Journal of Alzheimer's Disease Reports 7 (2023) 1277–1288
DOI 10.3233/ADR-230064
IOS Press

Research Report

Subtypes of Dementia with Lewy Bodies: Clinical Features, Survival, and Apolipoprotein E Effect

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Received 11 July 2023
Accepted 1 November 2023
Published 27 November 2023

Abstract.
Background: Dementia with Lewy bodies (DLB) is a progressive neurodegenerative disease with various clinical symptoms. Limited data have described the clinical subtypes of DLB.
Objective: We aimed to compare clinical subtypes of DLB according to initial symptoms and to study the effect of Apolipoprotein E (*APOE*) gene in DLB.
Methods: We included DLB patients classified into three groups based on initial symptoms: non-motor onset (cognitive and/or psychiatric) (NMO-DLB), motor onset (parkinsonism and/or gait disorders) (MO-DLB), and mixed onset (non-motor and motor symptoms) (MXO-DLB). Clinical and *APOE* genotype associations and survival were analyzed.
Results: A total of 268 patients were included (NMO-DLB = 75%, MXO-DLB = 15.3%, MO-DLB = 9.7%). Visual hallucinations were more frequent ($p = 0.025$), and attention was less commonly impaired in MXO-DLB ($p = 0.047$). When adjusting with *APOE* ε4 status (*APOE* genotype performed in 155 patients), earlier falls and frontal lobe syndrome were more common in MXO-DLB ($p = 0.044$ and $p = 0.023$, respectively). The median MMSE decline was 2.1 points/year and the median FAB decline was 1.9 points/year, with no effect of clinical subtypes. Median survival was 6 years. It was similar in DLB subtypes ($p = 0.62$), but shorter for patients with memory symptoms at onset ($p = 0.04$) and for males ($p = 0.0058$).
Conclusions: Our study revealed a few differences between DLB clinical subtypes. *APOE* ε4 appears to be associated with earlier falls and a higher prevalence of frontal syndrome in MXO-DLB. However, DLB clinical subtypes did not impact on survival. Nevertheless, survival analysis identified other poor prognosis factors, notably inaugural memory impairment and male gender.

Keywords: Alzheimer's disease, dementia, genetic, Lewy bodies, survival

INTRODUCTION

Dementia with Lewy bodies (DLB) is a progressive neurodegenerative disorder that belongs to the group of synucleinopathies [1]. It is the second most common cause of neurodegenerative dementia after

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Alzheimer's disease (AD) and accounts for 0.3 to 34.4% of all dementia cases [2]. Its classic clinical and neuropathological description was made by Kosaka et al. in 1984 [3] and the "Lewy body dementia" label was coined in 1996 [2]. Clinically, DLB is defined, according to the latest criteria of McKeith et al. (2017), by the presence of dementia associated with a variable combination of core clinical features including visual hallucinations, parkinsonism, cognitive fluctuations, and rapid eye movement sleep behavior disorders (RBD) [1]. A variety of other clinical symptoms are suggestive features and can help with diagnosis. In the prodromal phase of DLB, not all symptoms are present, leading to high clinical heterogeneity. The clinical variability may be related to heterogeneous underlying pathology [4, 5]. From an etiopathogenic point of view, DLB is a multifactorial disease combining environmental and genetic factors. Although the current understanding of the genetic etiology is still limited, several genes seem to play a potential role in DLB such as the Apolipoprotein E (*APOE*), synuclein (*SNCA*), and β-glucocerebrosidase (*GBA*) genes [6].

There are currently limited data on the different DLB clinical subtypes according to initial symptoms. A better understanding of their peculiarities could provide a redesigned insight into the underlying pathophysiology of DLB and the possible factors influencing the disease course.

Thus, the aim of our study was to compare the clinical subtypes of DLB according to initial symptoms and to study the effect of the *APOE* gene in DLB in a Tunisian cohort.

METHODS

Study subjects

An observational cross-sectional study was carried out in the Department of Neurology at Razi University Hospital, a tertiary referral center in Tunis in North Tunisia, over a period of 18 years (from January 2003 to December 2020). Patients with Major Neurocognitive Disorder (MNCD) according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [7] and with clinically diagnosed probable or possible DLB according to the revised Mc Keith Criteria were included [1]. The latter requires the presence of dementia/MNCD, which is the essential feature, associated with one (possible DLB) or two (probable DLB) core clinical features: fluctuating cognition, recurrent visual hallucinations, RBD and one or more spontaneous cardinal features of parkinsonism. The first 3 typically occur early and may persist throughout the course [1]. We excluded all patients with parkinsonism and/or dementia of other origins.

Clinical and neuropsychological assessment

All patients had a neurological examination performed by a neurologist and a systematic brain imaging (brain CT scan or brain MRI). Demographic, clinical, and neuropsychological data were collected using standardized case-report forms.

Information was obtained from the participants and their caregivers about family and personal medical history and medication. Disease onset was defined as the age of occurrence of either cognitive, psychiatric, or motor symptoms (parkinsonism and/or gait disorders). We conducted a retrospective re-categorization analysis based on initial symptoms to classify patients into three subgroups: non-motor onset (cognitive and/or psychiatric onset) (NMO-DLB), motor onset (parkinsonism and/or gait disorders) (MO-DLB), and mixed onset (non-motor and motor symptoms) (MXO-DLB). We specified the presence and the number of core clinical features, i.e., cognitive fluctuations, recurrent visual hallucination, RBD, and parkinsonism. We also specified the presence of supportive clinical features, including severe sensitivity to antipsychotic agents, postural instability, repeated falls, syncope, severe autonomic dysfunction, hypersomnia, hyposmia, hallucinations in other modalities, systematized delusions, apathy, anxiety, and depression. Unified Parkinson's disease Rating Scale (UPDRS) section-III was used to rate the severity of extrapyramidal symptoms. The degree of severity of parkinsonian symptoms was measured using the Hoehn & Yahr (H&Y) scale. Other motor signs were assessed on examination including other movement disorders. For the assessment of levodopa responsiveness, we used an acute pharmacological test, namely the Acute levodopa challenge (ALC), which is routinely performed in our department. We used a standard protocol by administering a single dose of levodopa/carbidopa 250/25 mg. Motor response was quantified using the MDS- UPDRS-III. During the ALC, motor examination was performed immediately before and every 30 min after levodopa intake until the motor conditions returned to the motor baseline status. We calculated the percentage of motor response as the ratio of the difference

between the baseline and the peak-of-dose motor scores by the baseline motor score.

$$\frac{\text{Baseline motor score - the peak of dose motor score}}{\text{Baseline motor score}} \times 100 = \%$$

Levodopa-responsiveness was defined as an improvement rate $\geq$30% of MDS- UPDRS-III [8].

Besides, each patient underwent a neuropsychological examination at first consultation comprising the 30-item Mini-Mental State Examination (MMSE) standardized and validated in Tunisia and adjusted for age and education [9] to assess overall cognitive efficiency. The validated Arab version of the frontal assessment battery (FAB) [10] was used to evaluate executive functions and a score less than 16 was considered abnormal.

