

Frequency and clinical features of Lewy Body Dementia in Italian Memory Clinics

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Abstract. *Background:* The latest developments in Lewy Body Dementia (DLB) raise some controversies on clinical features, neuroimaging and therapy. The aim of our study is to determine clinical, neuropsychological, neuroimaging and EEG profile of DLB through retrospective and prospective data of 102 patients. *Methods:* data were collected with an analytical form that was developed by an expertise of neurologists. *Results:* DLB represented 4.8% of the dementia population, with no sex difference. Family history of dementia was common (24.5%), while familiarity for parkinsonism was rare (4.9%). Cognitive disturbances were the predominant clinical presentation at onset (49%), followed by behavioral symptoms (29.4%) and parkinsonism (21.6%). Clinical features at consultation were: memory disturbances (almost all cases), symmetrical (68.6%) or asymmetrical (18.6%) parkinsonism, cognitive fluctuations (49%), visuospatial deficits (53.9%), and visual hallucinations (44.1%). Autonomic signs were present in a third of the cases, while sleep disorders were present in 44.1%. Some clinical response to antiparkinsonian drugs was evident in half of the cases. MRI, SPET, EEG and Neuropsychiatric Inventory data were available in a subgroup of patients. *Conclusions:* Most of our data were in accordance with the previous literature. However, some data underline the relationship between DLB, Alzheimer's and Parkinson's disease. (www.actabiomedica.it)

Key words: Lewy Body Disease, clinical features, EEG, sleep disturbances, autonomic signs

Introduction

Dementia with Lewy bodies (DLB) is a neurodegenerative disease characterized by parkinsonism, visual hallucinations and cognitive fluctuations. This disease is an increasingly recognized disorder and is now thought to be the second most common type of degenerative dementia in elderly people accounting

for 10-15% of cases at autopsy (1). Nevertheless, the frequency in neuropathological series appears greater than in the clinical practice (2-4). Clinical diagnostic criteria of DLB were firstly published in 1996 (1) but they had suboptimal sensitivity even if acceptable specificity. Recently, these criteria have been modified to improve the detection of DLB cases (5). These criteria take into account the relevance of other clinical

features (REM sleep behavior disorder - RBD-, severe neuroleptic sensitivity) and recognize the role of low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging for diagnosis. However, data on sensitivity and specificity of these criteria are still not available. Moreover, in the last years the emerging interest for DLB has produced a growing body of data that have impacted the comprehension of clinical features, neuroimaging and therapy. However, the latest developments raise some controversies and difficulties: the genetic underpinnings of DLB have only recently begun to unfold and the frequency of family history has not been well characterized; the relative frequency of the main clinical features is not well defined; the clinical evaluation of fluctuations in cognition and vigilance is not standardized (even if some questionnaires have been proposed (6)); the efficacy of LDopa and cholinesterase inhibitor (ChEI) treatment in these patients needs further investigations; and the utility of neuropsychological and neurophysiological studies for differential diagnosis in the clinical practice is controversial (7, 8).

Clinicians need to recognize all the features of the clinical picture in order to correctly identify the DLB patients and to design appropriate clinical treatments. For this purpose, we collected data on demographic characteristics, clinical, neuropsychological, neuroradiological and EEG profiles of DLB patients in several neurological units in the north of Italy.

Subjects and Methods

The multicentric Italian Group for the study of DLB and Dementias associated to Parkinsonism collected retrospective (2003-2004) and prospective (2005-2006) data on DLB patients. DLB subjects were identified according to the clinical diagnostic criteria for DLB of McKeith et al, 1996 (1), since the most recent clinical criteria (5) were not available when the study began (2004). However, we revised our clinical series to establish how many patients could be reassigned from the diagnosis of "possible" DLB to "probable" DLB, with the new criteria.

A detailed analytical form was developed both in a paper-and-pencil and in a computerized version. This

