveira:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Fernando Chiodini Machado:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Gustavo Sampaio:** Data curation, Resources, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Sheilla de Medeiros Correia Marin:** Methodology, Resources, Writing - original draft, Writing - review & editing. **Maria da Graça Naffah-Mazzacoratti:** Conceptualization, Methodology, Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Paulo Henrique Ferreira Bertolucci:** Conceptualization, Methodology, Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

## Acknowledgements

This work was supported by CAPES – *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (grant #1067/10) and FAPESP – The State of São Paulo Research Foundation (grant #2015/10109-5). The authors declare no financial or other conflicts of interest related to this study.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.clineuro.2020.105832.

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