If patients had a second neuropsychological assessment after 6 months or more, the cognitive progression was evaluated for Global cognitive function using the annual decline of MMSE and for executive function using the annual decline of FAB. We calculated the annual decline of MMSE and FAB according to the formula:

- Annual decline of MMSE = (MMSE1-MMSE2)/(Time between MMSE1 and MMSE2 (years))
- Annual decline of FAB = (FAB1-FAB2)/(Time between FAB1 and FAB2 (years))

MMSE1 and FAB1 corresponded to the scores at first evaluation and MMSE2 and FAB2 corresponded to the scores at second evaluation.

The different cognitive domains evaluated by neuropsychological assessment included orientation, attention, episodic memory, language, apraxia, agnosia, visuospatial functions, judgment, and reasoning. Beck's Depression Inventory (BDI) (if the age <65 years) and Geriatric Depression Scale (GDS) (if the age >65 years) were used to evaluate mood disturbances and detect depression. Behavioral disorders were identified by the Neuropsychiatric Inventory (NPI).

Genetic study

Genotyping of *APOE* was performed using the Restriction Fragment Length Polymorphism Polymerase Chain Reaction (RFLP-PCR). *APOE* genotypes were determined by scoring for a unique combination of fragment sizes, as depicted by Hixon et al. In fact, digestion by HhaI restriction enzyme gives various combinations of fragment sizes for each genotype as pursued: $\varepsilon2/\varepsilon2$, 91 and 83 bp; $\varepsilon3/\varepsilon3$, 91 and 48 bp; $\varepsilon4/\varepsilon4$, 72 and 48 bp and a mixed genotype: $\varepsilon2/\varepsilon3$, 91, 83, and 48 bp; $\varepsilon3/\varepsilon4$, 91, 72, and 48 bp; $\varepsilon2/\varepsilon4$, 91, 83, 72, and 48 bp.

Statistical analysis

Statistical analyses were performed using R software for Windows using the "multinom", "SNPassoc", "Hmisc", and "ggplot" packages. Categorical variables were expressed as counts and percentages. For continuous variables, mean and standard deviations (SD) or median and Interquartile range (IQR) were used when appropriate. A chi-square exact test and a Fisher's exact test were used to calculate differences in categorical data as appropriate. To analyze the continuous variables, ANOVA test or nonparametric tests were used according to the distribution of data. Multinomial logistic regression was used to model outcome variables according to *APOE* $\varepsilon4$ carrying status. Corrections for multiple comparisons were employed with a Bonferroni correction. Analysis with a value of $p < 0.05$ were considered statistically significant. Survival was explored using Kaplan Meier analysis. Demographic, clinical, neuropsychological features, and frequency of *APOE* $\varepsilon4$ allele were analyzed in the survival analysis.

Ethics

All subject investigations conformed to the principles outlined in the Declaration of Helsinki and have been performed with permission of the Razi hospital ethic committee. All subjects were informed about the purposes of the study and gave written consent (patients themselves or caregivers) to participate in the study.

RESULTS

General study population characteristics

We screened 4,132 patients with MNCD and 464 patients with atypical parkinsonian syndrome. A total of 268 patients meeting the McKeith et al. DLB criteria [1] were included in this study: 250 probable DLB and 18 possible DLB. Median time to meet probable DLB criteria was 1.0 year (0.5–2.0). Male

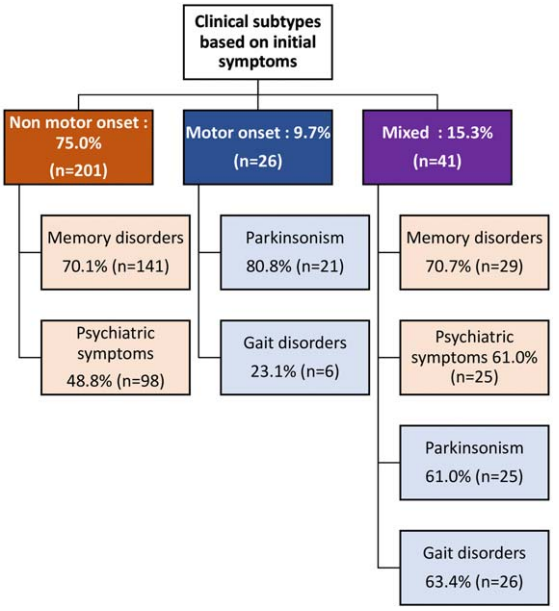

Fig. 1. Clinical subtypes of DLB according to initial symptoms.

predominance was noted with a sex-ratio equal to 1.4. The mean age at disease onset was 75.4 ± 7.9 years and ranged from 52 to 92 years and the mean age of onset of MNCD was 75.7 ± 7.9 years. The mean disease duration at 1st evaluation was 2.8 ± 1.8 years. Parental consanguinity was found in 35.5% of cases, with a family history of MNCD and parkinsonism in 43.7% and 16.4% of cases respectively. Clinical subtypes based on initial symptoms showed a non-motor onset in 75.0 %, a motor onset in 9.7%, and a mixed onset in 15.3% of cases (Fig. 1). There were no significant differences in age at disease onset, disease duration, sex ratio and family history between the 3 groups. Detailed demographic characteristics and family history of total DLB patients as well as stratified according to clinical subtypes were summarized in Table 1.

APOE genotype in DLB patients

The genetic study was performed in 155 patients. The *APOE* ε4 allele was found in 19.68% of cases and *APOE* ε2 in 5.16% of cases. The *APOE* ε3/ε3 genotype was the most frequent (54.83%) in the total DLB population as well as in the different clinical subtypes, followed by *APOE* ε3/ε4 (32.25%). The *APOE* ε4/ε4 genotype was found in only 3.25% of cases. There were no significant differences in allelic and genotypic frequencies of *APOE* gene across the clinical subtypes (Table 2).

Clinical features and APOE ε4 genotype effect in DLB clinical subtypes

Regarding symptoms at disease onset, memory complaints were the most frequent (63.4%), followed by psychiatric symptoms (45.9%), parkinsonism (17.2%), and gait disorders (11.9%). Memory disorders were equally common in both NMO-DLB and MXO-DLB, but psychiatric symptoms were more prevalent in MXO-DLB. Additionally, parkinsonism was more frequent in MO-DLB, while gait disorders were observed more often in MXO-DLB ($p < 0.001$) (Fig. 1).

At the time of the study, all core clinical features were present in 28.7%, three of them were present in 41.8%, two of them were present in 23.1% and only one core clinical feature was present in 6.3% of the cases. Among core clinical features, visual hallucinations were significantly more frequent in MXO-DLB than in MO-DLB ($p = 0.025$). Among supportive clinical features, postural instability was significantly more common in MO-DLB when adjusting with *APOE* ε4 carrying status ($p = 0.0027$) (Table 3).

