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ORIGINAL ARTICLE

Italian Frontotemporal Dementia Network (FTD Group-SINDEM): sharing clinical and diagnostic procedures in Frontotemporal Dementia in Italy

B. Borroni · R. Turrone · D. Galimberti · B. Nacmias · A. Alberici · A. Benussi · P. Caffarra · C. Caltagirone · S. F. Cappa · G. B. Frisoni · R. Ghidoni · C. Marra · A. Padovani · I. Rainero · E. Scarpini · V. Silani · S. Sorbi · F. Tagliavini · L. Tremolizzo · A. C. Bruni · The FTD Group-SINDEM

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Abstract In the prospect of improved disease management and future clinical trials in Frontotemporal Dementia, it is desirable to share common diagnostic procedures. To this aim, the Italian FTD Network, under the aegis of the Italian Neurological Society for Dementia, has been established. Currently, 85 Italian Centers involved in dementia care are part of the network. Each Center completed a questionnaire on the local clinical procedures, focused on (1) clinical assessment, (2) use of neuroimaging and genetics; (3) support for patients and caregivers; (4) an opinion about the prevalence of FTD. The analyses of the results documented a comprehensive clinical and instrumental approach to FTD patients and their caregivers in Italy, with about 1,000 newly diagnosed cases per year and 2,500 patients currently followed by the participating Centers. In analogy to other European FTD consortia, future aims will be devoted to collect data on epidemiology of FTD and its subtypes and to provide harmonization of procedures among Centers.

Keywords Frontotemporal dementia · Frontotemporal lobar degeneration · Network · Survey · Genetics · Counseling

B. Borroni (✉) · R. Turrone · A. Alberici · A. Benussi · A. Padovani
Center of Neurodegenerative Disorders, Neurology Unit, University of Brescia, P.le Spedali Civili 1, 25123 Brescia, Italy
e-mail: bborroni@inwind.it

D. Galimberti · E. Scarpini
Department of Pathophysiology and Transplantation, "Dino Ferrari" Center, University of Milan, Fondazione Cà Granda, IRCCS Ospedale Policlinico, Milan, Italy

B. Nacmias · S. Sorbi
Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

P. Caffarra
Department of Neuroscience, University of Parma and Center for Cognitive Disorders, Ausl of Parma, Parma, Italy

C. Caltagirone
Department of Clinical Behavioural Neurology, IRCSS Santa Lucia Foundation Rome, Italy Department of Neuroscience, University of Rome "Tor Vergata", Rome, Italy

S. F. Cappa
IUSS Pavia and San Raffaele Scientific Institute, Milan, Italy

G. B. Frisoni · R. Ghidoni
IRCCS Centro San Giovanni di Dio-Fatebenefratelli, Brescia, Italy

C. Marra
Research Center for Neuropsychology, Catholic University, Rome, Italy

I. Rainero
Neurology Unit, Department of Neuroscience, University of Turin, Turin, Italy

V. Silani
Department of Neurology-Stroke Unit and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano–"Dino Ferrari" Center, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

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Introduction

Frontotemporal Dementia (FTD) is considered one of the most important neurodegenerative conditions after Alzheimer Disease (AD), affecting the presenium as well as the aged population. Atrophy predominantly involves the frontal and temporal lobes, in which, at autopsy, the distinctive hallmarks are mainly constituted by microtubule associated protein tau (MAPT) depositions, TAR DNA-binding protein 43 (TDP-43) inclusions, or to a lesser extent, fused in sarcoma inclusions (FUS) [1]. Social misconduct, language and executive deficits, or motor impairment are the main features at disease onset, therefore encompassing different clinical syndromes: the behavioral variant FTD (bvFTD), the nonfluent/agrammatic (nf/av-PPA) and semantic (svPPA) variants of primary progressive aphasia [2–4]. Amyotrophic Lateral Sclerosis (ALS) or atypical extrapyramidal syndromes are variably represented during the disease course. Furthermore, the recognition of a common clinical, genetic and pathological overlap of FTD with Corticobasal Degeneration Syndrome (CBS), Progressive Supranuclear Palsy (PSP) and ALS (ALS/FTD) suggested the inclusion of these relatively rare conditions under the same nosological group. As the disease progresses, the different FTD variants tend to overlap, further contributing to the complexity of the clinical pictures. FTD is a sporadic disease, but a strong genetic background, with almost 40 % of patients showing a positive family history, prompted the identification of a number of genes causative of the disease. Mutations in *MAPT*, granulin (*GRN*), and more recently in the hexanucleotide repeat expansion in *C9orf72,* are considered the most frequent causes of genetic FTD [1].

