Prodromal characteristics of Dementia with Lewy Bodies: baseline results of the Memento nationwide cohort

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Abstract

Background: Isolated subjective cognitive impairment (SCI) and mild neurocognitive impairment (MCI) are prodromal phase of dementia with Lewy bodies (DLB). Memento is a nationwide study of patients with SCI and MCI with clinic, neuropsychology, biology and brain imaging data. We aimed to compare SCI and MCI patients with symptoms of prodromal DLB to others in this study at baseline.

Methods: Participants of the French Memento cohort study recruited for either SCI or MCI. Among them, 892 were included in the Lewy sub-study, designed to search specifically for symptoms of DLB. Probable prodromal DLB group (pro-DLB) was done using a two-criteria cut-off score among the four core clinical features of DLB. This Pro-DLB group was compared to two other groups at baseline: one without any core symptoms (NS group), and the one with one core symptom (1S group). A comprehensive cognitive battery, questionnaires on behavior, neurovegetative and neurosensory symptoms, brain 3D volumetric MRI, CSF, FDG PET and amyloid PET were done.

Results: The Pro-DLB group comprised 148 patients (16.6%). This group showed more multidomain (59.8%) MCI with slower processing speed and a higher proportion of patients with depression, anxiety, apathy, constipation, rhinorrhea, sicca syndrome, and photophobia. The Pro-DLB group had isolated lower P-Tau and on brain MRI widening of sulci including fronto-insular, occipital, and olfactory sulci (FDR corrected).

Conclusions: Patients with symptoms of prodromal DLB are cognitively slower, with more behavioral disorders, autonomic symptoms, and photophobia. Biomarkers confirmed the non-Alzheimer profile. The occipital, fronto-insular, and olfactory bulb involvement on brain MRI was consistent with symptoms and known neuropathology. The next step will be to study the clinical, biological, and imaging evolution of these patients.

Trial registration: Clinicaltrials.gov, NCT01926249 .

Introduction

The description of the prodromal phase of dementia with Lewy bodies (pro-DLB) is just emerging, in contrast to the description of the prodromal phase of Alzheimer's disease [1]. There is nevertheless a consensus on the key symptoms of pro-DLB, combining rapid eye movement (REM) sleep behavior disorders (RBD), cognitive and alertness fluctuations, hallucinations, and parkinsonism [1]. The presence of 2 of the 4 key symptoms with mild cognitive impairment (MCI) indicates probable prodromal pro-DLB [1]. Beyond the key symptoms of the disease, other symptoms have been described as prodromal, such as autonomic dysfunction symptoms, including constipation or erectile dysfunction [2, 3] or behavioral symptoms such as depression [4, 5]. Delirium could also occur in the prodromal phase of DLB [6]. Prospective cohorts are needed in the context of pro-DLB to better determine the different characteristics of this disease [5, 7, 8].

Previous studies have described the cognitive pattern of pro-DLB. The MCI pattern was amnestic multidomain in 33% to 50% of patients, non-amnestic multidomain in 24% to 39%, and non-amnestic unidomain in 27% to 49% [9-11]. Even if the cognitive profile in pro-DLB highlights the fact that cognitive difficulties are diffuse, attentional/executive and visuo-constructive tests appear to be the best predictor of DLB [9, 11]. Few studies exist on cerebrospinal fluid (CSF) in pro-DLB: the analysis of Tau, P-Tau and Abeta-42 is normal in most cases [5, 12]. Reduced insular cortical thinning [13] and a decrease in gray matter concentration [14] have been demonstrated in pro-DLB patients using image processing on brain MRI T1 sequences. Pro-DLB patients have antero-superior insula atrophy when compared to healthy controls [13], and more preserved hippocampi when compared to pro-AD patients [1]. FP-CIT dopaminergic SPECT is a recognized biomarker of DLB. However, in the prodromal phase, this biomarker is not sufficiently sensitive: the value of FP-CIT in distinguishing probable pro-DLB from pro-AD is 61% for sensitivity and 89% for specificity [15].

In a large prospective cohort of patients attending memory clinics presenting either subjective cognitive impairment (SCI) and MCI patients, we undertook an ancillary study aiming to detect symptoms of DLB in a longitudinal framework. The aim of the present study was to compare MCI and SCI patients with symptoms of prodromal DLB to others at the baseline for different characteristics: clinical, neuropsychological, cerebrospinal fluid (CSF), brain MRI, 18-Fluoro-Desoxy-Glucose (FDG) PET, and amyloid PET one.

Methods

The Memento cohort is a clinic-based study aimed to investigate the evolution of a large variety of cognitive symptoms and subjective complaints over time, without any specific a priori hypothesis regarding the relationship with incident dementia. It was set up as an initiative of the French Plan Alzheimer 2008-2012 [16]. Recruitment took place within the French national network of university-based memory clinics (Centre Mémoire de Ressources et de Recherche [CM2R]). Among the 26 CM2Rs of the Memento cohort (totaling 2323 patients), 12 CM2Rs agreed to become investigating centers for the Lewy Memento sub-study [16]. Between April 2011 and June 2014, 892 patients consented to participate in the ancillary Lewy Memento cohort over at least 4 years, including one visit per year.

Study Recruitment

Eligible adult participants for the Memento study, and therefore for Lewy Memento sub-study, had to undergo at baseline all clinical examinations, brain MRI and blood sampling. All participants had to have visual and auditory acuity compatible with neuropsychological testing and be affiliated to a health insurance scheme. The participants were screened for either MCI or SCI and they were recruited consecutively. MCI was defined as 1) performing worse than one standard deviation from the mean (compared to age and education norms) in one or more cognitive domains (memory, language, praxis, attention, executive functions, speed processing, visual spatial abilities), this deviation being identified for the first time through cognitive tests performed recently, i.e. less than 6 months before the screening phase, and 2) having a Clinical Dementia Rating scale score $\leq$0.5 and being non-demented. The battery of neuropsychological tests and detailed aspects of the inclusion/exclusion criteria were described previously for the Memento cohort [16].