Frequencies of repeated falls were not significantly different across clinical subtypes; however, they appeared at an earlier age in MXO-DLB subtype when adjusting with *APOE* ε4 genotype ($p = 0.044$) (Table 3).

Neurological examination showed that the parkinsonian syndrome involved mostly both trunk and limbs (77.83%), was mainly bilateral (94.35%), symmetrical (43.91%), and included mostly the 3 motor features (akinesia, tremor, and rigidity) (55.65%). Mean UPDRS-III score was 41.2 ± 17.1, mean Hoehn and Yahr score was 2.9 ± 0.9 and a positive response to levodopa was present in only 12.2% of cases. The comparison of the clinical subtypes showed no significant differences regarding parkinsonism characteristics. Frontal lobe syndrome was significantly more frequent in MXO-DLB when adjusting with *APOE* ε4 carrying status ($p = 0.023$) (Table 4).

At first neuropsychological assessment, the most impaired cognitive domains were executive functions (99.1%), memory (98.8%), and attention (98.7%) followed by and visuo-spatial functions (92.7%). Language was impaired in 83.7%, apraxia was noted in 81.0% and judgment and reasoning were impaired respectively in 63.6 % and 66.5% while agnosia was found in only 17.7% of cases and was the least affected cognitive domain. Mean MMSE and

Table 1
Demographic characteristics and family history of DLB patients

	Overall N = 268	Clinical subtypes			
		NMO-DLB, N = 201	MO-DLB, N = 26	MXO-DLB, N = 41	*p*
Gender (M/F), *n* (%)	155/113 (57.8/42.2)	117/84 (58.2/41.8)	14/12 (53.8/46.2)	24/17 (58.5/41.5)	0.743
Age at 1st evaluation, mean ± SD (y)	78.16 ± 7.98	78.25 ± 8.25	79.9 ± 6.15	76.61 ± 7.49	0.091
Disease duration at 1st evaluation, mean ± SD (y)	2.75 ± 1.78	2.85 ± 1.9	2.88 ± 1.34	2.20 ± 1.32	0.072
Age at disease onset, mean ± SD (y)	75.4 ± 7.94	75.39 ± 8.28	76.96 ± 6.1	74.44 ± 7.25	0.216
Educational level, *n* (%)					
Illiterate	184 (68.66)	138 (68.66)	17 (65.38)	29 (70.73)	0.412
Primary school	47 (17.54)	33 (16.42)	4 (15.38)	10 (24.39)	
High school	19 (7.09)	15 (7.46)	3 (11.54)	1 (2.44)	
University	12 (4.48)	10 (4.98)	1 (3.85)	1 (2.44)	
Not specified	6 (2.24)	5 (2.49)	1 (3.85)	0	
Parental consanguinity, *n* (%)	95 (35.45)	65 (32.34)	10 (38.46)	20 (48.78)	0.112
Family history of MNCD, *n* (%)	117 (43.7)	92 (45.77)	10 (38.46)	15 (36.59)	0.702
1st degree relative	56 (20.9)	47 (23.38)	3 (11.54)	6 (14.63)	0.967
2nd degree relative	57(21.3)	43 (21.39)	6 (23.08)	8 (19.51)	0.721
3rd degree relative	25 (9.33)	19 (9.45)	1 (3.85)	5 (12.2)	0.273
Family history of Parkinsonism, *n* (%)	44 (16.42)	28 (13.93)	8 (30.77)	8 (19.51)	0.416
1st degree relative	12 (4.48)	9 (4.48)	1 (3.85)	2 (4.88)	0.845
2nd degree relative	20 (7.46)	14 (6.97)	4 (15.38)	2 (4.88)	0.146
3rd degree relative	10 (3.73)	7 (3.48)	1 (3.85)	2 (4.88)	0.273

NMO-DLB, non-motor onset dementia with Lewy bodies; MO-DLB, motor onset dementia with Lewy bodies; MXO-DLB, mixed onset dementia with Lewy bodies.

Table 2
Allelic and genotypic frequencies of *APOE* gene in DLB patients

	Overall N = 155	Clinical subtypes			
		NMO-DLB N = 116	MO-DLB N = 16	MXO-DLB N = 23	*p*
Allelic frequencies, *n* (%)					
APOE ε2	16 (5.16)	13 (5.60)	0 (0.0)	3 (6.52)	0.639
APOE ε3	233 (75.16)	174 (75.0)	26 (81.25)	33 (71.74)	
APOE ε4	61 (19.68)	45 (19.4)	6 (18.75)	10 (21.74)	
Genotypic frequencies, *n* (%)					
APOE ε2/ε2	1 (0.64)	1 (0.9)	0 (0.0)	0 (0.0)	0.899
APOE ε2/ε3	13 (8.39)	10 (8.6)	0 (0.0)	3 (13.0)	
APOE ε2/ε4	1 (0.64)	1 (0.9)	0 (0.0)	0 (0.0)	
APOE ε3/ε3	85 (54.83)	64 (55.2)	10 (62.5)	11 (47.8)	
APOE ε3/ε4	50 (32.25)	36 (31.0)	6 (37.5)	8 (34.8)	
APOE ε4/ε4	5 (3.25)	4 (3.4)	0 (0.0)	1 (4.3)	

NMO-DLB, non-motor onset dementia with Lewy bodies; MO-DLB, motor onset dementia with Lewy bodies; MXO-DLB, mixed onset dementia with Lewy bodies.

FAB scores at first evaluation were respectively 15.5/30 ± 6.2 and 5.9/18 ± 3.4.

There were no significant differences between the different clinical subtypes in neuropsychological assessment except for attention which was less frequently impaired in MXO-DLB ($p = 0.047$) (Table 5).

On follow-up assessment, 71 patients had a second MMSE and 69 patients had a second FAB. Median MMSE decline was 2.1 points/ year and median FAB decline was 1.9 points/year. Clinical subtypes did not influence the rate of cognitive decline (Table 5).

On brain imaging, we found cerebral atrophy in 91.79% of the cases, mainly moderate and diffuse, and associated vascular lesions in half of the cases, with no significant difference across the clinical subtypes (Table 6).