form was developed by an expertise of neurologists working in Italian memory clinics (UVA). It is custom of the Italian Health System that patients with suspected dementia are sent to the UVA by the general practitioner in order to define the diagnosis. Initially, the form was administered to the patients by neurologists in order to evaluate possible defects, difficulties in supply, and any other absence. The form was then corrected and revised by the Group and was adopted by the staff of Memory Clinics (neurologists and geriatricians). The final form includes the following sections: demographic data (age, sex, education, civil status, caregiver, previous work), familiarity for dementia and parkinsonism, diagnosis ("possible" or "probable" DLB; time between onset and diagnosis), prevalent initial symptom, current symptoms and signs (in particular: presence of parkinsonism, gait disturbances and falls, cognitive fluctuations, behavioral and psychiatric symptoms, sleep disorders, autonomic failure, oculomotor disturbances, clinical evidence of temporo-spatial disorientation, memory, visuospatial, executive, praxic, gnostic or language deficits), pharmacological treatment, neuropsychological data (demonstration of temporo-spatial disorientation, memory, visuospatial, executive, praxic, gnostic or language deficits), the Neuropsychiatric Inventory (NPI), neuroimaging data (MRI/TC: focal or diffuse cerebral atrophy, cerebellar or brain stem atrophy, presence of cerebrovascular lesions; SPECT: focal cortical and/or subcortical hypoperfusion; DAT scan), and EEG patterns (diffuse or focal slowing activity, transient sharp waves, sleeping episodes).

Eight Italian Centers specifically devoted in following patients with dementia participated in the study (Milan: three Centres, Monza, Desio, Parma, Melegnano and Castellanza). All Centres were asked to supply the total number of patients evaluated for suspected dementia and the number of different final diagnosis (non demented, demented: Alzheimer's disease, DLB, frontotemporal dementia complex, vascular dementia, mixed dementia and other) for the year 2005. This was done in order to obtain data on the frequency of DLB in Italian clinics.

Data were collected with the consent of patients during routine clinical evaluations, and the research was carried out in accordance with the Helsinki Declaration.

Results

Data about 102 patients (56 retrospective and 46 prospective: the two groups had similar characteristics) were collected. Diagnosis of DLB was “probable” in 76.5% (78/102) of subjects, and “possible” in 23.5% of subjects (24/102) according to the 1996 McKeith criteria (1). When the new criteria were adopted (5) 82 patients had “probable” and 20 “possible” DLB. They represented 4.8% of all dementia patients (range 0.83-11.43) (see table 1 for details). The mean time from clinical onset and diagnosis of DLB was 2.5 ± 1.6 years (range 0.3-8.6).

Demographic characteristics. M:F ratio was 1:1 (52:50); mean age was 77.2 ± 6.9 years (range 55-91), mean education 6.5 ± 3.9 years (range 0-17). Distribution according to the decades of age is the following: 2% 50-59 years old, 8.8% 60-69 years old, 55.9% 70-79 years old and 33.3% 80 or more years old. A family history for dementia or parkinsonism was found in 25 (24.5%), and 5 patients (4.9%), respectively.

Clinical information. The most frequent prevalent clinical symptom at onset was cognitive impairment (49%, 51 patients), followed by psychiatric-behavioral symptoms (29.4%, 30 patients) and parkinsonism

(21.6%, 21 patients). The most frequent clinical features at evaluation were: memory disturbances which were observed in almost all cases, symmetrical (68.6%, 70 patients) or asymmetrical parkinsonism (18.6%, 19 patients), cognitive fluctuations (49%, 50 patients), visual hallucinations (44.1%, 47 patients). Table 2 gives more details on motor, cognitive and psychiatric-behavioral symptoms and signs at the moment of data collection.

Autonomic signs were evident in a third of cases (36 patients), sleep disorders were observed in 44.1% of cases (45 patients) and a REM Behavior Disorder was present in 13 patients (12.7 %) (table 3).

Pharmacological treatment. Antiparkinsonian drugs were administered in 49% of cases (41 patients): 30 patients were treated with levodopa (29.4%), 3 with dopamine agonists (2.9%) and 6 with an association of the two drugs (5.9%). The mean equivalent daily dose of levodopa (LEDD) was calculated on the basis of the following formula: 1mg of pergolide = 1 mg of lisuride = 1 mg of pramipexole = 2 mg of carbergoline = 5 mg of ropinirole = 10 mg of bromocriptine = 5 mg of apomorphine = 20 mg of dihydroergocriptine = 100 mg levodopa. The treated patients received a mean of 303 LEDD (range 36-800). Some clinical response was evident in 27/50, 54%. The re-

Table 1. Cases of suspected dementia (data of year 2005)

