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ORIGINAL ARTICLE

The Italian dementia with Lewy bodies study group (DLB-SINdem): toward a standardization of clinical procedures and multicenter cohort studies design

L. Bonanni[1] · A. Cagnin[2,14] · F. Agosta[3] · C. Babiloni[4,15] · B. Borroni[5] · M. Bozzali[6] · A. C. Bruni[7] · M. Filippi[3] · D. Galimberti[8] · R. Monastero[9] · C. Muscio[10] · L. Parnetti[11] · D. Perani[12] · L. Serra[6] · V. Silani[13,16] · P. Tiraboschi[10] · A. Padovani[5] · On behalf of DLB-SINdem study group

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Abstract Dementia with Lewy bodies (DLB) causes elevated outlays for the National Health Systems due to high institutionalization rate and patients' reduced quality of life and high mortality. Furthermore, DLB is often misdiagnosed as Alzheimer's disease. These data motivate harmonized multicenter longitudinal cohort studies to improve clinical management and therapy monitoring. The Italian DLB study group of the Italian Neurological Society for dementia (SINdem) developed and emailed a semi-structured questionnaire to 572 national dementia centers (from primary to tertiary) to prepare an Italian large longitudinal cohort. The questionnaire surveyed: (1) prevalence and incidence of DLB; (2) clinical assessment; (3) relevance and availability of diagnostic tools; (4) pharmacological management of cognitive, motor, and behavioural disturbances; (5) causes of hospitalization, with specific focus on delirium and its treatment. Overall, 135 centers (23.6 %) contributed to the survey. Overall, 5624 patients with DLB are currently followed by the 135 centers in a year (2042 of them are new patients). The percentage of DLB patients was lower (27 ± 8 %) than that of Alzheimer's disease and frontotemporal dementia (56 ± 27 %) patients. The majority of the centers (91 %) considered the clinical and neuropsychological assessments as the most relevant

✉ L. Bonanni
l.bonanni@unich.it

[1] Department of Neuroscience Imaging and Clinical Sciences, University G.d'Annunzio of Chieti-Pescara, Via dei Vestini, 66100 Chieti, Italy

[2] Department of Neurosciences, University of Padova, Padua, Italy

[3] Division of Neuroscience, Neuroimaging Research Unit, and Department of Neurology, Institute of Experimental Neurology, San Raffaele Scientific Institute, Milan, Italy

[4] Department of Physiology and Pharmacology, University of Rome "La Sapienza", Rome, Italy

[5] Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Piazza Spedali Civili 1, 25100 Brescia, Italy

[6] Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy

[7] Centro Regionale di Neurogenetica ASP CZ, Lamezia Terme, Italy

[8] Neurology Unit, Deptartment of Pathophysiology and Transplantation, Fondazione Ca' Granda, IRCCS Ospedale Policlinico, University of Milan, Milan, Italy

[9] Department of Experimental Biomedicine and Clinical Neuroscience (BioNeC), University of Palermo, Palermo, Italy

[10] Divisione di Neurologia V e Neuropatologia, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy

[11] Clinica Neurologica, Centro Disturbi della Memoria, Università di Perugia (I), Perugia, Italy

[12] Division of Neuroscience, Nuclear Medicine Unit San Raffaele Hospital, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

[13] Department of Neurology-Stroke Unit and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano, Milan 20149, Italy

[14] IRCCS San Camillo Hospital Foundation, Venice, Italy

[15] IRCCS San Raffaele Pisana, Rome, Italy

[16] Department of Pathophysiology and Transplantation, "Dino Ferrari" Center, Università degli Studi di Milano, Milan 20122, Italy

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procedure for a DLB diagnosis. Nonetheless, most of the centers has availability of magnetic resonance imaging (MRI; 95 %), electroencephalography (EEG; 93 %), and FP-CIT single photon emission-computerized tomography (SPECT; 75 %) scan for clinical applications. It will be, therefore, possible to recruit a large harmonized Italian cohort of DLB patients for future cross-sectional and longitudinal multicenter studies.

Keywords Dementia with Lewy bodies · Standardization of diagnostic procedures · Survey

Introduction

Dementia with Lewy bodies (DLB) is the second most common neurological cause of dementia after Alzheimer's disease (AD). Fluctuations in attention, visual hallucinations (VH), and extrapyramidal signs are the cardinal features of DLB [1]. The accuracy of the clinical diagnosis of DLB is not satisfactory, because some 'core' clinical features may not appear during the entire course of the disease [2] or may overlap with AD [3]. Therefore, DLB tends to be underdiagnosed and misdiagnosed as AD [4–6]. However, it is important to differentiate the two diseases at the earliest stages, because DLB patients may be more sensitive to adverse effects of neuroleptics [1, 7], may exhibit faster disease progression [8, 9], and different response to acetylcholinesterase inhibitors [10]. Great emphasis has recently been placed on the necessity to identify more specific and sensitive diagnostic markers.