Survival analysis

Survival data were available for 151 patients. Median survival from symptoms onset was 6 years. Median survival was significantly shorter for patients with memory symptoms at onset (5 years versus 9

Table 3
Essential feature, core clinical features and supportive features of DLB across clinical subtypes

	Overall N = 268 (%)	Clinical subtypes NMO-DLB N = 201	MO-DLB N = 26	MXO-DLB N = 41	*p*	p[1]
Cognitive complaint						
Memory complaint, *n* (%)	252 (94.03)	190 (94.52)	23 (88.46)	39 (95.12)	0.327	0.06
Age of onset of memory disorders, mean ± SD (y)	76.22 ± 7.9	75.9 ± 8.38	78.9 ± 6.18	75.79 ± 6.7	0.219	0.200
Core clinical features						
Number of core clinical features, mean ± SD	2.93 ± 0.88	2.95 ± 0.85	2.92 ± 0.93	2.83 ± 1.0	0.724	0.644
Cognitive fluctuations, *n* (%)	181 (67.54)	138 (68.65)	16 (61.53)	27 (65.85)	0.820	0.900
Visual Hallucinations[†], *n* (%)	243 (90.67)	187 (93.03)	21 (80.76)	35 (85.36)	**0.025**	**0.037**
Age of onset of VH, mean ± SD (y)	76.52 ± 7.8	76.5 ± 8.09	79.39 ± 4.96	74.80 ± 7.93	0.052	0.318
Disease duration at onset of VH, median [IQR] (y)	1 [0–2]	0.75 [0.0–2.0]	2.0 [1.0–4.0]	0.0 [0.0–1.0]	**0.0007**	**0.044**
Parkinsonism, *n* (%)	230 (85.82)	166 (82.58)	26 (100.0)	38 (92.68)	0.759	0.810
Age of onset of parkinsonism, mean ± SD (y)	76.65 ± 7.9	77.12 ± 8.23	77.15 ± 6.35	74.22 ± 7.19	0.095	0.653
Disease duration at onset of parkinsonism, median [IQR] (y)	2 [0.125–3.0]	2.0 [1.0–4.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	**<0.001**	**<0.001**
RBD, *n* (%)	140 (52.24)	100 (49.75)	12 (46.15)	16 (39.02)	0.438	0.396
Age of onset of RBD, mean ± SD (y)	71.01 ± 14.96	70.95 ± 15.46	76.25 ± 7.63	68.57 ± 14.6	0.444	0.446
Supportive clinical features						
Severe sensitivity to antipsychotic agents*, *n* (%)	44/101 (43.56)	34/82 (41.46)	5/8 (62.5)	5/11 (45.45)	0.281	0.814
Gait disorders, *n* (%)	161 (60.07)	109 (54.22)	19 (73.07)	33 (80.48)	0.211	0.645
Postural instability[‡], *n* (%)	32 (11.94)	18 (8.95)	8 (30.76)	6 (14.63)	0.103	**0.0027**
Age of gait disorder, mean ± SD (y)	77.3 ± 7.35	77.93 ± 7.52	78.18 ± 7.26	75.16 ± 6.68	0.098	0.197
Repeated falls, *n* (%)	123 (45.9)	87 (43.28)	16 (61.53)	20 (48.78)	0.478	0.242
Age of appearance of repeated falls[§], mean ± SD (y)	76.66 ± 7.5	77.95 ± 7.72	76.73 ± 6.87	72.95 ± 6.53	0.071	**0.044**
Syncope, *n* (%)	23 (8.58)	18 (8.95)	2 (7.69)	3 (7.31)	0.900	0.239
Severe autonomic dysfunction, *n* (%)	182 (67.91)	135 (67.16)	20 (76.92)	27 (65.85)	0.403	0.496
Hypersomnia, *n* (%)	52 (19.4)	40 (19.9)	5 (19.23)	7 (17.07)	0.778	0.333
Hyposmia, *n* (%)	16 (5.97)	12 (5.97)	2 (7.69)	2 (4.87)	0.643	0.947
Hallucinations in other modalities, *n* (%)	85 (31.72)	70 (34.82)	8 (30.77)	7 (17.07)	0,219	0.701
Systematized delusions, *n* (%)	145 (54.10)	115 (57.21)	13 (50.00)	17 (41.46)	0,245	0.163
Apathy, *n* (%)	45 (16.79)	38 (18.90)	1 (3.84)	6 (14.63)	0.416	0.824
Anxiety, *n* (%)	66 (24.63)	56 (27.86)	6 (23.07)	4 (9.75)	0.105	0.074
Depression, *n* (%)	100 (37.31)	75 (37.31)	10 (38.46)	15 (36.58)	0.879	0.071

[†]MO-DLB versus MXO-DLB: $p = 0.0017$. [‡]MO-DLB versus NMO-DLB: $p = 0.00137$ and MO-DLB versus MXO-DLB: $p = 0.00163$. [§]MO-DLB versus MXO-DLB: $p = 0.021$. *Calculated based on the number of patients who received antipsychotics. p[1]: adjusted for *APOE ε4* carrying status. NMO-DLB, non-motor onset dementia with Lewy bodies; MO-DLB, motor onset dementia with Lewy bodies; MXO-DLB, mixed onset dementia with Lewy bodies.

Table 4
Clinical characteristics of DLB patients across clinical subtypes

	Overall N = 268 (%)	Clinical subtypes NMO-DLB N = 201	MO-DLB N = 26	MXO-DLB N = 41	*p*	p[1]
Frontal syndrome[†], *n* (%)	56 (20.90)	37 (18.4)	5 (19.23)	14 (34.14)	0.067	**0.023**
Parkinsonian syndrome, *n* (%)	230 (85.82)	166 (82.58)	26 (100.0)	38 (92.68)	0.759	0.810
Distribution, *n* (%)						
Trunk	1 (0.43)	1 (0.60)	0 (0.0)	0 (0.0)	0.517	0.892
Limbs	38 (16.52)	28 (16.87)	5 (19.23)	5 (13.16)		
Trunk and limbs	179 (77.83)	128 (77.11)	20 (76.92)	31 (81.58)		
Not specified	12 (5.22)	9 (5.42)	1(3.85)	2 (5.26)		
Type, *n* (%)						
Tremo-akineto-rigid[‡]	128 (55.65)	85 (51.20)	20 (76.92)	23 (60.53)	**0.052**	0.077
Tremo-akinetic	7 (3.04)	6 (3.61)	0 (0.0)	1 (2.63)	0.679	0.306
Akineto-rigid	89 (38.70)	70 (42.16)	5 (19.23)	14 (36.84)	0.092	0.212
Not specified	6 (2.61)	5 (3.01)	1(3.85)	0 (0.0)	–	–
Distribution, *n* (%)						
Unilateral	4 (1.74)	2 (1.20)	1 (3.85)	1 (2.63)	0.836	0.255
Bilateral	217 (94.35)	157 (94.58)	24 (92.31)	36 (94.74)		
Not specified	9 (3.91)	7 (4.22)	1(3.85)	1 (2.63)		
Symmetry, *n* (%)						
Symmetrical	101 (43.91)	74 (44.58)	11 (42.31)	16 (42.11)	0.798	0.531
Asymmetrical	99 (43.04)	70 (42.17)	13 (50.0)	16 (42.11)		
Not specified	30 (13.04)	22 (13.25)	2 (7.69)	6 (15.79)		
UPDRS-III, mean ± SD	41.18 ± 17.1	39.38 ± 17.15	47.53 ± 15.18	40.65 ± 17.89	0.266	0.070
Sensitivity to Levodopa, *n* (%)	28 (12.17)	17 (10.24)	5 (19.23)	6 (15.78)	0.887	0.642
Levodopa response, mean ± SD	23.65 ± 17.03	24.42 ± 19.22	22.3 ± 15.43	23.19 ± 13.68	0.829	0.893
Hoehn and Yahr score, mean ± SD	2.90 ± 0.89	2.8 ± 0.84	3.19 ± 0.88	3.05 ± 1.01	0.741	0.088
Dystonia, *n* (%)	33 (12.31)	25 (12.43)	3 (11.53)	5 (12.19)	0.954	**0.021**
Myoclonus, *n* (%)	52 (19.4)	40 (19.9)	3 (11.53)	9 (21.95)	0.338	0.426

[†]MO-DLB versus MXO-DLB: $p = 0.05$. [‡]MO-DLB versus NMO-DLB: $p = 0.039$. MO-DLB versus MXO-DLB: $p = 0.017$. p[1]: adjusted for *ApoEε4* carrying status. NMO-DLB, non-motor onset dementia with Lewy bodies; MO-DLB, motor onset dementia with Lewy bodies; MXO-DLB, mixed onset dementia with Lewy bodies.