	U.V.A. ^a	U.V.A. Neurol Dept ^b	U.V.A. ^c	U.V.A. ^d	U.V.A. ^e	U.V.A. ^f	U.V.A. Neurol Dept ^g	U.V.A. ^h	
N° of suspected dementia	n°(mean)	n°(%)	n°(%)	n°(%)	n°(%)	n°(%)	n°(%)	n°(%)	
Not dementia	596(29.5)	51(25.5)	28(15.1)	282(31.0)	12(28.6)	21(9.5)	154(56.2)	20(28.2)	28(24.1)
Dementia	145(72.5)	157(84.9)	360(39.6)	25(59.5)	194(88.2)	120(43.8)	35(49.3)	73(62.9)	
AD	77(53.1)	76(48.4)	242(67.2)	10(40.0)	123(63.4)	68(56.7)	13(37.1)	43(58.9)	
VaD	11(7.6)	25(15.9)	70(19.4)	2(8.0)	4(2.1)	28(23.3)	9(25.7)	6(8.2)	
FTD	7(4.8)	24(15.3)	13(3.6)	4(16.0)	8(4.1)	12(10.0)	3(8.6)	6(8.2)	
Mix dementia	36(24.8)	21(13.4)	13(3.6)	7(28.0)	44(22.7)	9(7.5)	4(11.4)	12(16.4)	
DLB-PDD	14(9.7)	11(7.0)	22(6.1)	2(8.0)	15(7.7)	3(2.5)	6(17.1)	6(8.2)	
[DLB]	[36(4.8)]	[14(9.7)]	[4(2.5)]	[6(1.7)]	[2(8.0)]	[3(1.5)]	[1(0.8)]	[4(11.4)]	[2(2.7)]
U.E.	313(15.5)	4(2)	0(0.0)	268(29.5)	5(11.9)	5(2.3)	0(0.0)	16(22.5)	15(12.9)

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AD=Alzheimer's disease; VaD=Vascular dementia; FTD=Fronto-Temporal dementia; DLB=dementia with Lewy bodies;

PDD=Parkinson dementia; U.E.=under evaluation

Table 2. Clinical data: details about motor, cognitive and psychiatric-behavioral symptoms and signs at the time of data collection

	% of cases (n° of patients/102)
Motor symptoms and signs	
Parkinsonism	87.2%(89)
[<i>symmetric;asymmetric</i>]	[78.6%; 21.4%]
Gait disturbances and falls	50%(51)
Flex axial hypertonia	32.3%(33)
Rest tremor	14.7%(15)
Intentional tremor	11.8%(12)
Frontal release signs	36.3%(37)
Pyramidal signs	12.7%(13)
Coordination disturbances	12.7%(13)
Oculomotor deficits	8.8%(9)
Myoclonus	2.9%(3)
Cognitive symptoms and signs	
Temporal disorientation	52%(53)
Spatial disorientation	37.3%(38)
Memory deficits	71.5%(73)
Frontal deficits	11.8%(12)
Visuospatial deficits	13.7%(14)
Aphasia	8.8%(9)
Apraxia	24.5%(25)
Cognitive fluctuations	49%(50)
Psychiatric-behavioral symptoms	
[<i>isolated;>1</i>]	76.5%(78)
[38.5%; 61.5%]	
Hallucinations	
[<i>visual; anthropomorphic; zoomorphic; both</i>]	56.9%(58)
	[46%; 70.2%;
	6.4%; 23.4%]
Delusion	21.6%(22)
Depression	24.5%(25)
Anxiety	13.7%(14)
Apathy	22.5%(23)

sponse was defined as “good” in 7 patients and as “moderate” in 20 patients.

Sixty-five patients were treated with cholinesterase inhibitors (rivastigmine 78.5%, donepezil 21.5%). Neuroleptic medications were used in 49 patients (48%): atypical and typical neuroleptics were used in 77.5% (38) and 22.5% (11) of the treated patients respectively; 10,2% of the treated patients (5/49) showed hypersensitivity to the neuroleptic drugs therapy. Other frequently used psychotropic drugs were: anti-depressants (34.3%-35/102), benzodiazepines (22.5%-23/102) and antiepileptics (3/102-2.9%).

Table 3. Clinical data: details about sleep disorders and autonomic dysfunctions at the time of data collection

	% (n° of patients/102)
Sleep disorders [<i>isolated;>1</i>]	
Insomnia	44.1% (45) [80%; 20%]
Hypersomnia in the daytime	25.5%(26)
RBD	10.8%(11)
Prolonged mental confusion on awaking	12.7%(13)
	4.9%(5)
Autonomic failure [<i>isolated;>1</i>]	
	35.3% (36)
	[80.6%; 19.4%]
Orthostatic hypotension and Cardiovascular symptoms (postural Syncope, periferical edema, arrhythmias)	20.6%(21)
Urinary incontinence	13.7%(14)
Urinary retention	0.9%(1)
Constipation	9.8%(10)

Table 4. Neuropsychological data derived from formal tests at the time of data collection