International studies carried out by single centers indicate for DLB elevated outlays for the National Health System, high rates of institutionalization, reduced quality of life and high rates of mortality [11].

The attention of the international research on the aforementioned issues is growing, as witnessed by the recent flourishing of longitudinal studies [12–19]. However, barriers to such research include the challenges in recruiting a sufficiently large and unbiased cohort, and lack of knowledge about which instruments are sensitive to change in DLB. To overcome these issues, longitudinal multicentre studies would be of great value.

The European scientific community has recently established a collaborative network of experienced clinical researchers in DLB and Parkinson's disease (PD) (E-DLB consortium) from ten different European countries, with the objective of designing "best practice" guidelines for conducting longitudinal cohort studies in DLB, focusing on recruitment sources, inclusion and exclusion criteria, diagnostic procedures, and longitudinal outcome measures, including both clinical and biomarker features.

In Italy, multicenter longitudinal cohort studies that support research into the provision and outcomes of health and social care are lacking. Italy has no available descriptive epidemiological studies to inform policy planning for DLB patients.

The recruitment of a sufficient number of DLB patients to perform relevant observational or interventional trials has not been reached yet, due to the variability and complexity of clinical profiles in DLB patients, who refer to a variety of primary dementia centers disseminated in the national territory with diverse specialized approaches, including psychiatric, neurological and geriatric, or to specialized movement disorder or sleep medicine clinics.

It appears necessary to reach a consensus on the definition of clear guidelines based on validated and standardized procedures, on the most appropriate diagnostic tools, and on the outcome measures to apply.

Finally, the knowledge of the earliest clinical manifestations of DLB is still shallow, whereas it would be essential to study the prodromal stages of the disease, to facilitate the application of timely and appropriate therapeutic approaches.

Toward these aims, the Italian Neurological Society for dementia (SINdem) promoted the constitution of an Italian DLB study group.

The general objectives of the study group were defined as follows:

a. To improve DLB identification by physicians working in dementia centers, since in Italy, the diagnosis of neurodegenerative dementia by primary dementia centers, especially for patients seen in the geriatric setting, is unbalanced toward AD.
b. To identify the DLB cohorts available in Italy and develop an efficient method of data collection.
c. To provide general guidelines and detailed recommendations for prospective cohort studies, which should include the use of sensitive and specific biomarkers and of clinical scales with proper psychometric properties.
d. To develop strategies to define and identify prodromal DLB.

The working plan of the DLB Group-SINdem network included two main steps:

1. The distribution of a semi-structured questionnaire to the primary dementia centers and to the tertiary centers participating in the SINdem.
2. Based on the data collected through the semi-structured questionnaire, the identification of a group of experts to achieve the following specific goals:
   a. To identify possible recruitment sources and bottlenecks.

b. To identify the best clinical scales to measure clinically relevant parameters and their changes overtime.
c. To provide guidelines for the selection of diagnostic and prognostic biomarkers.
d. To perform a genetic study to assess the presence of possible genetic clusters in the DLB populations afferent to the different centers involved.

Here, we report the results of the semi-structured questionnaires completed by the participating centers.

Methods

A semi-structured questionnaire was e-mailed to the dementia centers belonging to SINdem. The centers reached by the survey included both primary and tertiary referral centers, covering the Country from North to South. Each center was required to fill in a 22-point questionnaire.

Participants were asked to specify the site they worked in and their specialization. The questionnaire included either closed (yes/no) or multiple-choice responses. Clinicians were asked to mark on a visual rating scale their opinion about the broad prevalence of DLB as compared to AD and Frontotemporal Dementia (FTD). In addition, the clinicians were asked to indicate the number of new patients diagnosed and followed per year in their center.

A multiple-choice query investigated the comprehensive workup adopted for diagnosing DLB in clinical practice, according to consensus criteria for the diagnosis of DLB [1], as follows: (1) clinical assessment adopted to diagnose DLB, (2) diagnostic tools considered relevant to both DLB and prodromal DLB diagnosis, (3) application of the "one-year rule" to differentiate DLB from PD with dementia, (4) the availability of diagnostic tools in the center, (5) drugs adopted to treat cognitive decline, extrapyramidal signs and behavioural disturbances in DLB and in prodromal DLB, (6) the most frequent cause of hospitalization for patients with DLB, (7) the percentage of DLB patients who developed delirium, and (8) drugs adopted to treat delirium in DLB. Tables 1 and 2 specifically detail the content of each question.

Data analysis

Statistical analysis was performed using Statistical Package for the Social Sciences, SPSS vers. 13.0. Results were calculated according to the percentage of responses. Unpaired *T* test was applied to compare data collected from all centers.

Results

One hundred thirty-five out of 572 centers present in the Italian territory (Fig. 1a) responded to the survey (response rate: 23.6 %), and all agreed to participate to the DLB Group-SINdem network. Among the 136 centers, 102 were primary dementia centers, while 34 were tertiary dementia centers.