Table 5
Neuropsychological characteristics of DLB patients across clinical subtypes

		Clinical subtypes				
	Overall N = 268	NMO-DLB N = 201	MO-DLB N = 26	MXO-DLB N = 41	*p*	p[1]
Cognitive impaired domain, %						
Attention[†]	98.7	99.4	100	94.6	**0.047**	0.844
Memory	98.8	98.9	100	97.4	0.651	0.823
Visuo-spatial	92.7	93.9	100	84.2	0.252	0.572
Executive	99.1	98.8	100	100	0.698	0.826
Linguistic	83.7	85.5	78.3	78.4	0.429	0.428
Apraxia	81.0	82.7	77.3	74.3	0.459	0.692
Agnosia	17.7	20.0	9.5	10.8	0.243	0.273
Judgment	63.6	61.9	65.2	70.3	0.626	0.752
Reasoning	66.5	65.7	72.7	66.7	0.806	0.540
MMSE, mean ± SD/median [IQR] (/30)	15.46 ± 6.21 15.5 [12–19.0]	15.34 ± 6.32 15 [11.25–19]	16.12 ± 6.02 17 [13–19]	15.74 ± 5.88 15.7 [12.2–20.5]	0.861	0.652
FAB score, mean ± SD/median [IQR] (/18)	5.86 ± 3.36 5.0 [4.0–7.0]	5.68 ± 3.19 5.0[4.0–7.0]	6.04 ± 3.30 5.0 [3.5–9.0]	6.74 ± 4.19 6.0 [3.5–8.5]	0.416	0.857
Annual MMSE decline, mean ± SD/median [IQR] (/y)	3.95 ± 5.22 2.11 [0.0–5.82]	3.86 ± 5.38 2.0 [0.0–5.25]	5.14 ± 4.10 3.98 [0.64–8.79]	3.66 ± 5.31 0.72 [0.0–4.23]	0.604	0.992
Annual FAB decline, mean ± SD/median [IQR] (/y)	1.92 ± 2.61 1.92 [0.0–2.89]	1.77 ± 2.39 0.82 [0.0–2.8]	2.33 ± 4.17 0.96 [0.42–7.2]	2.63 ± 3.09 1.93 [0.0–3.56]	0.699	0.349
Mood evaluation						
GDS score, mean ± SD/median [IQR]	12.82 ± 6.72 13 [7.0–18.0]	12.9 ± 6.38 13 [7.75–17.0]	14.71 ± 8.01 18 [8.50–20.0]	11.38 ± 7.97 14 [3.0–17.0]	0.285	0.345
BECK score, mean ± SD/median [IQR]	19.6 ± 22.8 16 [5.0–19.0]	58.0 58 [58–58]	2.5 ± 3.54 2.50 [1.2–3.75]	17.5 ± 2.12 17.5 [16.7–18.2]	0.589	–
Evaluation of psychiatric and behavioral symptoms						
NPI score: FxG mean ± SD/ median [IQR]	48.96 ± 28.4 47 [26.25–65.7]	50.99 ± 28.4 48.5 [33–67.7]	39.56 ± 24.67 32 [21.7–55.7]	44.76 ± 30.62 45 [19–68]	0.793	0.673
NPI score: R[‡] mean ± SD/median [IQR]	23.97 ± 15.5 22 [15.0–31.0]	24.08 ± 11.52 23 [16.5–32.0]	16.08 ± 9.07 18 [10.0–19.0]	27.83 ± 29.64 22 [13.0–28.5]	**0.0386**[‡a]	**0.0028**[‡b]

[†]MO-DLB versus MXO-DLB: $p = 0.027$. [‡a]MO-DLB versus MXO-DLB: $p = 0.029$. [‡b]MO-DLB versus MXO-DLB: $p = 0.0169$ and MO-DLB versus NMO-DLB: $p = 0.035$. p^1: adjusted for *APOE* ε4 carrying status. NMO-DLB, non-motor onset dementia with Lewy bodies; MO-DLB, motor onset dementia with Lewy bodies; MXO-DLB, mixed onset dementia with Lewy bodies.

Table 6
Brain imaging characteristics of DLB patients across clinical subtypes

	Overall N = 268 (%)	Clinical subtypes			*p*	p^1
		NMO-DLB N = 201	MO-DLB N = 26	MXO-DLB N = 41		
Atrophy, *n* (%)	246 (91.79)	184 (91.54)	25(96.15)	37 (90.24)	0.361	0.495
Site						
Localized	21 (8.54)	15 (8.15)	3 (12.00)	3 (8.11)	0.650	0.841
Diffuse	220 (89.43)	167 (90.76)	21(84.00)	32 (86.49)		
Not specified	5 (2.03)	2 (1.09)	1 (4.00)	2 (5.41)		
Degree						
Mild	76 (30.89)	62 (33.70)	6 (24.00)	8 (21.62)	0,492	0.382
Moderate	82 (33.33)	59 (32.07)	8 (32.00)	15 (40.54)		
Severe	36 (14.63)	25 (13.59)	4 (16.00)	7 (18.92)		
Not specified	52 (21.14)	38 (20.65)	7 (28.00)	7 (18.92)		
Vascular leukopathy, *n* (%)	154 (57.46)	107 (53.23)	18(69.23)	29 (70.73)	0.576	0.402

p^1: adjusted for *APOE* ε4 carrying status. NMO-DLB, non-motor onset dementia with Lewy bodies; MO-DLB, motor onset dementia with Lewy bodies; MXO-DLB, mixed onset dementia with Lewy bodies.

years without, $p = 0.04$) and for males (5 years versus 7 years for women, $p = 0.0058$). There was no significant effect of clinical subtypes ($p = 0.62$) and *APOE* ε4 carrying status ($p = 0.89$) on survival in our DLB patients (Fig. 2).

DISCUSSION

In the present study, we classified the patients into three clinical subtypes according to initial symptoms and highlighted the characteristics of each subtype. To our knowledge, this large cohort of DLB patients is the first Tunisian and African study describing the clinical and cognitive features, genetic and prognostic factors of DLB according to clinical subtypes [11].