Standard Protocol Approvals, Registrations, and Patient Consents

All participants provided written informed consent for the Memento cohort and the Lewy Memento sub-study, and the protocol was approved by the ethics committee (Comité de Protection des Personnes Sud-Ouest et Outre Mer III). The protocol is registered in ClinicalTrials.gov (Identifier: NCT01926249, https://clinicaltrials.gov/ct2/show/NCT01926249).

Study Examinations

The baseline data collected at the memory clinic were described previously [16]. The Lewy Memento sub-study included three additional sections added to the basic Memento package. The first section focused on key symptoms of DLB: features of parkinsonism were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS, part III), including akinesia, amimia and rigidity (rated from 0 [no symptoms] to 4 [serious symptoms]) and falls. Fluctuations were assessed with the Mayo Clinic Fluctuations Scale [17] and the Newcastle-upon-Tyne Clinician Assessment of Fluctuation scale (CAF) [18]. The Hallucinations Parkinson's disease-associated psychotic symptoms questionnaire was used to evaluate the presence of hallucinations [19]. RBD was evaluated using a questionnaire based on the article by Gjerstad et al., 2008 [20] simplified into two questions for the patient and the caregiver, one concerning movements during sleep and the other concerning vivid dreams and nightmares. The second section focused on autonomic disorders and sensorineural symptoms and included: 5 minutes lying and standing blood pressure at 1, 2, and 3 minutes with a heart rate measurement; questionnaire on dry eyes, mouth, and nose, rhinorrhea, lacrimation, and salivation, constipation, libido and erectile dysfunction and photophobia. Each item was rated from 'no symptom = 0' to 'daily symptom = 2'. The third section focused on neuropsychological aspects with the following sub-tests using the *Visual Object and Space Perception Battery (VOSP) allowing* the evaluation of visuo-perceptual and visuo-spatial abilities*:* "Incomplete Letters"; "Position Discrimination" and "Number Location". The DSM IV MINI500 test was used for the diagnosis of major depression.

Definition of the Groups

The pro-DLB group included patients with SCI or MCI, and with at least two of the core features of DLB (fluctuations, RBD, hallucinations, and parkinsonism) during the first visit. The one symptom group (1S) included patients with only one key DLB symptom, and the no symptom group (NS) patients without any core features of DLB. Each symptom was considered to be present as follows: for RBD if the score was 2/2; for hallucinations, if sensation of passage, sensation of presence, illusions, non-visual and

visual hallucinations and delusion were detected; for fluctuations, if a cut-off score of 2/4 or over on the Mayo Clinic Fluctuations Scale was recorded (caregiver or patients); for parkinsonism, if one criterion among akinesia, rigidity, amimia, or falls was present, as described in the McKeith et al., criteria [1].

Imaging and Cerebrospinal Fluid

Neuroimaging acquisitions (brain MRI, 18F-FDG PET, amyloid PET) were coordinated by the Center for Automated Treatment of Images (CATI), a platform dedicated to multicenter neuroimaging [21]. The MRI and PET protocols as well as standardization and quality control procedures were described previously [16]. In our sample, brain MRI was available for 98.0% of participants (88% on a 3.0 T MRI scan, 1.5 T otherwise). FDG PET, amyloid-PET and lumbar puncture were optional and were performed in respectively 68.6%, 30.8%, and 19.5% of participants. Detailed CSF and blood analysis aspects were described previously [16]. Apolipoprotein E (APOE) genotypes were determined by KBiosciences (Hoddesdon, the UK).

Data and Statistics

The data presented are those obtained at the first Lewy Memento visit. The cognitive deficit categories (isolated SCI or MCI staging according to Petersen's criteria [22]) were based on the results of the neuropsychological battery. As previously described [23], we focused on 4 items of the Instrumental Activities of Daily Living (IADL) questionnaire (ability to use the telephone, mode of transport, responsibility for his own medication, and ability to handle finances) as a proxy of dependence. Blood pressure was measured in three steps: after 5 min of rest in the supine position and after 1 min and 3 min in the standing position. Hypotension was defined as a decrease of at least 20 mmHg between the supine position and the standing position for systolic blood pressure, and 10 mmHg for diastolic blood pressure. We defined pathological levels of CSF biomarkers as follows: Abeta42: lower than 750 pg/mL, P-Tau: higher than 60 pg/mL, Total Tau: higher than 350 pg/mL and Abeta42/40: lower than 0.065 [24]. Brain MRI biomarkers of interest were hippocampal volume (mean of both hemispheres), obtained using the SACHA software [25], brain parenchymal fraction (BPF) computed from SPM8 software, and total white matter hyperintensities (WMH) using the WHASA software [26]. Mean and regional cortical thicknesses by hemisphere were obtained using FreeSurfer 5.3. Cortical sulcus modifications were studied: the average distance between the two walls of the pial surface was computed. This distance provides an estimation of the local atrophy leading the fold to open up [27]. Mean and regional FDG-PET singular uptake value ratios (SUVRs) were normalized to the cerebellum [28]. The amyloid PET (florbetapir or flutemetamol) pipeline of analysis was described previously [29].

Data are presented with numbers and percentages for qualitative variables, and with medians and first and third quartile for qualitative variables. Comparisons across subgroups were done using Fisher's Chi-square tests or Kruskal-Wallis tests, as appropriate.

The associations between groups and biomarkers were assessed using logistic regressions for dichotomous variables (i.e. pathological level of Abeta-42, Total Tau, P-Tau and amyloid PET status) and linear regressions for MRI and FDG PET measures. Associations were adjusted for age, gender, education, and APOE. For brain MRI markers, additional adjustment covariates were the type of MRI (manufacturer and magnet size), and intracranial volume (except for BPF). Comparisons were considered statistically significant for P-values below α=0.05. For FDG PET and MRI, when analyses were done at a regional level (a ROI or a sulcus), we used the false discovery rate (FDR) method. Analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Among the 892 patients, 148 (16.6%) were in the Pro-DLB group, 275 (30.8%) were in the 1S group, and 469 (52.6%) were without any DLB core features (NS group).