Despite the great effort to find genes associated with the disease, FTD is still poorly recognized, as demonstrated by sparse and controversial epidemiological data on its prevalence, incidence or main demographic characteristics [2–4]. Literature data provide several clinical classification systems, promoting a wider recognition of the disease although limited to experienced clinical settings. The wide clinical, pathological and genetic variability, along with the small number of patients, have, so far, prevented the development of large clinical trials for a devastating condition still orphan of any therapeutic approach.

In this scenario, it is desirable to share common diagnostic procedures to improve major disease recognition along with its management, also in the prospect of future clinical trials. To this aim, the Italian FTD network, under the aegis of the Italian Neurological Society for Dementia (SINDEM), promoted a survey among its participants to collect data about general clinical ground, focused on (1) the clinical assessment, (2) the use of neuroimaging and genetics; (3) the support for patients and caregivers; (4) and the personal opinion about the prevalence of FTD.

Subjects and methods

This multicenter, national survey has been developed under the auspices of the Italian Neurological Society for Dementia (SINDEM). A semi-structured questionnaire was e-mailed to dementia Centers belonging to SINDEM. The group was made by both primary and tertiary Referral Centers, covering the Country from the North to South. Each Center was required to fill in a 15-point questionnaire to map existing services and resources in Italy. Participants were asked to specify the site they worked in and their specialization (see supplementary data, i.e. the English translation of the questionnaire).

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 FTD as compared to AD. In addition, the number of new patients diagnosed and followed per year was requested.

The questionnaire focused on the diagnostic procedures in clinical practice, as follows: (1) clinical assessment adopted to diagnose FTD, (2) the use of neuroimaging investigations, (3) the availability of biomarkers and genetic analyses, and (4) the resources for supporting patients and caregivers.

In particular, the clinicians were asked to identify clinical features suggesting FTD, encompassing the onset in the presenium, behavioral disorders, language disorders and positive family history for dementia. They indicated their opinion about the co-occurrence of ALS and a positive psychiatric history.

A multiple choice query investigated the comprehensive workup adopted for diagnosis, including specific neuropsychological battery test examination, structural neuroimaging (CT or MRI) or functional neuroimaging (brain FDG-PET), along with genetic and cerebrospinal fluid (CSF) analysis. The in loco specific facilities were recorded.

F. Tagliavini
Department of Diagnostics and Applied Technology,
Division of Neurology 5 - Neuropathology,
Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan,
Italy

L. Tremolizzo
Neurology Section, DCMT, University of Milano Bicocca
Monza and NeuroMi-Milan Center for Neuroscience,
Milan, Italy

A. C. Bruni
Regional Neurogenetic Center, ASPCZ, Lamezia Terme, Italy

Furthermore, psychosocial services offered to patients and caregivers, including genetic counseling and cognitive/rehabilitative programs, were investigated. Modalities to hospital admission for diagnosis were defined.

Data analysis

Statistical analysis was performed using Statistical Package for the Social Sciences, SPSS vers. 19. Results were calculated according to the percentage of responses.

Results

Ninety-four out of 107 referral Centers filled in the questionnaire (response rate: 87.8 %), and 85 agreed to participate in the FTD Group-SINDEM network.

The geographical distribution of the participating Centers is reported in Fig. 1; 60 % were from the North of Italy, 22 from the Center and 18 % from the South. University Centers were 36.4 % of the total.

The majority of clinicians resulted specialized in Neurology (95 %), whilst the others in Geriatrics (4 %) or had a genetics and neuropsychological professional background (1 %).

Data of the visual rating scale indicated that FTD is considered less frequent compared to AD in aged population, and as prevalent as AD in early-onset disease.

Fig. 1 Geographical distribution of the Italian Centers participating in the FTD-Group SINDEM

The key symptoms for suspecting FTD were language deficits and behavioral disorders (98.9 and 95.7 % of cases, respectively), followed by early disease onset (76.3 %) and positive family history for dementia (62.7 %) (see Fig. 2, Panel A).