The geographical distribution of the participating centers, which resulted to be proportional to the number of centers present in each region, is reported in Fig. 1b. The majority of the clinicians worked in Neurology Centers (89.5 %), whilst the others were evenly distributed among Geriatric or Psychiatric Centers (10.5 %).

Overall, a total number of 2042 newly diagnosed DLB patients in the last year were collected, summing the number indicated by each center. The number of patients with DLB currently followed in Italy by the participating centers was 5624. A total number of 1136 prodromal DLB were collected during the last year by the participating centers, and the number of patients with prodromal DLB currently followed in Italy by the participating centers was 1796.

Figure 2 shows the distributions of DLB/prodromal DLB populations as total and annual referral as compared to AD patient populations.

DLB was considered to be less prevalent than AD (mean ± SD:26.8 % ± 7.8), and less prevalent than FTD (56.4 % ± 27).

Table 1 shows the results of the single specific multichoice questions.

Among the diagnostic tools for DLB diagnosis, the clinical/neuropsychological assessment was considered the most relevant by 93.8 % of the centers. The key symptoms for suspecting DLB were VH for 90 % of the centers, extrapyramidal signs for 71 % and fluctuating cognition (FC) for 61 %.

Interestingly, a high percentage of centers was aware that the administration of a neuropsychological test battery more focused on specific DLB symptoms (therefore, different than batteries designed for AD patients) is key for diagnostic accuracy: up to 30 % of the centers use a test battery different from that applied to AD already in the first evaluation and 57 % as a second-level diagnostic assessment.

The "one-year rule" to differentiate DLB from PD with dementia was applied by 74 % of the centers.

(123)I-FP-CIT single photon emission-computed tomography (FP-CIT SPECT) scan was considered a relevant diagnostic tool by 82.3 % of the centers. Only 52 % of the centers believed that structural magnetic resonance imaging (MRI)/computerized tomography (CT) are

Table 1 Summary of the data collected through the semi-structured questionnaire

Variables explored	Tertiary centers (34)	Primary centers (102)	*p* value
DLB prevalence in comparison with AD (%)	21.1 ± 10.9	24.5 ± 10.0	ns
DLB prevalence in comparison with FTD (%)	51.4 ± 23.5	57.5 ± 20.9	ns
Clinical signs considered relevant for DLB diagnosis (% of the centers)			
VH	94.1 ± 0.2	89.3 ± 0.3	ns
FC	76.5 ± 0.4	55.3 ± 0.5	0.03
Extrapyramidal signs	61.8 ± 0.5	73.8 ± 0.4	ns
Diagnostic tools considered relevant for DLB diagnosis			
Clinical/neuropsychological test batteries	97.1 ± 0.2	91.3 ± 0.3	ns
MRI/CT scan	44.1 ± 0.5	51.5 ± 0.5	ns
FP CIT SPECT scan	82.4 ± 0.4	80.6 ± 0.4	ns
EEG	26.5 ± 0.4	16.5 ± 0.4	ns
CSF	8.8 ± 0.3	8.7 ± 0.3	ns
Use of specific neuropsychological tests batteries (different than batteries designed for AD patients) at first assessment	29.4 ± 0.5	30.1 ± 0.5	ns
Use of specific neuropsychological tests batteries (different than batteries designed for AD patients) as second level assessment	58.8 ± 0.5	54.4 ± 0.5	ns
Application of the 1-year rule to differentiate DLB from PDD	79.4 ± 0.4	71.8 ± 0.5	ns
Clinical signs considered relevant for prodromal DLB diagnosis			
RBD	79.4 ± 0.4	74.5 ± 0.4	ns
Hyposomia	35.3 ± 0.5	29.4 ± 0.5	
Dysautonomic disorder	58.8 ± 0.5	46.1 ± 0.5	ns
Somatization	2.9 ± 0.2	6.9 ± 0.3	ns
No symptoms	0.0 ± 0.0	5.9 ± 0.2	ns
All symptoms	14.7 ± 0.4	17.6 ± 0.4	ns
Diagnostic tools available			
MRI (≥1.5T)	100.0 ± 0.0	96.1 ± 0.2	ns
EEG	100.0 ± 0.0	93.1 ± 0.3	ns
FP CIT SPECT scan	82.4 ± 0.4	75.5 ± 0.4	ns
Polisomnography (%)	79.4 ± 0.4	49.0 ± 0.5	0.002

When not differently stated, data are reported as percentage of the centers

DLB dementia with Lewy bodies, *AD* Alzheimer's disease, *FTD* frontotemporal dementia, *PDD* Parkinson's disease-dementia, *VH* visual hallucinations, *FC* fluctuating cognition, *RBD* REM sleep behaviour disorder, *MRI* magnetic resonance imaging, *CT* computerized tomography, *EEG* electroencephalography, *FP CIT SPECT* (123)I-FP-CIT single photon emission computed tomography

relevant. Low percentages of centers considered EEG (19 %) and cerebrospinal fluid (CSF) analysis (10 %) as particularly relevant for DLB diagnosis.