Presence of Key Symptoms

The demographic characteristics and cognitive and behavioral findings for the three groups are provided in Table 1. Within the Pro-DLB group, 103 (69.6%) patients had two core features of DLB, 36 (24.3%) had three core features, and 9 (6.1%) had four core features. The most frequent symptoms of hallucinations in the Pro-DLB group were passage sensation (26.7% of patients), presence

sensation (24.3%), and well-formed visual hallucinations (17.6%). For parkinsonism, the most frequent symptom in this group was amimia, found in 37.2% of patients. On the Mayo Clinic Fluctuations Scale, the two items most frequently present in the Pro-DLB group were drowsiness (53.4% of patients) and cognitive fluctuations expressed through changes in thought or language (32.0%). The CAF score was abnormal in 21.7% of patients in the Pro-DLB group, 7.6% of patients in the 1S group, and 2% in the NS group.

Table 1

Characteristics of the groups. Group with at least 2 DLB core features (pro-DLB), group with only one DLB core feature (1S group), and group without any core DLB feature (NS group).

'	NS group (N=469)	'	1S group (N=275)	'	pro-DLB group (N=148)	'	P
Age, years [a]	71.4	(66.1; 77.2)	71.7	(66.0; 77.7)	71.1	(63.1; 80.5)	.98
Gender F/M	298/171		163/112		94/54		.48
Education [b]	57.4%		58.2%		47.6%		.079
APOE-4, %	27.6%		25.6%		30.9%		.53
CDR=0.5, %	48.6%		47.6%		60.4%		**.037***
MMSE [a]	29	(27 ;30)	29	(27 ;30)	28	(27 ;29)	**.021***
IADL (N=8) restriction, N (%)	.		.		.		**.0031***
No	390	(84.2)	221	(81.5)	101	(70.1)	.
One	47	(10.2)	33	(12.2)	24	(16.7)	.
At least two	26	(5.6)	17	(6.3)	19	(13.2)	.
RBD	0%		56.7%		75.0%		NA
Movements during sleep	0%		49.8%		56.2%		NA
Nightmares, restless nights	0%		20.1%		45.2%		NA
Hallucinations	0%		13.8%		63.5%		NA
Passage hallucination	0%		3.6%		26.7%		NA
Presence hallucination	0%		4.0%		24.3%		NA
Visual hallucinations	0%		2.5%		17.6%		NA
Auditory hallucinations	0%		2.5%		12.8%		NA
Olfactory/taste hallucinations	0%		3.6%		12.8%		NA
Visual illusion	0%		2.5%		12.3%		NA
Delusion	0%		1.1%		12.8%		NA
Parkinsonism [c]	0%		24.4%		55.4%		NA
Facial expression (0/1/2/3/4)	100/0/0/0/0		88.8/10.9/0.4/0/0		62.8/31.7/3.4/2.1		NA
Rigidity	100/0/0/0/0		91.7/7.1/1.1/0/0		77.9/17.2/4.1/0.7/0		NA
Akinesia	100/0/0/0/0		87.2/12.8/0/0/0		71.0/23.4/4.1/0.7/0.7		NA
Falls	1.5%		3.3%		9.6%		NA
Fluctuations	0%		5.1%		42.6%		NA
Drowsiness/lethargy	10%		22.9%		53.4%		NA
Sleep>2hours	0.6%		3.6%		20.3%		NA

'	NS group (N=469)	'	1S group (N=275)	'	pro-DLB group (N=148)	'	P
Staring into space	0.4%		4.7%		18.4%		NA
Disorganized speech	2.1%		5.8%		32.0%		NA
Memory complaint [a]	5	(3.0; 6.0)	5	(3.0; 7.0)	6	(4.0; 7.0)	.0021*
Attentional complaint [a]	4	(3.0; 6.0)	5	(3.0; 6.0)	6	(4.0; 7.0)	.0001*
FCSRT sum of 3 free recall [a]	30	(24.0; 35.0)	29	(24.0; 34.0)	28	(23.0; 34.0)	.25
Fluency letter P [a]	21	(16.0; 26.0)	21	(17.0; 26.0)	20	(14.0; 25.0)	.15
Fluency Animals [a]	29	(23.0; 35.0)	28	(22.0; 34.0)	27	(20.0; 32.0)	.0065*
Rey figure 3 min recall [a]	18	(11.0; 23.0)	16.5	(10.0; 21.0)	16	(10.3; 22.0)	.128
TMT A sec/good move [a]	1.7	1.4; 2.3)	1.8	(1.3; 2.3)	1.9	(1.5; 2.5)	.030*
TMT B sec/ good move [a]	3.6	(2.6; 5.0)	3.6	(2.7; 5.1)	4.2	(2.8; 5.6)	.074
VOSP Position discrimination [a]	20	(19.0; 20.0)	20	(19.0; 20.0)	20	(19.0; 20.0)	0.0022*
VOSP Number location [a]	9	(8.0; 10.0)	10	(9.0; 10.0)	9	(9.0; 10.0)	0.68
VOSP Fragmented letters [a]	20	(19.0; 20.0)	20	(19.0; 20.0)	20	(19.0; 20.0)	0.041*
Cognitive profile, N (%)	.		.		.		.0003*
SCI	125	(27.4)	69	(25.6)	28	(19.7)	.
Pure a-MCI	26	(5.7)	30	(11.1)	12	(8.5)	.
Multidomain a-MCI	135	(29.6)	83	(30.7)	55	(38.7)	.
Pure na-MCI	114	(25.0)	60	(22.2)	17	(12.0)	.
Multidomain na-MCI	56	(12.3)	28	(10.4)	30	(21.1)	.
NPI-C ≥1 depression, N (%)	32.5%		36.9%		49.2%		.0032*
MINI 500 Depression, N (%)	6.7%		11.1%		26.2%		<.0001*
NPI-C ≥1 anxiety, N (%)	43.9%		45.8%		61.0%		.0033*
NPI-C ≥1 apathy, N (%)	17.8%		25.1%		36.1%		<.0001*