In almost all the Centers, the diagnostic workup was accomplished by full neuropsychological evaluation (95.7 %) and structural neuroimaging (91.5 %). Functional neuroimaging (brain FDG-PET) is provided in almost 75 % of case, whilst genetic (53.2 %) and cerebrospinal fluid (50.0 %) analyses were available in half of the cases (see Fig. 2, Panel B).

History of a psychiatric disorder was taken into account in 74 % of the sample, and the presence of motor neuron disease was frequently assessed clinically (65 %). Only 17 % of the Centers adopted, if necessary, neurophysiological examinations to examine motor neuron involvement suggestive of ALS (ALS/FTD).

Facilities for biomarkers assessment (i.e. cerebrospinal fluid analyses) were available in 56 % of the Centers. Genetic analyses were carried out locally in only 36 % of the Centers, with genetic counseling in the half of the cases (52 %) (see Fig. 3).

Concerning psychological support, only 52 % of the involved Centers may provide patient/caregiver support, and 42 % have programs of cognitive stimulation/rehabilitation (see Fig. 3).

A total number of about 1,000 newly diagnosed patients per year were collected summing up the number indicated by each Center, 67 % of them accessing to an outpatient facility (see Fig. 3). The number of patients with FTD currently followed in Italy by the participating Centers was 2,500. Considering that the Italian population is about 60,000,000 of inhabitants, the broad prevalence of the disease was four cases out of 100,000.

Considering the population over 50 years of age (almost 24,000,000), FTD prevalence was estimated at 10 cases out of 100,000.

Discussion

In this study, we present the results from the first survey involving a large number of Italian dementia Centers concerning the general recognition, management and opinion on FTD.

Among all the Centers invited to complete the e-mail questionnaire, eighty-five Italian Centers took part in the interview and agreed to be part of the Italian FTD Network.

A preliminary analysis of the results showed that presenile onset and a positive family history for dementia and/or psychiatric disorder are additional elements considered in the diagnostic workup. Co-occurrence of ALS is also