A prodromal DLB was suspected by 77 % of the centers in the presence of REM sleep behaviour disorder (RBD), which was by far the symptom considered the most relevant, followed by autonomic disturbances (for 50 % of the centers), and hyposmia (30 %). Somatoform disorders were recognized as relevant only by 5 %. A combination of all the aforementioned symptoms was considered useful for the diagnosis of prodromal DLB by 15 % of the centers.

The data collected on pharmacological treatments are summarized in Table 2.

The pharmacological management of cognitive decline in DLB mainly included the use of cholinesterase inhibitors (95 %).In prodromal DLB, cholinesterase inhibitors were used by 43 % of the centers and antidepressants in 16 %, while 40 % of the centers did not use any treatment in the prodromal stage.

Extrapyramidal symptoms are treated with L-dopa by 89 % of the centers, and with dopamine agonists by 13 %.

Behavioural disturbances were treated mainly with quetiapine (94 %) or clozapine (57 %); nonetheless olanzapine, risperidone and typical neuroleptics were used by 9–16 % of the centers.

The most frequent causes of hospitalization were acute worsening of behavioural symptoms (62 %), followed by

Table 2 Data on pharmacological treatment management for the different classes of symptoms in DLB patients

	University centers (34)	Primary centers (102)	*p* value
Cognitive decline in DLB patients			
AChEI	100.0 ± 0.0	92.2 ± 0.3	ns
Memantine	14.7 ± 0.4	20.6 ± 0.4	ns
L-Dopa	11.8 ± 0.3	16.7 ± 0.4	ns
Antidepressants	11.8 ± 0.3	12.7 ± 0.3	ns
No drugs	0.0 ± 0.0	3.9 ± 0.2	ns
Cognitive decline in prodromal DLB			
AChEI	35.3 ± 0.5	45.1 ± 0.5	ns
Memantine	5.9 ± 0.2	7.8 ± 0.3	ns
L-Dopa	2.9 ± 0.2	7.8 ± 0.3	ns
Antidepressants	14.7 ± 0.4	15.7 ± 0.4	ns
No drugs	50.0 ± 0.5	39.2 ± 0.5	ns
Extrapyramidal signs			
L-Dopa	97.1 ± 0.2	85.3 ± 0.4	ns
Dopamineagonists	5.9 ± 0.2	14.7 ± 0.4	ns
Behavioural disturbances			
Quetiapine	91.2 ± 0.3	93.1 ± 0.3	ns
Clozapine	67.6 ± 0.5	52.0 ± 0.5	ns
Risperidone	2.9 ± 0.2	10.8 ± 0.3	ns
Olanzapine	5.9 ± 0.2	18.6 ± 0.4	ns
BZD	26.5 ± 0.4	19.6 ± 0.4	ns
Typical neuroleptics	2.9 ± 0.2	11.8 ± 0.3	ns
Delirium			
Haloperidol	8.8 ± 0.3	20.6 ± 0.4	ns
BZD	32.4 ± 0.5	15.7 ± 0.4	0.04
Quetiapine	85.3 ± 0.4	79.4 ± 0.4	ns
Clozapine	70.6 ± 0.5	41.2 ± 0.5	0.003
Risperidone	5.9 ± 0.2	14.7 ± 0.4	ns
Olanzapine	8.8 ± 0.3	7.8 ± 0.3	ns
AChEI	29.4 ± 0.5	29.4 ± 0.5	ns
Melatonine	8.8 ± 0.3	12.7 ± 0.3	ns

Data are reported as percentage of centers

DLB dementia with Lewy bodies, *AChEI* acetyl-cholinesterase inhibitors, *BZD* benzodiazepines

motor deterioration (56 %). Infections were the cause of hospital admission for 32 % of the centers. The percentage of patients developing delirium during hospitalization was calculated as 60 ± 23.3 %. Quetiapine and clozapine resulted to be the most common medications used to treat delirium (82 and 49 %, respectively), 31 % of the centers used cholinesterase inhibitors to control delirium, 20 % used benzodiazepines and 19 % haloperidol. Melatonine was administered by 12 % of the centers.

We also analyzed separately data from University and primary centers. Only a few differences in the data collected were found: FC is considered more relevant for DLB diagnosis by University centers ($p = 0.03$); benzodiazepines and clozapine are more frequently used by University centers to treat delirium ($p = 0.04$ and $p = 0.003$, respectively); polysomnography is more available in University than in primary centers ($p = 0.002$) (Tables 1, 2).

The great majority of the centers (98 %) resulted to be endowed with structural MRI (at least 1.5T), 95 % can perform EEG, 78 % has access to FP-CIT SPECT scan, and 56 % has access to polysomnography.

Discussion

Within the DLB Group-SINdem network activity, the present survey collected data on DLB diagnostic procedures and management from 135 dementia centers in Italy.