'	NS group (N=469)	'	1S group (N=275)	'	pro-DLB group (N=148)	'	P

[a] Median (Q1=first quartile-Q3=third quartile). [b] School leaving certificate; percentage. [c] As rated on UPDRS, out of 4. Abbreviations: a-MCI, amnestic mild cognitive impairment; ATD, antidepressant; ChEI, cholinesterase inhibitor; CSF, cerebrospinal fluid; Dopa=, L-Dopa; FAB, Frontal Assessment Battery; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental Status Examination; na-MCI, non-amnestic MCI; NL, neuroleptics; N, number; RBD rapid eye movement sleep behavior disorder; SCI, subjective cognitive impairment; TMTA, Trail Making Test A; TMTB, Trail Making Test B; UPDRS, Unified Parkinson's Disease Rating Scale.

Autonomic and Sensorineural Symptoms

Autonomic symptoms were more frequent in the Pro-DLB group than in the other two groups (Table 2). The most frequent in the Pro-DLB group were sicca syndrome (especially dry mouth) (43.8%), constipation (34.7%), sexual dysfunction (including decreased libido or erectile dysfunction, 32.8%), and rhinorrhea (27.9%). Photophobia was quite frequent in this group (36.3%). There was no difference in the cardiovascular metrics across groups.

Table 2

Autonomic and sensorineural symptoms in the prodromal dementia with Lewy bodies patients' group (pro-DLB group), compared to the group with only one core feature (1S), and the group without any DLB core feature (NS)

	NS group (N=469)		1S group (N=275)		Pro-DLB group (N=148)		P
Dry mouth, N (%)	84	(18.5)	80	(29.3)	64	(43.8)	**<.0001***
Eye dryness, N (%)	54	(11.9)	62	(22.7)	35	(24.0)	**<.0001***
Nasal dryness, N (%)	26	(5.8)	31	(11.4)	27	(18.5)	**<.0001***
Hypersalivation, N (%)	.		.		.		**<.0001***
Occasional hypersalivation	11	(2.4)	16	(6.0)	20	(13.8)	.
Daily hypersalivation	4	(0.9)	1	(0.4)	4	(2.8)	.
Lacrimation, N (%)	.		.		.		**<.0001***
Occasional lacrimation	35	(7.6)	41	(15.4)	26	(18.2)	.
Daily lacrimation	3	(0.7)	3	(1.1)	7	(4.9)	.
Rhinorrhea, N (%)	.		.		.		**<.0001***
Occasional rhinorrhea	38	(8.3)	28	(10.3)	29	(19.7)	.
Daily rhinorrhea	9	(2.0)	8	(3.0)	12	(8.2)	.
Photophobia, N (%)	.		.		.		**<.0001***
Occasional photophobia or with certain types of light	61	(13.2)	58	(21.3)	44	(30.1)	.
Permanent photophobia or with all types of light	7	(1.5)	5	(1.8)	9	(6.2)	.
Constipation, N (%)	.		.		.		**<.0001***
Occasional constipation but not requiring treatment	47	(10.2)	46	(16.9)	26	(17.7)	.
Frequent constipation requiring the use of laxatives	22	(4.8)	11	(4.0)	25	(17.0)	.
Sexual dysfunction, N (%)	.		.		.		**<.0001***
Slightly modified	52	(11.6)	27	(10.5)	20	(14.6)	.
Severely modified	21	(4.7)	31	(12.1)	25	(18.2)	.
SBP mmHg, (Q1-Q3) [a]	133.5	(122.3; 147.0)	130.5	(118.7;144.7)	135.3	(119.3; 149.3)	.144
DBP mmHg, (Q1-Q3) [a]	77.2	(69.3; 84.0)	76	(69.0; 84.0)	77.3	(69.7; 86.0)	.50
HR bpm, (Q1-Q3) [a]	70.7	(64.7; 79.3)	70.7	(64.3; 79.7)	72	(66.0; 80.0)	.49
Systolic hypotension N (%)	39	(9.4)	36	(14.5)	20	(16.0)	.052
Diastolic hypotension N (%)	29	(7.0)	26	(10.4)	13	(10.4)	.24
Variation in HR at orthostatism in bpm, (Q1-Q3) [a]	7	(3.0; 12.0)	7	(4.0; 12.0)	8	(5.0; 12.0)	.134

[a] Median (Q1=first quartile-Q3=third quartile). Abbreviations: Bmp, beats per minute; DBP, diastolic blood pressure;(diastolic hypotension= if DBP decreased by more than 10 mmHg); HR, heart rate; SBP, systolic blood pressure (systolic hypotension= if SBP decreased by more than 20 mmHg).

Cognitive, Functional and Behavioral Results

Overall, our results depict a more impaired cognitive, functional, and behavioral profile in the Pro-DLB group than in the other two groups (Table 1). The median MMSE was slightly lower in the pro-DLB group (P=.02). The cognitive complaint was more severe in the Pro-DLB group, whether at the memory (P=.0021) or attention level (P<.0001). No cognitive impairment was detected (i.e. SCI profile) in 19.7% of Pro-DLB, 25.6% of 1S and 27.4% of NS patients. The cognitive profile in the Pro-DLB group was for most patients multidomain; semantic fluency, Trail Making Test A (TMTA), fragmented letters and position discrimination of the Visual Object and Space Perception (VOSP) battery were more deficient in the Pro-DLB group than in the other two groups (Table 1).