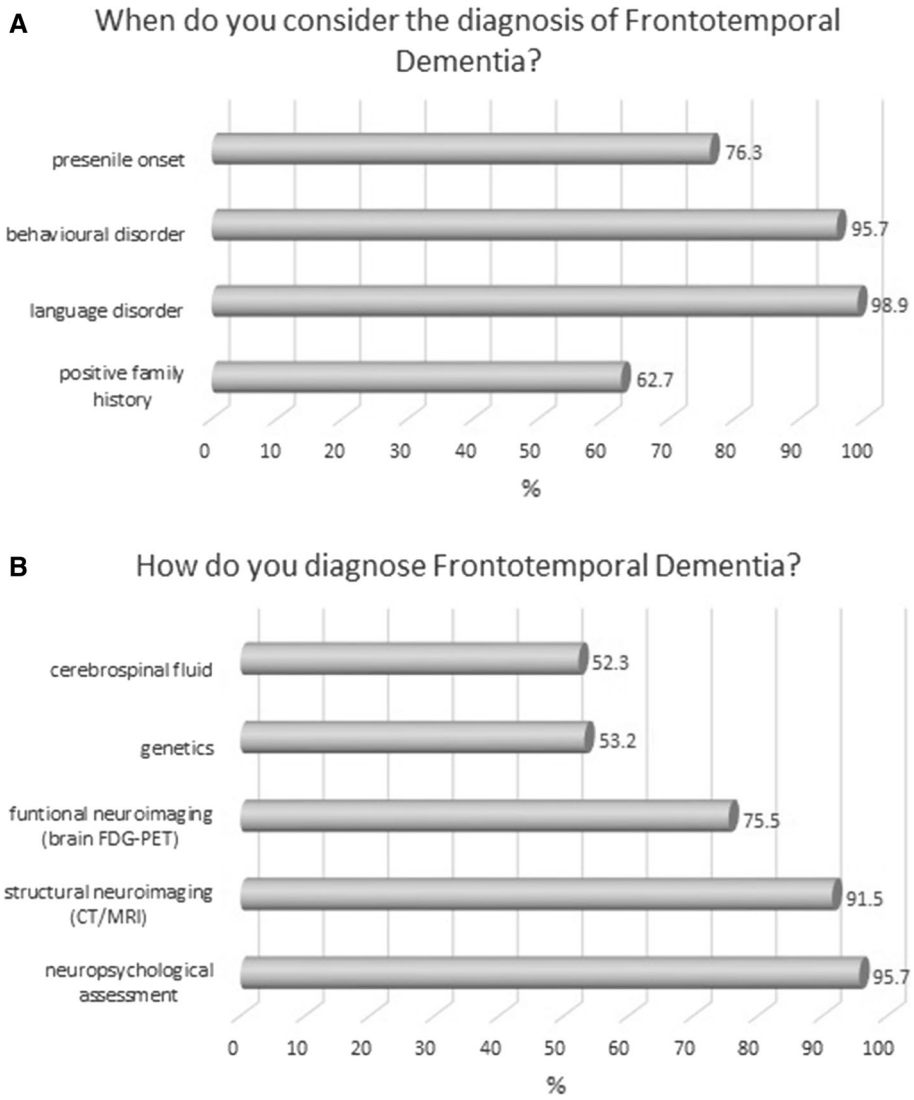


Fig. 2 Survey of diagnostic procedures in Italy Panel **a** Symptoms suggestive for Frontotemporal Dementia. Panel **b** Diagnostic workup carried out for Frontotemporal Dementia diagnosis

widely considered. The vast majority of dementia centers accomplish diagnosis using specific neuropsychological evaluation and a structural neuroimaging examination. In most of the cases, functional neuroimaging is also performed. In half of the cases, genetic and cerebrospinal fluid analyses are available, along with genetic counseling. Regarding the determination of CSF biomarkers, the analysis was performed in patients with memory disturbances to exclude an amyloid-based pathology, whereas in the presence of typical symptoms (behavioral and/or language impairment) and structural neuroimaging showing focal frontal left atrophy, criteria for diagnosis [3] were met without any further additional procedure.

The genetic analysis is available in 36 % of the Centers, mainly due to technical required expertise and high costs required to perform the analysis. Nevertheless, the low percentage reported is in part due to ethical concerns of local committees in disclosing a monogenic disease, with clear implications on family members.

About half of the Centers provide patient/caregiver support and cognitive rehabilitation. Early-onset FTD is considered to be as prevalent as early-onset AD.

The general scenario from these data document a comprehensive and satisfactory general clinical and instrumental approach to FTD patients and their caregivers, with about 1,000 newly diagnosed cases per year.

Future goals will be directed at implementing the network between tertiary referral Centers and participating primary care Centers, with the aim to improve FTD diagnosis and management.

In analogy to other European FTD consortia, future aims of the Italian FTD Network will be devoted to collect further data on the epidemiology of FTD and its subtypes, to develop guidelines for early diagnosis and follow-up,

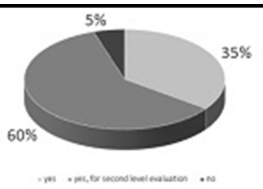
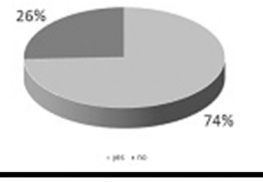
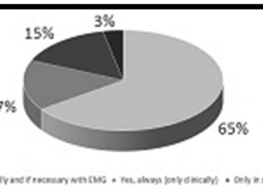
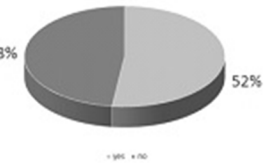
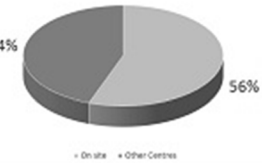
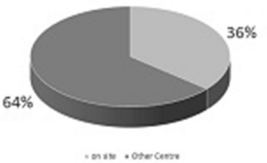
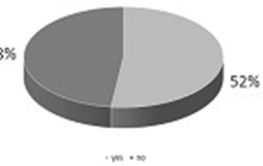
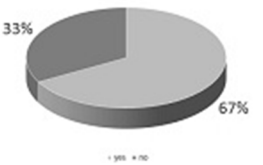
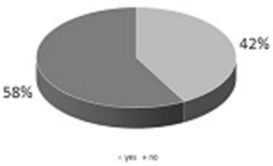
a. Do you request / administer a different neuropsychological assessment battery, with specific tests for the detection of frontal and executive deficits, compared to that used for patients with Alzheimer's disease?	
b. Do you consider a history of psychiatric disorder as a risk factor for Frontotemporal Dementia?	
c. Do you assess motor neuron disease in patients diagnosed with Frontotemporal Dementia?	
d. Is psychological support provided for patients in the early stage of illness or for family members?	
e. Cerebrospinal fluid analyses are done on-site or at another Centre?	
f. Genetic analyses are done on-site or at another Centre?	
g. Is counselling carried out for genetic analyses?	
h. Is the patient hospitalized for diagnosis (ward / day-hospital)?	
i. Are stimulation / cognitive rehabilitation activities provided?	