Our survey showed that DLB was considered as prevalent as about 20 % as compared to AD, a percentage

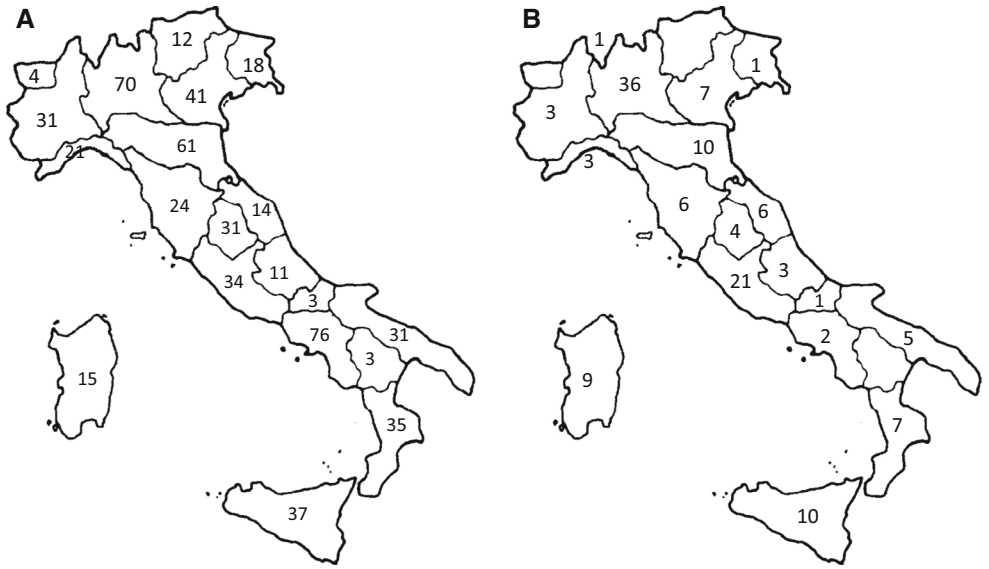

Fig. 1 **a** Geographical map distribution of all the dementia centers present in the Italian territory. **b** Geographical map distribution of the dementia centers which responded to the SINdem DLB group survey

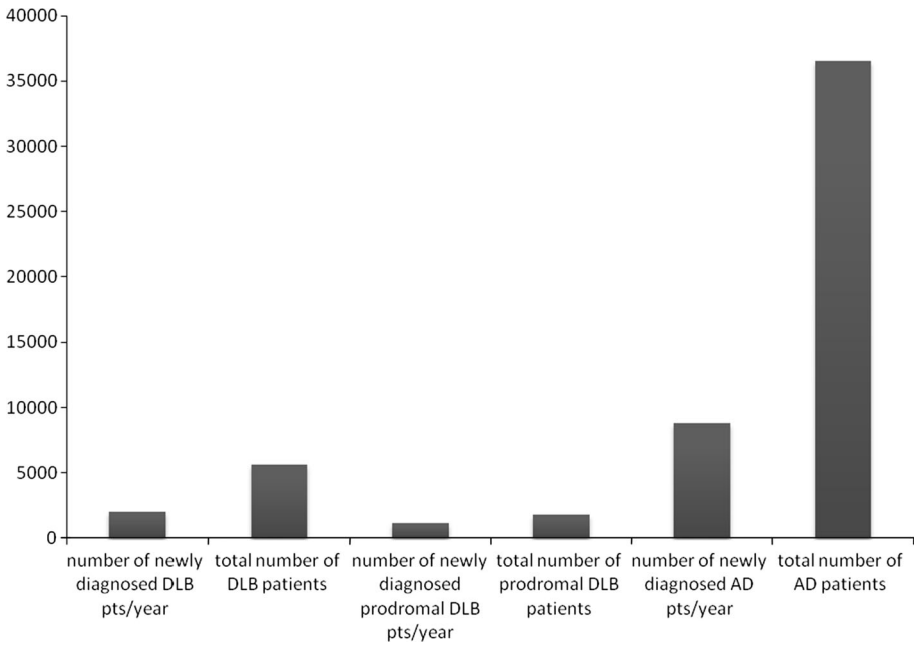

Fig. 2 Graphical representation of the Italian cohorts of DLB and prodromal DLB patients as compared to the overall referral of AD patients to the dementia centers which responded to the survey

slightly lower than the mean prevalence reported in the literature. DLB is, in fact, the second to third most common dementia after AD [1], therefore affecting more than a million individuals across Europe. Surprisingly, the prevalence of DLB was estimated to be about half of FTD prevalence, which accounts actually for only 5–15 % of all cases of dementia [20].