The scores on the functional scales were also worse in the Pro-DLB group: the CDR 0.5 was more frequent (60.4%) than in the 1S group (47.6%) or the NS group (48.6%) (P=.037); a restriction of IADL was found in 29.1% of patients in the prodromal group, compared to 18.5% in the 1S group, and 15.8% in the NS group (P=.0031).

On the NPI-C, when compared to the other two groups, a higher proportion of patients in the pro-DLB group presented symptoms of anxiety (P=.0033), apathy (P<.0001), and depression (P=.0032). According to the scores on the questionnaire for depression (MINI 500), 26.2% of the Pro-DLB group could be considered to have major depression (P<.0001).

Genetic, Alzheimer's Biomarkers and FDG PET Results

The acceptance rates were comparable across the groups for all examinations, but lower in the Pro-DLB group for amyloid PET (21%, P=.04). In terms of genetic aspects, no difference was found for ApoE4 status (P=.53; Table 1). The CSF biomarker analysis showed that the pro-DLB group had lower P-Tau (50.6 versus 57.1 pg/ml for the NS group; P=.031) but this was not significant after adjustment (Figure 1, Table 3, P=.15). The proportion of patients with abnormal CSF biomarkers was significantly higher for P-Tau and Tau in the NS group (Figure 2). For FDG PET and amyloid PET, local and global analysis did not find any differences between the groups.

MRI Results

Among 892 patients, 874 (98%, comparable across groups) patients had a brain MRI. No difference was found for hippocampal volume (P=.61), total intracranial volume (P=.41), mean cortical thickness (P=.36), ROI cortical thickness (P=.26), or white matter hypersignals volume (P=.094) (Table 3). The BPF was significantly different across groups (P=.015, Table 3), but the decrease was observed only in the 1S group (P=.004). Focal cortical thickness analysis found a lower cortical thickness in the left fusiform (P=.0088) and right superior temporal (P=.024) gyri in the Pro-DLB group, but not if FDR-corrected. Sulcus-based brain MRI analysis, FDR-corrected, showed fold opening of different sulci combining the fronto-insular, occipital, temporal and olfactory regions in the 1S and Pro-DLB groups (Figure 3).

Table 3

Associations between the three groups of patients and biomarkers. Prodromal dementia with Lewy bodies group (pro-DLB), group with one core symptom (1S group), group without any core DLB symptoms (NS group)

	1S (vs NS)		Pro-DLB (vs NS)		
	OR	**[IC95%]**	**OR**	**[IC95%]**	**P-value**
ABeta42 abnormal (vs normal)	0.99	[0.36; 2.71]	0.25	[0.04; 1.61]	.33
T-Tau abnormal (vs normal)	0.36	[0.15; 0.91]	0.40	[0.10; 1.66]	.067
P-Tau abnormal (vs normal)	0.48	[0.21; 1.08]	0.48	[0.14; 1.64]	.15
ABeta42/40 abnormal (vs normal)	0.66	[0.25; 1.71]	0.86	[0.20; 3.66]	.69
Amyloid PET + (vs -)	0.88	[0.40; 1.93]	1.13	[0.36; 3.58]	.91
	Beta*	**[IC95%]**	**Beta***	**[IC95%]**	**P-value**
Intracranial volume, in cm3	-5.55	[-22.4;11.28]	-14.3	[-35.6; 7.01]	.41
BPF, in %	-1.11	[-1.85; -0.36]	-0.42	[-1.36; 0.53]	**.015**
Hippocampal volume, mm3	0.02	[-0.14; 0.17]	-0.09	[-0.29; 0.11]	.61
Mean cortical thickness in mm	-0.01	[-0.02; 0.01]	-0.01	[-0.03; 0.01]	.36
ROI cortical thickness ROI, in mm	-0.01	[-0.03; 0.01]	-0.02	[-0.05; 0.01]	.26
WMH volume, in log(mm3)	0.15	[0.01; 0.29]	0.11	[-0.07; 0.29]	.094
SUVR PET-FDG	0.02	[-0.02; 0.06]	-0.02	[-0.07; 0.03]	.43
SUVR PET-FDG for disease specific ROI	-0.00	[-0.05; 0.04]	-0.03	[-0.09; 0.04]	.68

The models in the table are adjusted for sex, age, education level, ApoE, type of MRI (if MRI measurement), and intracranial volume (if MRI and except for intracranial volume and BPF).

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; BPF, brain parenchymal fraction; FDG, fluorodeoxyglucose; PET, positron emission tomography; ROI, region of interest; WMH, white matter hypersignals.

* For a change in 1 unit of the biomarker

Discussion

We describe here a large nationwide study that specifically addressed the prodromal phase of dementia with Lewy bodies, at the baseline of the study. Clinically, patients in the Pro-DLB group were more likely to have symptoms of RBD and hallucinations, particularly passage and presence hallucinations. Among fluctuations, drowsiness and cognitive fluctuations were frequent in the Pro-DLB group. The most frequent symptom of parkinsonism in the Pro-DLB group was amimia. Sicca syndrome, constipation, sexual dysfunction, and rhinorrhea were the most frequent autonomic symptoms and photophobia was rather frequent, in the Pro-DLB group when compared to 1S and NS groups. Pro-DLB patients usually had a multidomain cognitive profile, with attentional and memory complaints. Concerning behavior, the Pro-DLB group had an over-representation of depression and anxiety. Cross-sectional brain imaging analysis showed a global decrease in brain volume (BPF) in the 1S group and a fold opening of occipital, olfactory, temporal, and fronto-insular regions in the 1S and pro-DLB groups. These results might suggest that a weak and localized atrophy process could be in progress.