Fig. 3 Clinical, instrumental and psychosocial services offered to patients and caregivers in the involved dementia Centers

and disseminate procedures for genetic analyses and counseling. Providing harmonization of procedures and allowing selection for evidence-based therapeutic strategies, will play a key role for a better management of the disease.

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FTD Group-SINDEM co-authors (in alphabetic order)

Agosta F.[14], Alberoni M.[15], Appollonio I.[12], Arighi A.[2], Avanzi S.[16], Baglio F.[15], Benussi L.[7], Bianchetti A.[17], Binetti G.[7], Bonanni L.[18], Bottacchi E.[19], Bruno G.[20], Canevelli M.[20], Canu E.[21], Cerami C.[22], Chiari A.[23], Conti MZ.[24], Costa A.[25], Costa M.[26], Cotelli M.[27], Cotelli MS.[28], Cupidi C.[13], Daniele A.[29], D'Anna S. [30], De Caro MF.[31], De Togni L.[32], Dell'Osa MT.[33], Di Stefano F.[34], Ferrarese C.[12]; Ferrari C. [3], Filastro F.[35], Floris G.[34], Franceschi M.[36], Gennuso M.[37], Ghidoni E. [38], Giordana MT.[39], Gragnaniello D.[40], Grimaldi L.[41], Lanari A.[42], Le Pira F.[43], Lombardi G.[3], Lorusso S.[44], Ludovico L.[45], Luzzi S.[46], Magnani G.[14], Manfredi LG.[47], Marano P.[48], Marcone A.[22], Marrosu MG.[49], Martorana A.[50], Mascia MG.[51], Masullo C.[52], Mauri M.[53], Mazzone A.[54], Mela A.[21], Merlo P.[55], Micheli A.[56], Milia A.[51], Mina C.[57], Montella P.[58], Mura G.[59], Murru MR.[49]; Nemni R.[15], Paci C.[60], Pantieri R.[61], Panza F. [62], Parnetti L.[63], Perini M.[64], Pettenati C.[65], Piccininni M.[66], Piccoli T.[67], Pilia G.[51], Pinessi L.[9], Piras MR.[49], Realmuto S.[68], Ricca I.[69], Rizzetti MC.[70], Rozzini L.[71], Rubino E.[9], Sambati L.[72], Seripa D.[62], Siano P.[73], Sinforiani E.[74], Sorrentino G.[75], Specchio LM.[76], Stracciari A.[77], Susani E.[12],Talarico G.[20], Tartaglione B.[31], Tessitore A.[58], Thomas A.[18], Tiezzi A.[78], Tiraboschi P.[11], Tognoni G.[79], Tondelli M.[23], Trebbastoni A.[80], Turla M.[28], Ursini F.[81], Valluzzi F.[82], Vista M. [83], Zannino G.[84], Zanusso G.[85].