It is possible that both the clinical characteristics and fast progression of FTD, which affects relatively young individuals, and the presence of an established FTD Italian network [21] raised the attention of the clinicians to its diagnosis. Another explanation may be that the majority of the centers believe that the diagnostic procedures for DLB could simply rely on clinical/neuropsychological measurements, with inherent implication for underestimation of the disease. Furthermore, the criteria for clinical diagnosis of DLB have low sensitivity [1], indicating that the diagnosis is often missed, especially in the early stages, when the frequency of patients presenting the core symptoms is low [1].

Most centers demonstrated good awareness of the importance of recognizing specific clinical symptoms for

diagnosing DLB. A high percentage of centers is aware that the administration of a neuropsychological test battery more focused on specific DLB symptoms (therefore different than batteries designed for AD patients) is crucial for the accuracy of DLB diagnosis. Despite the recognized relevance of evaluating the presence of specific features, the importance given to the different core features for the diagnosis did not reflect the data reported in literature. Among the core features of DLB [1], VH was considered the most specific (91 %), whereas FC was considered relevant by 62 % of the centers, less than extrapyramidal signs (71 %), which are considered in the literature non-specific symptoms in the differential diagnosis with AD [22]. In our network, RBD was recognized as the most relevant symptom to suspect the presence of prodromal DLB.

Regarding neuroimaging, FP-CIT SPECT scan—which, at present, represents the gold-standard for the diagnosis of DLB [23]—was considered the most relevant instrumental diagnostic tool for DLB diagnosis by 82 % of the centers. EEG and CSF analysis were considered less relevant for the diagnosis especially by primary centers, suggesting that the two diagnostic tools are still considered more useful for research purpose than for clinical practice.

The pharmacological management of cognitive decline of both DLB and prodromal DLB patients resulted to be optimal by all the centers. Extrapyramidal signs are correctly treated with L-dopa. Behavioural disturbances are correctly treated with either quetiapine or clozapine by 94 % of the centers, but 9–16 % of the centers make use of typical neuroleptics or olanzapine and risperidone which are considered unsafe in patients with parkinsonisms [24] and especially in DLB, burdened by neuroleptic hypersensitivity [1]. Worsening of behavioural symptoms, of motor symptoms or infections, all resulted to be frequent causes of hospital admission. The majority of the centers demonstrated to have good knowledge of delirium and its management, but 19 % of the centers treat delirium in DLB with haloperidol, which even though represents a recognized efficacious and safe pharmacological choice for delirium in the general population, it is not indicated for DLB patients [1].

Of interest, no differences were found between University and primary centers, in terms of accuracy of diagnostic criteria applied (besides a higher awareness by the University centers on the importance to check for the presence of FC), in terms of diagnostic tools choice and of pharmacological treatment use. Finally, most of the centers reported to have access to MRI, EEG, and FP-CIT SPECT scan facilities, and all the centers accepted to be part of the DLB Italian network. Accordingly, the DLB Group-SINdem network will allow to recruit a large Italian harmonized cohorts for future cross-sectional and longitudinal multicenter studies.