The onset of the disease was non-motor in 75.0%, motor in 9.7%, and mixed in 15.3% of cases. Non-motor onset was more frequent than in other atypical parkinsonian syndromes (APS) reported in our previously reported Tunisian APS series, where non-motor onset symptoms were noted in 6.7% of multiple system atrophy cases, 13.6% of supranuclear palsy cases and 20.7% of corticobasal degeneration cases. Conversely, the motor onset was less frequent than in other APS, where it varied between 62.9 and 66.7% of cases [11]. Hence, clinical subtype at disease onset could be used as an additional distinctive tool for the differential diagnosis of DLB versus other APS. In our study, the most frequent inaugural symptoms were memory disorders, followed by psychiatric manifestations, parkinsonism, and gait disorders. Along with our results, Morenas-Rodriguez et al. also reported, in their series including 81 DLB, the preponderance of a cognitive-predominant onset (56.8%), followed by neuropsychiatric-predominant onset (27.2%), then parkinsonism-predominant onset (16.0%) [12]. This predominance of isolated cognitive symptoms at onset highlights the difficulty in diagnosing DLB and distinguishing it from AD, at prodromal stages. Indeed, misdiagnosis during the initial assessments is common in DLB. In the post-mortem study of Smirnov et al., 71% of DLB confirmed after postmortem pathology were classified as AD at first assessment and only 26% were classified as DLB [13]. The variability of inaugural phenotypes of DLB may be related to pathological heterogeneity and a particular distribution of α-synuclein in the brain. Besides, Fujishiro et al. compared the distribution of amyloid deposition in patients with Lewy body diseases among different clinical phenotypes and noticed a greater amyloid overload in patients whose disease was initiated by cognitive disorders. Thus, the predominance of cognitive disorders could be explained by the associated amyloidopathy which would act "in synergy" with α-synuclein [14].

In our cohort, MXO-DLB patients developed more visual hallucinations, had an earlier age of onset of falls, less frequent attentional deficit, and more frequent frontal lobe syndrome, compared to MO-DLB and NMO-DLB. These two latter subgroups did not exhibit any specific characteristics. The minor clinical differences are likely to be the reflection of α-synuclein distribution. Ferman et al. (2020) noticed indeed that visual hallucinations and cognitive fluctuations were more common and parkinsonism less frequent in DLB patients with diffuse α-synuclein deposition compared to transitional DLB [5].

The median annual decline in MMSE score was 2.1 points in our cohort and clinical subtypes did not influence the rate of decline. This mean progression of decline was comparable to that previously reported [15, 16]. The clinical predictive factors of cognitive decline are currently unknown and of those studied, gender, initial MMSE score and core clinical features did not seem to have an impact on cognitive progression [15]. It appears interesting to mention that cognitive decline according to initial symptoms has not been described. However, Morenas-Rodriguez et al. who also studied the different clinical subtypes of DLB based on the main clinical features during the prodromal phase of the disease using cluster analysis, reported that the cognitive-predominant cluster was characterized by a long prodromal phase [12]. One of the only predictors of cognitive decline described in DLB is the presence of AD concomitant pathology measured in CSF or found in neuropathological studies [17–19]. Furthermore, previous studies also concluded to a faster disease progression in the presence of *APOE* ε4 allele in synucleinopathies without any relation with associated AD pathology. Indeed, Davis et al., who studied the effect of the *APOE* ε4 and *APOE* ε2 alleles in transgenic mice, demonstrated the presence of elevated levels of phosphorylated synuclein and greater gliosis in mice with *APOE* ε4 [20]. Although DLB phenotypes may be related to a particular brain distribution of α-synuclein [5], the brain imaging study of our DLB patients did not show any specific signs, in particular, no specific localized atrophy and there were no significant differences between the clinical subtypes.