Clinical Issues

The proportion of patients with probable pro-DLB in this study (16.6%) is consistent with the proportion of DLB in neuropathological studies, where it is between 4% and 24.7% of demented people [30]. Seventy-five percent of patients of the Pro-DLB group in our study presented RBD, the same proportion as in autopsy confirmed DLB demented patients [31]. Asking about hallucinations at an early stage makes it possible to have a description of them not by relatives but by the patients themselves. The most frequent symptoms were passage (26.7% of patients) and presence (24.3%) hallucinations, which is consistent with a previous study on MCI

patients [32]. Globally, 63.5% of the pro-DLB group had hallucinations and 31% had at least two types of hallucinations. Pro-DLB patients had delusion in 12.8%. Delusion was previously described as a way of entering in the disease [33].

We found symptoms of anxiety and depression respectively in 61% and 49.2% and a diagnosis of major depression in 26.2%. In this connection, a Japanese study reported that 14% of people aged over 50 years hospitalized for depression had prodromal or demented DLB [4]. For fluctuations, more than half of the Pro-DLB group reported drowsiness, before cognitive fluctuations. The scales for fluctuations detected fluctuations in the pro-DLB group in 21.7% of patients with CAF and 42.6% with the Mayo Clinic Fluctuations Scale. Using the latter scale, such fluctuations were previously reported in 76% of pro-DLB cases [34]. Parkinsonism was very discreet in our pro-DLB patients. A decrease in facial expression was the most common motor symptom in our study. This is consistent with a study of 26 prodromal DLB patients that found this to be an early symptom [35].

Autonomic dysfunction symptoms increased in parallel with DLB symptoms. Sicca syndrome was the autonomic dysfunction symptom most frequently described by patients, twice as many as in the NS group. To our best knowledge, this has never been described before in prodromal DLB or even in DLB. Sicca syndrome is a key symptom of primary Sjogren's syndrome during which dementia could appear [36]. In contrast, facial secretion symptoms, such as rhinorrhea, lacrimation and salivation, were also frequently found in our study. In prodromal DLB increased saliva was previously described [37, 38] unlike rhinorrhea and lacrimation. The frequency of constipation is rather heterogeneous depending on the studies and countries: a study in the general population in France previously found a frequency of 22.4% [39]. In the Pro-DLB group, we found a frequency of 34.7% against 15% in the NS group. This symptom has been described as occurring 9.3 years before the dementia phase of DLB [2]. Erectile dysfunction is an early symptom of DLB [35]. In our study, the frequency of sexual dysfunction (including erectile dysfunction but also a decrease or abolition of libido) in Pro-DLB group was 32.8%. In practice, autonomic disorders should therefore be systematically looked for in a context of mild cognitive disorder, particularly in the case of sicca syndrome, constipation, and rhinorrhea. The description of photophobia in Parkinson's disease was recently done but not in DLB [40]. In our study, the higher the number of core symptoms of DLB present, the higher the frequency of photophobia, with a maximum of 36.3% in the Pro-DLB group.

Globally, the 1S group could represent a possible pro-DLB group and, interestingly, the proportion of usual symptoms of DLB was intermediate between the NS group and the probable pro-DLB group: this was the case for autonomic, sensorineural, and behavioral symptoms. The 1S group therefore could correspond to an intermediate phase.

Cognitive Profile

The cognitive profile of the Pro-DLB group was more multidomain, non-amnestic and amnestic, and less SCI, than the NS and 1S groups. This is consistent with previous studies [9, 34, 41]. The main characteristics found in the Pro-DLB group was low speed processing, low semantic fluency and visuoperceptual and visuo-spatial impairment (Table 1).

Biomarkers

For CSF, the proportion of patients with abnormal Alzheimer's biomarkers was higher in the NS group than in the other two groups but no difference was found for ABeta42 and ABeta42/40, and no difference was found for amyloid PET. These results are consistent with a previous study [12], and argues in favor of the absence of tangles in the Pro-DLB group. However, the number of subjects tested was low, representing less than one third of the cohort.

Brain MRI and FDG PET

At the global and focal level, there was no difference between groups for FDG PET. On the contrary, brain MRI showed a smaller BPF in the 1S group. Moreover, the widening of sulci including fronto-insular sulci, occipital, temporo-occipital sulci and olfactory sulci (FDR corrected) in the 1S and pro-DLB groups is of high interest. First, the modifications in the olfactory sulci are highly consistent with neuropathology, where patients even with incidental Lewy bodies had these lesions in the olfactory bulbs [42]. Second, the fronto-insular involvement in the prodromal phase of DLB has been demonstrated previously, particularly in the anterior part of the insula [13, 43]. Third, the temporo-occipital involvement is of interest regarding hallucinations since these regions are in the ventral stream of the visual pathway (the "what" pathway) devoted to visual gnosis.

Limitations

Even if we used different biomarkers, including CSF, amyloid PET, FDG PET and MRI, no specific biomarker for DLB, such as FP-CIT dopaminergic imaging, was used in our study [15]. The questionnaire used for RBD might be too sensitive; however, the high proportion of RBD in our pro-DLB cohort is quite consistent with previous studies [35, 44].

Conclusion

This study provides a description of a nationwide cohort of pro-DLB patients at the baseline of the study. We have reported new, frequently occurring symptoms in this group of patients: sicca syndrome, photophobia, lacrimation, and rhinorrhea. The cognitive profile, biomarkers, and PET results are consistent with the literature. Changes in brain sulci, particularly olfactory and insula sulci, are also consistent with both neuropathological and other cohort data. The next step will be to investigate the clinical, biological, and imaging evolution of these patients.

Abbreviations

Apolipoprotein E (APOE)

Cerebrospinal fluid (CSF)

Brain parenchymal fraction (BPF)

Dementia with Lewy bodies (DLB)

False discovery rate (FDR)

18-Fluoro-Desoxy-Glucose (FDG)

Mild cognitive impairment (MCI)

Rapid eye movement (REM)

Sleep behavior disorders (RBD)

Subjective cognitive impairment (SCI)

White matter hyperintensities (WMH)

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the guidelines of the Declaration of Helsinki. The MEMENTO study protocol has been approved by the local ethics committee (“Comité de Protection des Personnes Sud-Ouest et Outre Mer III”; approval number 2010-A01394-35). All participants provided written informed consent.