Acknowledgments DLB-SINdem coauthors are listed below: Alberici A.[1]; Alberoni M.[2]; Amici S[3]; Appollonio I.[4]; Arena M.G.[5]; Arighi A[6]; Avanzi S.[7]; Bagella C.F.[8]; Baglio F.[2]; Barocco F.[9]; Belardinelli N.[10]; Bonuccelli U.[11]; Bottini G.[12]; Bruno Bossio R.[13]; Bruno G.[14]; Buccomino D.[15]; Cacchiò G.[16]; Calabrese E.[2]; Campanelli A.[17]; Canevelli M.[14]; Canu E.D.G.[18]; Cappa A.[19]; Capra C.[20]; Carapelle E.[21]; Caratozzolo S.[1]; Carbone G.F.S.[19]; Cattaruzza T.[22]; Cerami C.[23]; Cester A.[24]; Cheldi A.[25]; Cherchi R.[26]; Chiari A.[27]; Cirafisi C.[28]; Colao R.[29]; Confaloni A.[30]; Conti M.Z.[31]; Costa A.[32]; Costa B.[33]; Cotelli M.S. [34]; Cova I.[35]; Cravello L.[36]; Cumbo E.[37]; Cupidi C.[29]; De Togni L.[38]; Del Din G.[39]; Del Re M. L.[40]; Dentizzi C.[41]; Di Lorenzo F.[42]; Di Stefano F.[43]; Dikova N.[44]; Farina E. [2]; Floris G.[43]; Foti A.[45]; Franceschi M.[46]; Fumagalli G.G.[6]; Gabelli C.[47]; Ghidoni E.[48]; Giannandrea D.[49]; Giordana M.T.[50]; Giorelli M.[51]; Giubilei F.[52]; Grimaldi L.[53]; Grimaldi R.[37]; Guglielmi V.[54]; Lanari A.[55]; Le Pira F.[56]; Letteri F.[57]; Levi Minzi G.V.[58]; Lorusso S.[59]; Ludovico L.[60]; Luzzi S.[61]; Maggiore L.[35]; Magnani G.[62]; Mancini G.[63]; Manconi F.M.[64]; Manfredi L.[65]; Maniscalco M.[66]; Marano P.[67]; Marcon M.[68]; Marcone A.[23]; Marra C.[54]; Martorana A.[42]; Mascia M.G. [64]; Mascia V.[69]; Mauri M.[70]; Mazzei B.[71]; Meloni M.[72]; Merlo P.[73]; Messa G.[74]; Milia A.[64]; Monacelli F.[75]; Montecalvo G.[76]; Moschella V.[77]; Mura G.[78]; Nemni R.[2]; Nobili F.[79]; Notarelli A.[80]; Di Giacomo R.[81]; Onofrj M.[81]; Paci C.[82]; Padiglioni C.[49]; Perini M.[83]; Perotta D.[36]; Perri (Formenti A.)[84]; Perri R.[85]; Piccininni C.[54]; Piccoli T.[86]; Pilia G.[64]; Pilotto A.[1]; Poli S.[87]; Pomati S.[35]; Pompanin S.[88]; Pucci E.[89]; Puccio G.[29]; Quaranta D.[54]; Rainero I.[90]; Rea G.[91]; Realmuto S.[92]; Riva M.[93]; Rizzetti M.C.[94]; Rolma G.[95]; Rozzini L.[93]; Sacco L.[96]; Saibene F.L.[2]; Scarpini E.[6]; Sensi S.[97]; Seripa D.[98]; Sinforiani E.[99]; Sorbi S.[100]; Sorrentino G.[101]; Spallazzi M.[9]; Stracciari A.[102]; Talarico G.[14]; Tassinari T.[103]; Thomas A.[81]; Tiezzi A.[104]; Tomassini P.F.[105]; Trebbastoni A.[14]; Tremolizzo L.[4]; Tripi G.[106]; Ursini F.[107]; Vaianella L.[30] Istituto Superiore di Sanità; Valluzzi F.[108]; Vezzadini G.[7]; Vista M.[109]; Volontè M.A.[62]. [1]U.O.Spedali Civili di Brescia, Dipartimento di Scienze Cliniche e Sperimentali; [2]Fondazione Don C. Gnocchi Onlus,Irccs S. Maria Nascente, Milano; [3]USL Umbria 1; [4]Clinica Neurologica, Università Milano Bicocca e Ospedale San Gerardo Monza; [5]Unità Valutazione Alzheimer UOC Neurologia Policlinico Universitario di Messina; [6]IRCCS Ospedale Maggiore Policlinico di Milano; [7]Fondazione San Maugeri, Castelgoffredo; [8]Istituto Neurologico Carlo Besta; [9]AOU di Parma; [10]UOC di Neurologia Az.OORRMN, Marche Nord; [11]Azienda Ospedaliero Universitaria Pisana, Pisa; [12]Centro Neuropsicologico Cognitivo Niguarda Milano; [13]U.O.Neurologia ASP di Cosenza; [14]Clinicadella Memoria, Dipartimento di Neurologia e Psichiatria, "Sapienza" Università di Roma; [15]Centro di Salute Mentale e UVA Cosenza Coordinatore Centri UVA (CDCD) ASP Provinciale di Cosenza; [16]UO NeurologiaAscoli Piceno; [17] Dipartimento di Neurologia e Psichiatria Policlinico Umberto I Roma; [18]UVA Macomer-ASL 4 NU; [19]UVA Italian Hospital Group,Guidonia, Roma; [20]UVA Sanluri,Cagliari; [21]A.O.U.OO.RR.Neurologia Universitaria Foggia; [22]UCO Neurologia Ospedaledi Cattinara (TS)Centro studio e cura Disturbi della Memoria e Cognitivi; [23]Riabilitazione Spec. Disturbi Neurologici, Cognitivi e Motori, Ospedale San Raffaele Milano; [24]CDCD Dolo, Veneto; [25]H.Desio,Lombardia; [26]Sardegna; [27]CDC Nuovo Ospedale Civile S.Agostino Estense Modena; [28]Centro UVA DSM Agrigento Ambulatorio di Sciacca; [29]Centro Regionale di Neurogenetica ASP CZ—Lamezia Terme, Italy; [30]Istituto Superiore di Sanità; [31]A.O. Papa Giovanni XXIII, Fondazione Cardinal Gusmini, Vertova; [32]Centro di Neuroscienze Cognitive e Comportamentali IRCCS Mondino Università di Pavia; [33]CDC Legnago AULSS 21; [34]ASL Vallecamonica Sebino Esine; [35]CDCD Ospedale Luigi Sacco Milano; [36]Centro Regionale Alzheimer A.O. G.Salvini, Rho; [37]Centro U.V.A. e Demenze,U.O. Mal. Neurodegenerative ASP2 Caltanissetta; [38]CDCD ULSS 20 Territoriale e Ospedale San Bonifacio, Verona; [39]Centro Demenze di Reggio Emilia; [40]UOS Psicogeriatria, Centro diagnosi e assistenza Alzheimer, Pescara;