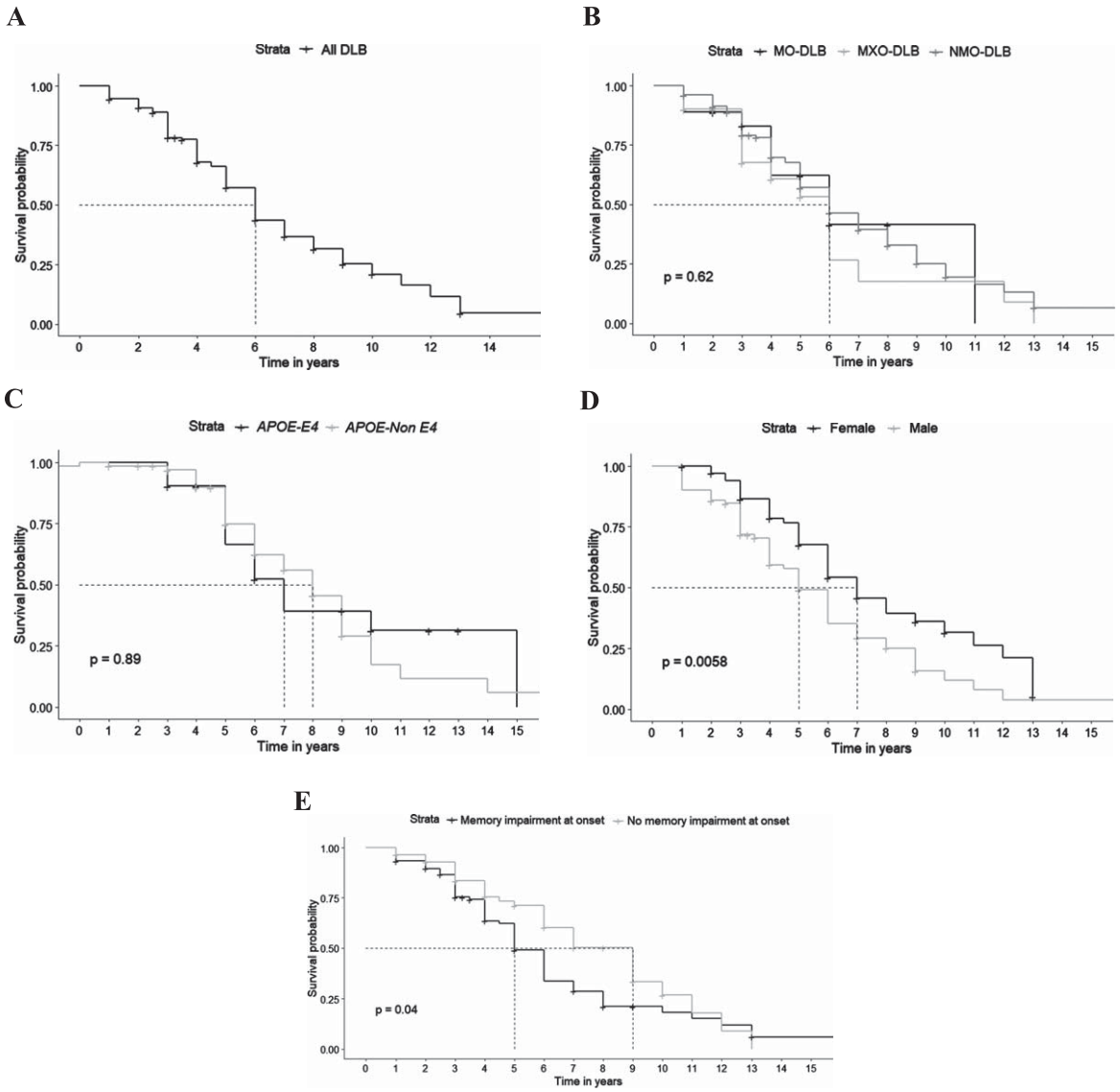

Fig. 2. Survival in DLB patients. A) Global survival. B) Survival according to clinical subtypes (NMO-DLB, non-motor onset dementia with Lewy bodies; MO-DLB, motor onset dementia with Lewy bodies; MXO-DLB, mixed onset dementia with Lewy bodies). C) Survival according to *APOE* status. D) Survival according to gender. E) Survival according to the presence of memory complaint at onset.

The genetic study of our cohort revealed that the *APOE* ε4/ε4 genotype was found in only 3.3% of cases and the *APOE* ε3/ε4 in 32.3% of DLB. Comparing the *APOE* genotype distribution in DLB with AD and controls in Tunisia, the frequencies *APOE* ε3/ε4 genotype in DLB was higher than in the general population and lower than in AD [21]. Furthermore, the frequency of the *APOE* ε3/ε4 genotype in our cohort was comparable to that of this genotype in pure DLB in the Caucasian population where it was 30.8% [22]. The presence of the *APOE* ε4 allele did not influence the clinical phenotype of our DLB patients, including the cognitive profile and cognitive decline.

Finally, the median survival of DLB in our study was 6 years. In agreement with our data, previous studies have reported a median survival in DLB ranging from 2 to 7 years [23, 24]. Clinical subtypes did not appear to influence survival in our study, in contrast to the literature, where inaugural visual hallucinations were correlated with shorter survival and parkinsonism was rather associated with a longer survival [24–27]. Indeed, Jellinger et al. showed that

the presence of parkinsonism as the initial symptom in Lewy body dementia (LBD), which encompasses both DLB and Parkinson's disease with dementia (PDD), can have a significant impact on mortality and is associated with a longer survival rate. However, these patients with inaugural parkinsonism experienced a delayed onset of dementia, suggesting that they may align more closely with the diagnosis of PDD. Consequently, it is expected that this subgroup will show a higher survival rate [26]. Nevertheless, in our cohort, DLB patients with memory symptoms at onset had shorter survival. Moreover, in accordance with previous studies, median survival was significantly shorter for males. As far as genetic factors are concerned, the *APOE* ε4 allele carrying-status, which has been formerly described as a factor of short survival in DLB, did not influence survival in our cohort [24–27].

The findings of our study have to be seen in light of some limitations. Our study is cross-sectional reflecting little about the dynamics of developing non-motor and motor signs in DLB patients and their chronology providing, as a consequence, limited insight about the evolution of clinical subtypes of DLB across time. Besides, the study of cognitive decline and survival as well as *APOE* genotyping were not performed in all patients. Nonetheless, it still was carried out on a large enough sample to allow statistical analysis.

Conclusion

Our study revealed few differences across DLB clinical subtypes, showing more visual hallucinations and less attention deficits in MXO-DLB. *APOE* ε4 seems to play a role in defining earlier falls and common marked frontal syndrome in MXO-DLB. These DLB clinical subtypes appear to have no impact on cognitive decline or survival. Yet, the survival analysis identified other poor prognosis factors in DLB patients, notably male gender and inaugural memory impairment. These findings do call for longitudinal studies assessing the evolving presentation of DLB clinical subtypes and the impact of genetic background on disease prognosis.

ACKNOWLEDGMENTS

We thank all patients who gave their consent and participated in the present study.

FUNDING

The authors have no funding to report.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available within the article and/or its supplementary material.

REFERENCES

[1] McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, Aarsland D, Galvin J, Attems J, Ballard CG, Bayston A, Beach TG, Blanc F, Bohnen N, Bonanni L, Bras J, Brundin P, Burn D, Chen-Plotkin A, Duda JE, El-Agnaf O, Feldman H, Ferman TJ, ffytche D, Fujishiro H, Galasko D, Goldman JG, Gomperts SN, Graff-Radford NR, Honig LS, Iranzo A, Kantarci K, Kaufer D, Kukull W, Lee VMY, Leverenz JB, Lewis S, Lippa C, Lunde A, Masellis M, Masliah E, McLean P, Mollenhauer B, Montine TJ, Moreno E, Mori E, Murray M, O'Brien JT, Orimo S, Postuma RB, Ramaswamy S, Ross OA, Salmon DP, Singleton A, Taylor A, Thomas A, Tiraboschi P, Toledo JB, Trojanowski JQ, Tsuang D, Walker Z, Yamada M, Kosaka K (2017) Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* **89**, 88-100.

[2] McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen ENH, Ballard C, de Vos RAI, Wilcock GK, Jellinger KA, Perry RH (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology* **47**, 1113-1124.

[3] Kosaka K, Yoshimura M, Ikeda K, Budka H (1984) Diffuse type of Lewy body disease: Progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree–a new disease? *Clin Neuropathol* **3**, 185-192.

[4] Fujishiro H, Iseki E, Nakamura S, Kasanuki K, Chiba Y, Ota K, Murayama N, Sato K (2013) Dementia with Lewy bodies: Early diagnostic challenges: Early diagnostic challenges of DLB. *Psychogeriatrics* **13**, 128-138.

[5] Ferman TJ, Aoki N, Boeve BF, Aakre JA, Kantarci K, Graff-Radford J, Parisi JE, Van Gerpen JA, Graff-Radford NR, Uitti RJ, Pedraza O, Murray ME, Wszolek ZK, Reichard RR, Fields JA, Ross OA, Knopman DS, Petersen RC, Dickson DW (2020) Subtypes of dementia with Lewy bodies are associated with α-synuclein and tau distribution. *Neurology* **95**, e155-e165.

[6] Outeiro TF, Koss DJ, Erskine D, Walker L, Kurzawa-Akanbi M, Burn D, Donaghy P, Morris C, Taylor J-P, Thomas A, Attems J, McKeith I (2019) Dementia with Lewy bodies: An update and outlook. *Mol Neurodegener* **14**, 5.

[7] Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, Petersen RC (2014) Classifying neurocognitive disorders: The DSM-5 approach. *Nat Rev Neurol* **10**, 634-642.

[8] Zhou W, Jiang J, Peng W, Zhou X, Du J, Mo L, Tan C, Liu X, Chen L (2021) Levodopa responsiveness in Parkinson's disease patients and white matter alterations in diffusion tensor imaging: A cross-sectional tract-based spatial statistics study. *Neuroreport* **32**, 636-642.