MMSE score [mean±SD(range)]	[18.7±4.6(5-29)]
	%(n° of patients/92)
Spatial-temporal disorientation	66.3%(61)
Memory disturbances	
[<i>vSTM;vsSTM;vLMT;vsLTM</i>]	90.2%(83)
	[25.3%;18.1%;
	71.1%;36.1%]
Frontal deficits	56.5%(52)
Attention deficits	59.8%(55)
Visuospatial deficits	59.8%(55)
Language disturbances	18.5%(17)
Comprehension deficits	30.4%(28)
Constructive apraxia	53.3%(49)

vSTM = verbal Short Term Memory; VsSTM = visuospatial Short Term Memory; vLTM = verbal Long Term Memory; vsLTM = visuospatial Long Term Memory

Neuropsychological data. According to MMSE (9) 39 patients (39.4%) were affected by mild dementia (MMSE range score 20-29), 54 (54.5%) were affected by moderate dementia (MMSE 11-20) and 6 (6.10%) were affected by severe dementia (MMSE≤10). Most patients (92/102) received an extensive neuropsychological evaluation with formal tests. Results are shown in table 4.

NPI data. NPI score was available (mean 21.42±15.51; range0-68) for more than a half of pa-

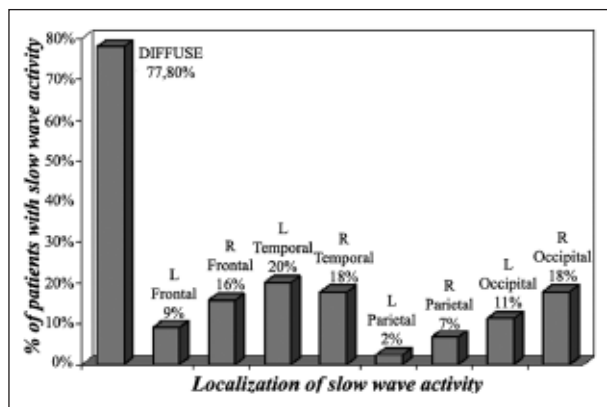


Figure 1. EEG data collected in 45 patients

tients (58/102). Apathy was the most frequent psychiatric manifestation (34/58-57%), followed by: hallucinations (30/58-52%), depression (28/58-48%), sleep disorders (6/58-45%), anxiety (25/58-43%), delusions (21/58-36%), and psychomotor agitation (19/58-33%).

Neuroimaging data. MRI/CT scan was available in a subgroup of 64 patients. Diffuse cerebral atrophy was evident in 49/64 patients. Moreover, 15 patients showed focal atrophy in one or multiple cerebral regions: frontal (10), parietal (2), temporal (8). No patient showed focal occipital atrophy. Concomitant slight vascular lesions, mainly perivascular white matter enlargement, were evident in 33 patients.

Twenty-two patients underwent a SPECT perfusion analysis. In two cases the exam was normal; in the remaining cases the examination showed focal hypoperfusion respectively in frontal (8), parietal (9), temporal (9), occipital regions (5) and in the basal ganglia(3). Only a few patients (4) received a DAT scan which resulted positive in all cases.

EEG data. EEG data were available in almost half of the collected cases (45 pts.). Figure 1 shows further details.

Discussion

As already described (7) this study confirmed that DLB is a disorder of late life. Differently from what is

generally accepted in Alzheimer's disease (AD), and in accordance with epidemiological studies (10), we found no sex preference in our DLB population.

In a clinical setting the relative frequency of this form of dementia appears lower than the frequency described in neuropathological data in literature. Previous epidemiological studies have reported contrasting results on the prevalence of clinical DLB, with a range from 0% to 5% regarding the general population, and from 0 to 30.5% of all dementia cases (10). The low frequency of DLB cases found in our multicenter study should be accepted with caution since subjects were referred to neurological units specifically designed for the diagnosis and care of cognitive disorders (UVA). However, similar results were obtained in a larger population from the Emilia-Romagna Region registry of dementia (11) where 2105 out of 3376 subjects referred for cognitive dysfunction were found to be demented with a prevalence rate of 2.4% for DLB. It is possible that higher values in terms of prevalence of DLB might result taking into account cases from centers devoted to the study of movement and psychiatric disorders.

We have observed a family history for dementia in a fourth of cases, in accordance with a previous report (12). Higher values (67%) for positive dementia family history were found in an autopsy-verified study (13) but this one was limited by the small sample size.

Only a minority of our cases showed a positive family history for parkinsonism. Some familial cases of DLB and some genetic mutations have been described (e.g. mutations in alfasynuclein gene) (14-16). However, the frequency of positive family history for parkinsonism in the general DLB population is still unclear.