[41]UVA Campobasso; [42]Policlinico Tor Vergata; [43]Centro UVA Policlinico Universitario di Cagliari; [44]CDC di Castelsangiovanni, AUSL Piacenza; [45]CDCDSan Filippo Neri Roma; [46]Neurologia Multimedica Castellanza(Va); [47]CRIC Padova; [48]Arcispedale S.Maria Nuova Reggio Emilia; [49]Neurologia, Usl Umbria 1, area Nord, Ospedale di Gubbio,Gualdo Tadino; [50]Dip Neuroscienze Università di Torino; [51]UVA P.O. Barletta; [52]Centro Demenze A. O. S. Andrea Sapienza Università di Roma; [53]U.O.C.Neurologia, UVA fondazione Istituto G.Giglio,Cefalù; [54]Clinica della Memoria, Policlinico Universitario "A. Gemelli"; [55]UO Neurologia Ospedale C. Poma-Mantova; [56]Clinica Neurologica Università di Catania; [57]Centro UVA Policlinico Umberto I di Roma; [58]Ospedale San Carlo Borromeo Milano; [59]Lab di Neuropsicologia, U.O.Neurologia, Ospedale Rimini; [60]Consultorio Disturbi Cognitivi Distretto di idenza Azienda UsL di Parma; [61]CDCD Clinica Neurologica, Università Politecnica delle Marche, Ancona; [62]Dipartimento di Neurologia, Ospedale San Raffaele, Milano; [63]Neurologia, Ospedale G.B. Grassi,ASL RM D; [64]U.O.Neurologia Riabilitativa P.O. SS. Trinità ASL Cagliari; [65]San Pio X; [66]UVA Ospedale Mauriziano Torino; [67]U.O.di Riabilitazione CdC Carmide, Villa dei Gerani Catania; [68]CDCD Neurologia Ospedale S Bortolo Vicenza; [69]S.Lucia Assemini, Cagliari; [70]UVA Varese Ospedale di Circolo; [71] IRCCS-INRCA POR di Cosenza; [72]Centro Malattia di Parkinson e Disordini del movimento, Policlinico Universitario Monserrato, Cagliari; [73]Humanitas Gavazzeni,UO di Neurologia; [74]CDCD AUSL Parma; [75]UVA Clinica Geriatrica, IRCCS AUO San Martino, Genova; [76]UVA Neurologia Sondrio; [77]UOC Neurologia Ospedale S. Camillo De Lellis ASL di Rieti; [78]U.O.Neurologia Osp. "Giovanni Paolo II" Olbia; [79]Clinica Neurologica Genova; [80]UVA AUSL 11 Toscana; [81]Dipartimento di Neuroscienze, Imaging e Scienze Cliniche, Università G. D'Annunzio Chieti; [82]UVA della UOC Neurologia, San Benedetto Del Tronto; [83]Azienda Ospedaliera S. Antonio Abate Gallarate; [84]Ospedale San Gerardo Monza; [85]Fondazione Santa Lucia, Roma; [86]AOUP Policlinico Paolo Giaccone, U.O. Neurologia e Neurofisiopatologia; [87]CDCD ULSS 5 Ovest Vicentino, Neurologia Arzignano; [88]Azienda OspedalieraPadova; [89]UO Neurologia, ASUR Marche AV3, Macerata; [90]Centro Alzheimer, Neurologia 1, Dipartimento di Neuroscienze, Università di Torino; [91]Centro Demenze UVA ASL Salerno; [92]U.O. di Neurologia Policlinico Universitario di Palermo; [93]Centro Demenze, Università degli Studi di Brescia, Spedali Civili di Brescia; [94]U.O. Riabilitazione Parkinson, Ospedale S. Isidoro Ferb Onlus Trescore Balneario; [95]Medicina Generale centro di riferimento per le demenze A.MA. PD; [96]Neurocentro della Svizzera Italiana; [97]Centro di Riabilitazione per le Demenze e la Demenza di Alzheimer, San Valentino; [98]U.O.C. Geriatria e Laboratorio di Gerontologia,Geriatria Dipartimento di Scienze MedicheIRCCS Casa Sollievo dellaSofferenza, San Giovanni Rotondo; [99] Centro UVA IRCCS Mondino Pavia; [100]Dipartimentodi NeurologiaeScienze Psichiatriche, Universitàdi Firenze; [101]Istituto di Diagnosi e Cura Hermitage Capodimonte, Napoli; [102]UO Neurologia, Policlinico S.Orsola-Malpighi, Bologna; [103]S.C.Neurologia, Ospedale S. Corona Pietra Ligure; [104]UVA Arezzo; [105]UVA Distretto di Macerata; [106]UVA Trapani; [107]Policlinico Universitario Campus Bio-Medico Di Roma; [108]P.O. Monopoli ASL Bari UO Neurologia; [109]CDCD Lucca.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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