[9] Bellaj T, Jemaa SB, Romdhane NA, Dhiffallah M, Ali NB, Bouaziz M, Mrabet A (2008) Version arabe du mini mental state examination (A-MMSE): Fidélité, validité et données normatives. *Tunis Med* **86**, 10.

[10] Jemaa SB, Bellaj T, Romdhane NA, Chérif A, Zakraoui NO, Bouaziz M (2008) La Frontal Assessment Battery (FAB): Fidélité, Validité et Étalonnage d'une forme arabe. *Tunis Med* **86**(07), 793-800.

[11] Nasri A, Ben Djebara M, Sghaier I, Mrabet S, Zidi S, Gargouri A, Kacem I, Gouider R (2021) Atypical parkinsonian syndromes in a North African tertiary referral center. *Brain Behav* **11**, e01924.

[12] Morenas-Rodríguez E, Sala I, Subirana A, Pascual-Goñi E, Sánchez-Saudinós MB, Alcolea D, Illán-Gala I, Carmona-Iragui M, Ribosa-Nogué R, Camacho V, Blesa R, Fortea J, Lleó A (2018) Clinical subtypes of dementia with Lewy bodies based on the initial clinical presentation. *J Alzheimers Dis* **64**, 505-513.

[13] Smirnov DS, Galasko D, Edland SD, Filoteo JV, Hansen LA, Salmon DP (2020) Cognitive decline profiles differ in Parkinson disease dementia and dementia with Lewy bodies. *Neurology* **94**, e2076-e2087.

[14] Fujishiro H, Iseki E, Higashi S, Kasanuki K, Murayama N, Togo T, Katsuse O, Uchikado H, Aoki N, Kosaka K, Arai H, Sato K (2010) Distribution of cerebral amyloid deposition and its relevance to clinical phenotype in Lewy body dementia. *Neurosci Lett* **486**, 19-23.

[15] Kramberger MG, Auestad B, Garcia-Ptacek S, Abdelnour C, Olmo JG, Walker Z, Lemstra AW, Londos E, Blanc F, Bonanni L, McKeith I, Winblad B, de Jong FJ, Nobili F, Stefanova E, Petrova M, Falup-Pecurariu C, Rektorova I, Bostantjopoulou S, Biundo R, Weintraub D, Aarsland D (2017) long-term cognitive decline in DLB in a large multicentre, international cohort. *J Alzheimers Dis* **57**, 787-795.

[16] Rongve A, Soennesyn H, Skogseth R, Oesterhus R, Hortobágyi T, Ballard C, Auestad BH, Aarsland D (2016) Cognitive decline in dementia with Lewy bodies: A 5-year prospective cohort study. *BMJ Open* **6**, e010357.

[17] Ferreira D, Przybelski SA, Lesnick TG, Lemstra AW, Londos E, Blanc F, Nedelska Z, Schwarz CG, Graff-Radford J, Senjem ML, Fields JA, Knopman DS, Savica R, Ferman TJ, Graff-Radford NR, Lowe VJ, Jack CR, Petersen RC, Mollenhauer B, Garcia-Ptacek S, Abdelnour C, Hort J, Bonanni L, Oppedal K, Kramberger MG, Boeve BF, Aarsland D, Westman E, Kantarci K (2020) β-Amyloid and tau biomarkers and clinical phenotype in dementia with Lewy bodies. *Neurology* **95**, e3257-e3268.

[18] Howlett DR, Whitfield D, Johnson M, Attems J, O'Brien JT, Aarsland D, Lai MKP, Lee JH, Chen C, Ballard C, Hortobágyi T, Francis PT (2015) Regional multiple pathology scores are associated with cognitive decline in Lewy body dementias. *Brain Pathol* **25**, 401-408.

[19] Sarro L, Senjem ML, Lundt ES, Przybelski SA, Lesnick TG, Graff-Radford J, Boeve BF, Lowe VJ, Ferman TJ, Knopman DS, Comi G, Filippi M, Petersen RC, Jack CR Jr, Kantarci K (2016) Amyloid-β deposition and regional grey matter atrophy rates in dementia with Lewy bodies. *Brain* **139**, 2740-2750.

[20] Davis AA, Inman CE, Wargel ZM, Dube U, Freeberg BM, Galluppi A, Haines JN, Dhavale DD, Miller R, Choudhury FA, Sullivan PM, Cruchaga C, Perlmutter JS, Ulrich JD, Benitez BA, Kotzbauer PT, Holtzman DM (2020) *APOE* genotype regulates pathology and disease progression in synucleinopathy. *Sci Transl Med* **12**, eaay3069.

[21] Rassas AA, Mrabet Khiari H, Hadj Fredj S, Sahnoun S, Batti H, Zakraoui NO, Cherif A, Anane N, Ben Ali N, Messaoud T, Mrabet A (2012) High APOE epsilon 4 allele frequencies associated with Alzheimer disease in a Tunisian population. *Neurol Sci* **33**, 33-37.

[22] Tsuang D, Leverenz JB, Lopez OL, Hamilton RL, Bennett DA, Schneider JA, Buchman AS, Larson EB, Crane PK, Kaye JA, Kramer P, Woltjer R, Trojanowski JQ, Weintraub D, Chen-Plotkin AS, Irwin DJ, Rick J, Schellenberg GD, Watson GS, Kukull W, Nelson PT, Jicha GA, Neltner JH, Galasko D, Masliah E, Quinn JF, Chung KA, Yearout D, Mata IF, Wan JY, Edwards KL, Montine TJ, Zabetian CP (2013) APOE ε4 increases risk for dementia in pure synucleinopathies. *JAMA Neurol* **70**, 223-228.

[23] Mueller C, Soysal P, Rongve A, Isik AT, Thompson T, Maggi S, Smith L, Basso C, Stewart R, Ballard C, O'Brien JT, Aarsland D, Stubbs B, Veronese N (2019) Survival time and differences between dementia with Lewy bodies and Alzheimer's disease following diagnosis: A meta-analysis of longitudinal studies. *Ageing Res Rev* **50**, 72-80.

[24] Vergouw LJM, Bosman B, van de Beek M, Salomé M, Hoogers SE, van Steenoven I, Roks G, Bonifati V, van Swieten JC, Lemstra AW, de Jong FJ (2020) Family history is associated with phenotype in dementia with Lewy bodies. *J Alzheimers Dis* **73**, 269-275.

[25] Savica R, Turcano P, Bower JH, Ahlskog JE, Mielke MM (2019) Survival, progression in synucleinopathy phenotypes with parkinsonism: A population-based study. *Mayo Clin Proc* **94**, 1825-1831.

[26] Jellinger KA, Wenning GK, Seppi K (2007) Predictors of survival in dementia with Lewy bodies and Parkinson dementia. *Neurodegener Dis* **4**, 428-430.

[27] Lemstra AW, de Beer MH, Teunissen CE, Schreuder C, Scheltens P, van der Flier WM, Sikkes SAM (2017) Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry* **88**, 113-118.