Consent for publication

Not applicable.

Consortia

On behalf of the Memento study group

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on a reasonable request.

Competing interests

F.B. was the national coordinator for France for the Eisai Delphia (E2027) and Axovant Headway-DLB therapeutic trials; he is currently the national coordinator for France of the Roche Graduate

therapeutic trial; he had received honoraria from Roche and Biogen for oral presentations. The other author declare that they have no competing interests related to
the present work.

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Author's Contribution

FB, VB, CD, and JFM conceived or designed the study; acquired, analyzed and interpreted data; supervised or coordinated the study; and drafted the manuscript and revised it for important intellectual content. FB, CP, MC, FP, AG, MC, PLS, PKS, RD, CF, JFD, DW, OM, MS, CB, SH, AB, TA, CD, IN, MOH, SK, OB, MV, CM, NP, GC, BC conceived or designed the study, acquired data and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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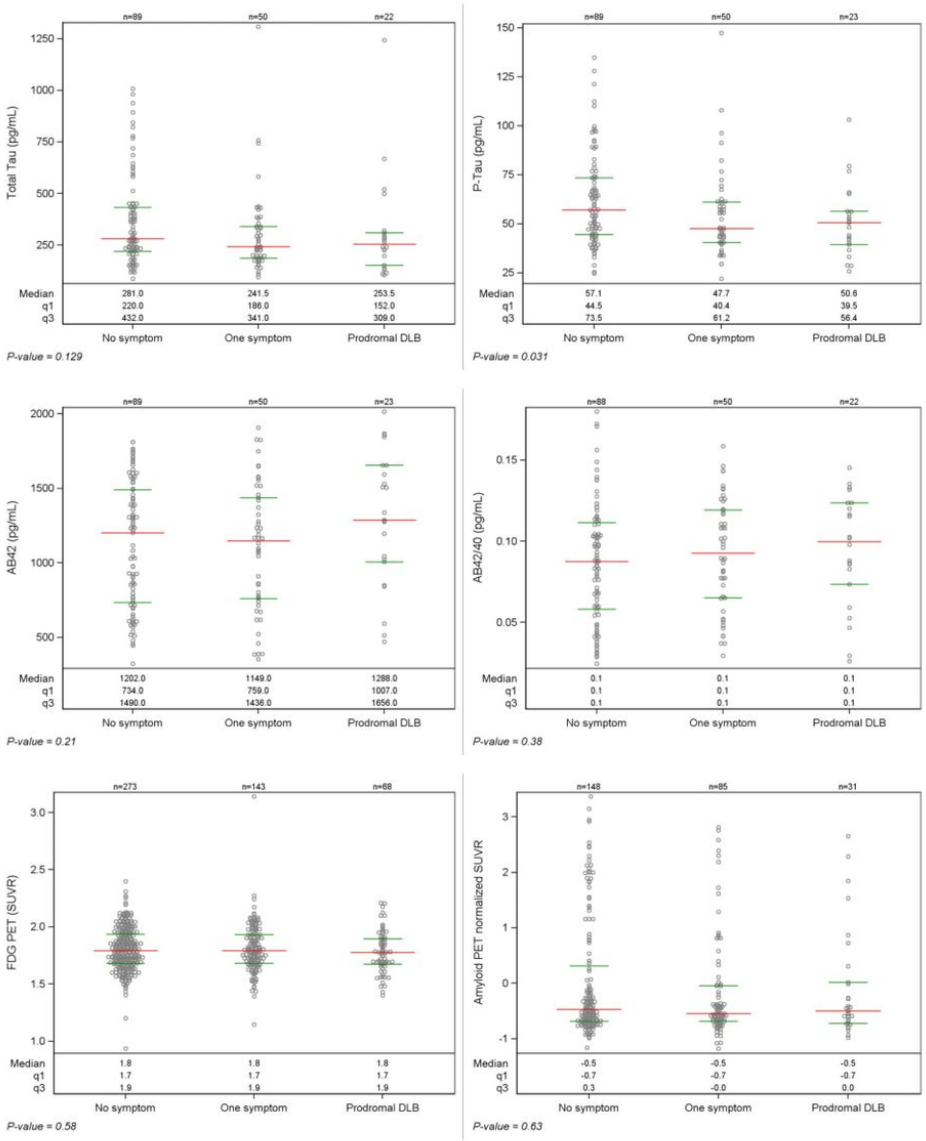
Figures



For descriptive purposes, amyloid PET SUVRs were standardized for each radioligand.

Figure 1

CSF, FDG PET and amyloid PET analysis of the three groups: pro-DLB group (2 or more core symptoms of DLB), one symptom group (one core symptom), and no symptom group (no core symptom)