[2]Department of Pathophysiology and Transplantation, "Dino Ferrari" Center, University of Milan, Fondazione Cà Granda, IRCCS Ospedale Policlinico, Milan; [3]Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence; [7]IRCCS S. Giovanni di Dio Fatebenefratelli, Brescia; [9]Neurology Unit, Department of Neuroscience, University of Turin, Turin; [11]Department of Diagnostics and Applied Technology, Division of Neurology 5–Neuropathology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan; [12]Neurology Section, DCMT, University of Milano Bicocca, Monza and "NeuroMi-Milan Center for Neuroscience; [13]Regional Neurogenetic Center, ASP CZ Lamezia Terme; [14]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, Department of Neurology San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy; [15]IRCSS S.M. Nascente, Milan; [16]IRCCS Maugeri, Castel Goffredo, Mantova; [17]S. Anna Hospital, ICSA Gruppo San Donato, Brescia; [18]Department of Neuroscience and Imaging, University of Chieti-Pescara, Chieti; [19]Regional Hospital, Aosta; [20]Clinica della Memoria, Dip. di Neurologia e Psichiatria, Univ. Sapienza Roma; [21]San Francesco Hospital, Nuoro; [22] Clinical Neurosciences Department, San Raffaele Hospital (OSR), Milan; [23]Civile Hospital S.Agostino Estense; Modena; [24]Gusmini Foundation, Bergamo; [25]Genetic Unit, IRCSS Mondino Pavia; [26]Ramazzini Hospital, Carpi, Modena; [27]IRCCS Neuropsicology, Brescia; [28]Vallecamonica Hospital, Brescia; [29]Catholic University, Institute of Neurology, Rome; [30]Portogruaro Hospital, Portogruaro-VE; [31]Policlinico Hospital, Neurologia II, Bari; [32]ULSS 20, Verona; [33]UVA, ASL Sassari; [34]Centro UVA, Neurologia, AOU Cagliari; [35]Centro UVA Girifalco, ASP Catanzaro; [36]Neurology Department, Multimedica Castellanza, Varese; [37]UVA Maggiore Hospital, Crema; [38]S. Maria Nuova Hospital, Reggio Emilia; [39]Department of Neuroscience, University of Turin, Turin; [40]AO Ferrara, Ferrara; [41]San Raffaele Hospital, Cefalu'- PA; [42]Poma Hospital, Mantova; [43] University of Catania, Catania; [44]Rimini Hospital, Rimini; [45]AUSL Parma–Fidenza, Parma; [46]Department of Experimental and Clinical Medicine, Marche Polytechnic University; [47]Pio X Hospital, Milan; [48]Villa Gerani Hospital, Catania; [49]Neurological Clinic AOU Sassari, Sassari-Multiple Sclerosis Centre, ASL 8-Cagliari/Department of Public Health, Clinical and Molecular Medicine, University of Cagliari; [50]Tor Vergata University, Rome; [51]S. Trinità Hospital, Cagliari; [52]Catholic Univeristy, S. Giovanni Hospital, Rome; [53]Circolo Hospital, Varese; [54]Geriatric UVA San Gerardo Hospital, Monza; [55]U.O. of Neurology -UVA, Humanitas Gavazzeni, Bergamo; [56]S. Francesco Clinic, Bergamo; [57]UVA Sapienza University, Roma; [58]II° University of Naples, Naples; [59]G.Paolo II Hospital, Olbia; [60]San Benedetto del Tronto Hospital, San Benedetto T.- AP; [61]IRCCS Istituto delle scienze neurologiche di Bologna, Ospedale Bellaria, Bologna; [62]IRCSS "Casa sollievo della sofferenza" S.G. Rotondo–FG; [63]University of Perugia, Perugia; [64]AO Gallarate, Varese; [65]AO G.Salvini, Passirana-Rho-MI; [66]ASL 10, Firenze; [67]Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche, Università degli Studi di Palermo, Palermo; [68]U.O. di

Neurologia e Neurofisiopatologia, Dipartimento di Emergenza urgenza e neuroscienze, AUOP Paolo Giaccone, Palermo; [69]Experimental Neurobiology Lab., C. Mondino National Neurological Institute, Pavia; [70]S. Isidoro Hospital -FERB Onlus, Trescore Balneario -BG; [71]UVA Spedali Civili Hospital, Brescia; [72]University of Bologna, Bologna; [73]AOU S.Giovanni e Ruggi, Salerno; [74]Alzheimer's Assessment Unit/Laboratory of Neuropsychology, C. Mondino National Neurological Institute, Pavia; [75]Ist. Hermitage–Capodimonte, Naples; [76]Riuniti Hospital, Foggia; [77]Neurology, S.Orsola-Malpighi Hospital, Bologna; [78]AUSL 8, Arezzo; [79]AO Pisa, Pisa; [80]UVA NPD 01 Sapienza University Rome; [81]Campus Bio-Medico University, Rome; [82]ASL Monopoli–BA; [83]UVA ASL 2 Lucca, Lucca; [84]UVA Trebisacce Hospital, Cosenza; [85]University of Verona, Verona.

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