Up to 78% of DLB patients present extrapyramidal syndrome (17) while in our sample the rate was slightly higher (87.2%). Such a high percentage could be attributed to the fact that parkinsonism is the easiest core symptom to be detected. Available data indicate the presence of the symmetrical form of parkinsonism, which is considered a typical pattern that distinguishes DLB from PD (17). In a fifth of our cases this was not true.

Gait difficulties and postural instability were evident in half of the patients. It shows some implication

in making differential diagnosis from AD (according to Allan et al: 75% of DLB versus 25% of AD patients (18)) allowing a prompt management and treatment in order to prevent falls.

Visual hallucinations represented the second most common core feature: these were less frequent in our series (56.9%) than previously reported by other authors (70%) (19). However, at the disease onset, hallucinations (19.6%) were as common as parkinsonism (20.5%). The hallucinations were mostly anthropomorphic, and more rarely zoomorphic as already described (20). The third core feature, fluctuations, were less common in our series (49%) than previously reported by other authors (21, 22). This clinical symptom is considered rare at the disease onset (less than 8% of cases) and it is likely that the different rates of appearance may depend upon clinical judgment, with poor levels of interrater reliability (22, 23). We agree that, in order to reliably evaluate fluctuations, clinicians need convenient instruments: in fact, standardized fluctuation scales may improve the accuracy of differential diagnosis between DLB and AD (21, 22).

In our study, autonomic failure is evident in more than a third of cases: it can represent an useful sign in supporting DLB diagnosis according to the recent McKeith criteria (5). While urinary incontinence and constipation are frequently reported in other types of dementia, orthostatic hypotension and cardiovascular symptoms were prevalent in our patients. According to the literature these two symptoms are characteristically associated with DLB rather than with AD (24) and may help in the differential diagnosis of these diseases.

Sleep disorders were present in almost half of the cases in our series: the most frequent disorder is insomnia followed by RBD, and hypersomnia in the daytime. The association of RBD and DLB was firstly observed in 1995 and sleep disturbances, frequently associated with underlying synucleinopathies, are currently viewed as suggestive features of DLB (5). Thus routine clinical investigations of sleep disorders is considered useful in improving the differential diagnosis between DLB and Alzheimer type dementia (25). The presence of oculomotor deficits in our patients was very low (8.8%) but not surprising as suggested by other authors (26,27): the occurrence of DLB pathol-

ogy at autopsy in patients with a diagnosis of PSP during life (due to the presence of supranuclear oculomotor palsy), and a patient meeting the DLB diagnostic criteria with severe impairment of vertical gaze movements have been described (28).

Although memory disturbances are not considered true cognitive markers of the early phase of DLB, (29, 30), they were very common in our sample both at clinical examination and neuropsychological assessment similarly to what is reported in AD (31). On the contrary, employing formal neuropsychological tests largely improves the detection of visuospatial and executive deficits which are considered relatively "specific" for DLB (29,32). At NPI, beyond typical DLB symptoms (e.g., hallucinations and sleep disorders), psychobehavioral disturbances often described also in AD (e.g., apathy, depression, and anxiety), were detected in almost half of patients.

Structural imaging with MRI/CT scan mostly showed diffuse atrophy and selective occipital atrophy did not emerge. On the contrary, functional investigations (EEG and SPECT) detected prominent occipital abnormalities in some subjects. Only four patients received DATscan (positive in all cases). It can be explained by two different reasons: firstly, the utility of DATscan to confirm the diagnosis of DLB has been only recently established (33); secondly, this procedure is very expensive and it is available only in a few Italian Services of nuclear medicine.

A significant number of DLB patients showed some response to LDopa, even if only in a minority of patients the motor improvement was considered clinically relevant by clinicians. Available literature is controversial on this subject. On one hand, the first studies suggested that clinical response to LDopa was poor and limited to only a third of cases (34, 35). On the other hand, a positive response of LDopa in about 75% of subjects has been recently suggested, particularly in the youngest without any worsening of cognitive functions (36). According to the literature on the significant positive effects of cholinesterase inhibitors on cognition in DLB (37, 38) these drugs were frequently used in our experience. On the other hand, although the neuroleptic sensitivity effect on this type of dementia is well known, in some cases such drugs were also administered. This could be due to the clin-

ician's need to reduce frequent psychobehavioral disturbances, in front of the familiar distress.

In conclusion, even though our study is neither epidemiologically nor autopsy based, this survey may result useful in the clinical everyday practice to improve the diagnosis of DLB, also taking into account the considerable overlapping of clinical manifestations in DLB and other neurodegenerative disorders such as AD and PD.

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