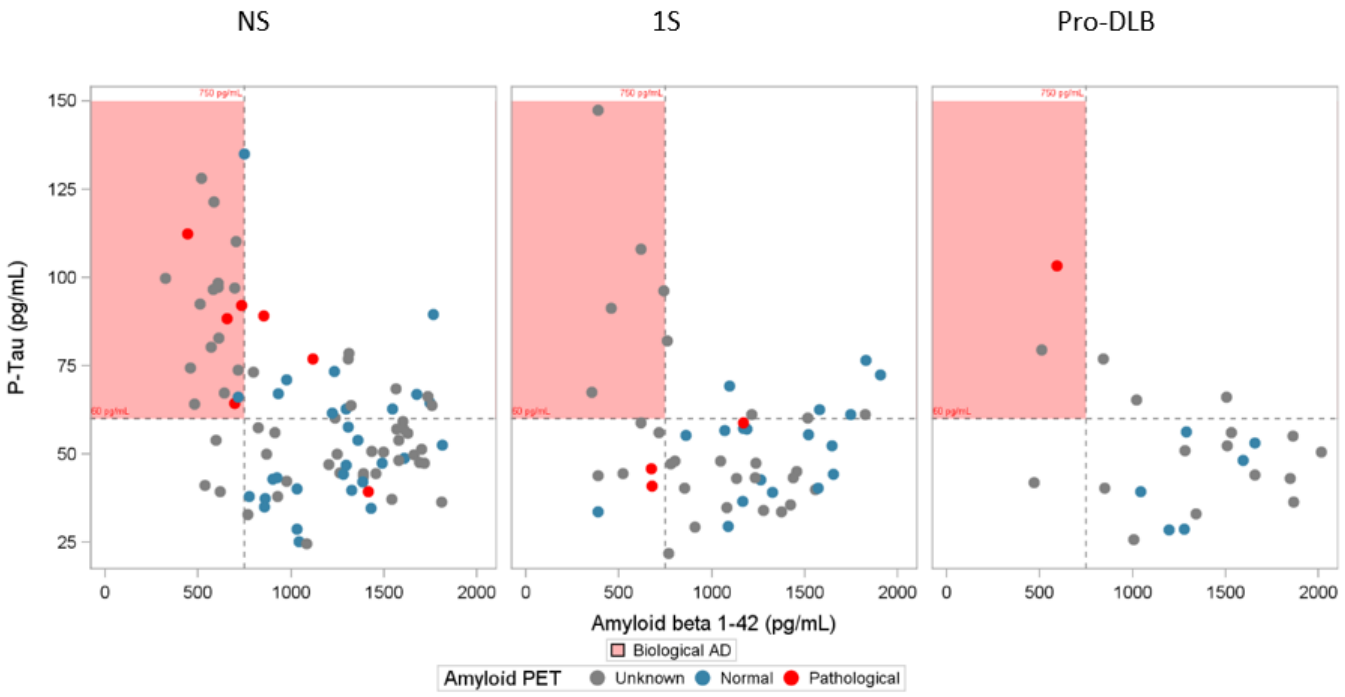


Figure 2

Results of the CSF and Amyloid PET biomarkers for prodromal dementia with Lewy bodies group (pro-DLB), group with only one core symptom (1S), group without any core DLB symptoms (NS)

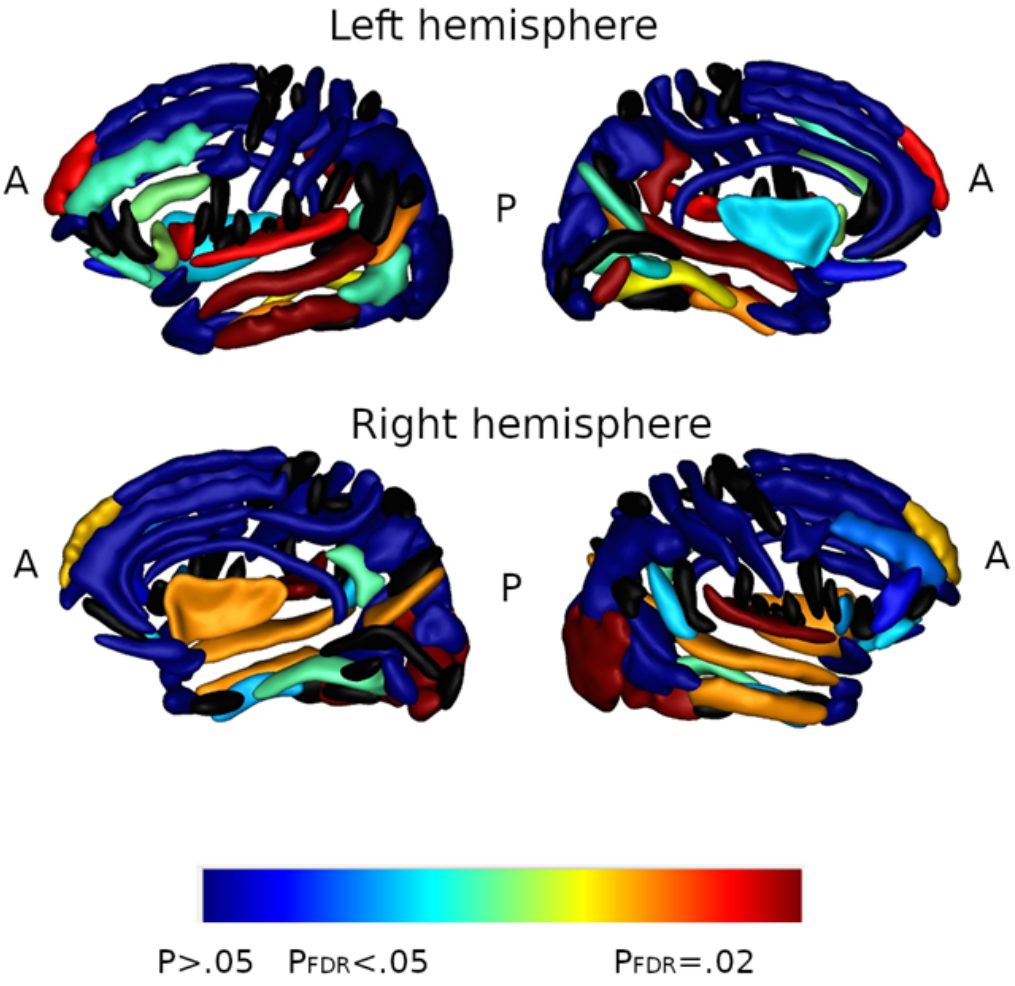


Figure 3

Enlargement of brain sulci in patients with one (1S group) or two (Pro-DLB) core symptoms of prodromal dementia with Lewy bodies