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RESEARCH ARTICLE

Differences and similarities between familial and sporadic frontotemporal dementia: An Italian single-center cohort study

Alberto Benussi[1,2] | **Ilenia Libri**[1] | **Enrico Premi**[3] | **Antonella Alberici**[2] | **Valentina Cantoni**[1] | **Yasmine Gadola**[1] | **Jasmine Rivolta**[1] | **Marta Pengo**[4] | **Stefano Gazzina**[5] | **Vince D. Calhoun**[6] | **Roberto Gasparotti**[7] | **Henrik Zetterberg**[8,9,10,11,12] | **Nicholas J. Ashton**[8,13,14,15] | **Kaj Blennow**[8,9] | **Alessandro Padovani**[1,2] | **Barbara Borroni**[1,2]

[1]Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

[2]Neurology Unit, Department of Neurological and Vision Sciences, ASST Spedali Civili, Brescia, Italy

[3]Stroke Unit, Department of Neurological and Vision Sciences, ASST Spedali Civili, Brescia, Italy

[4]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy

[5]Neurophysiology Unit, Department of Neurological and Vision Sciences, ASST Spedali Civili, Brescia, Italy

[6]The Mind Research Network, Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, New Mexico, USA

[7]Neuroradiology Unit, University of Brescia, Brescia, Italy

[8]Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden

[9]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

[10]UK Dementia Research Institute at UCL, London, UK

[11]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

[12]Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China

[13]Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Mölndal, Sweden

[14]King's College London, Institute of Psychiatry, Psychology & Neuroscience, Maurice Wohl Clinical Neuroscience Institute, London, UK

[15]NIHR Biomedical Research Centre for Mental Health & Biomedical Research Unit for Dementia at South London & Maudsley NHS Foundation, London, UK

Correspondence
Barbara Borroni, Clinica Neurologica, Università degli Studi di Brescia, P.le Spedali Civili 1, 25123, Brescia, Italy.
E-mail: bborroni@inwind.it

Abstract

Introduction: The possibility to generalize our understandings on treatments and assessments to both familial frontotemporal dementia (f-FTD) and sporadic FTD (s-FTD) is a fundamental perspective for the near future, considering the constant advancement in potential disease-modifying therapies that target particular genetic forms of FTD. We aimed to investigate differences in clinical features, cerebrospinal fluid (CSF), and blood-based biomarkers between f-FTD and s-FTD.

Methods: In this longitudinal cohort study, we evaluated a consecutive sample of symptomatic FTD patients, classified as f-FTD and s-FTD according to Goldman scores (GS). All patients underwent clinical, behavioral, and neuropsychiatric symptom

assessment, CSF biomarkers and serum neurofilament light (NfL) analysis, and brain atrophy evaluation with magnetic resonance imaging.

Results: Of 570 patients with FTD, 123 were classified as f-FTD, and 447 as s-FTD. In the f-FTD group, 95 had a pathogenic FTD mutation while 28 were classified as GS = 1 or 2; of the s-FTD group, 133 were classified as GS = 3 and 314 with GS = 4. f-FTD and s-FTD cases showed comparable demographic features, except for younger age at disease onset, age at diagnosis, and higher years of education in the f-FTD group (all $P < .05$). f-FTD showed worse behavioral disturbances as measured with Frontal Behavioral Inventory (FBI) negative behaviors (14.0 ± 7.6 vs. 11.6 ± 7.4, $P = .002$), and positive behaviors (20.0 ± 11.0 vs. 17.4 ± 11.8, $P = .031$). Serum NfL concentrations were higher in patients with f-FTD (70.9 ± 37.9 pg/mL) compared to s-FTD patients (37.3 ± 24.2 pg/mL, $P < .001$), and f-FTD showed greater brain atrophy in the frontal and temporal regions and basal ganglia. Patients with f-FTD had significantly shorter survival than those with s-FTD ($P = .004$).

Discussion: f-FTD and s-FTD are very similar clinical entities, but with different biological mechanisms, and different rates of progression. The parallel characterization of both f-FTD and s-FTD will improve our understanding of the disease, and aid in designing future clinical trials for both genetic and sporadic forms of FTD.

KEYWORDS
C9orf72, familial, frontotemporal dementia, genetic, *GRN*, sporadic

Highlights

- Do clinical features and biomarkers differ between patients with familial frontotemporal dementia (f-FTD) and sporadic FTD (s-FTD)?
- In this cohort study of 570 patients with FTD, f-FTD and s-FTD share similar demographic features, but with younger age at disease onset and diagnosis in the f-FTD group.
- f-FTD showed higher serum neurofilament light concentrations, greater brain damage, and shorter survival, compared to s-FTD.
- f-FTD and s-FTD are very similar clinical entities, but with different cognitive reserve mechanisms and different rates of progression.

1 | INTRODUCTION

Frontotemporal dementia (FTD) encompasses a heterogeneous group of neurodegenerative disorders with a wide range of clinical, genetic, and neuropathological features.[1] The disease is characterized by insidious and progressive personality changes, impairment of executive functions, and language deficits.[2,3] Different phenotypes have been classically defined on the basis of presenting clinical symptoms, including the behavioral variant of FTD (bvFTD), which is associated with early behavioral and personality changes;[3] the agrammatic variant of primary progressive aphasia (avPPA), with progressive deficits in speech, grammar, and word output; and the semantic variant of PPA (svPPA), a progressive disorder of semantic knowledge and naming.[2] The occurrence of associated motor symptoms, as in progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and motor neuron disease (FTD-MND), enriches the spectrum of FTD-related disorders.[4]

The majority of cases typically present sporadically (s-FTD) but about one third of patients have an autosomal dominant family history (familial FTD [f-FTD]),[5] with mutations of three main genes, microtubule-associated protein tau (*MAPT*), granulin (*GRN*), and chromosome 9 open reading frame 72 (*C9orf72*), together accounting for 10% to 20% of all FTD and 70% of all genetic FTD cases.[6,7] Some individuals with f-FTD have a family history consistent with an autosomal

dominant syndrome or with significant familial aggregation but do not have a known underlying mutation. To estimate this, the modified Goldman score (GS) has been developed, which enables the stratification of a family history based on the number of a patient's relatives who are or were affected, with scores strongly correlating with the likelihood of identifying a causal mutation.[5]

With the onset of potential disease-modifying therapies targeting the pathophysiology of specific genetic mutations, it has become fundamental to carefully characterize and compare sporadic and familial forms to advance our understanding of whether treatments and assessments developed based on studies of f-FTD are generalizable to s-FTD, and vice versa.

Only few studies to date have tried to assess this issue, with initial results suggesting that sporadic and familial FTD cases are clinically similar.[8,9] However, a comprehensive comparison including cerebrospinal fluid (CSF) and blood-based biomarkers, imaging, and survival, is currently lacking.

These premises prompted the objective of the present study, aimed at comprehensively comparing characteristics of a large cohort of f-FTD and s-FTD patients, including clinical features, imaging and biological markers of neurodegeneration, and progression rates.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. The possibility to generalize our understandings on treatments and assessments to both familial frontotemporal dementia (f-FTD) and sporadic FTD (s-FTD) is a fundamental perspective for the near future, considering the constant advancement in potential disease-modifying therapies that target particular genetic forms of FTD.
2. **Interpretation**: f-FTD and s-FTD are very similar clinical entities, but with different biological and cognitive reserve mechanisms, and different rates of progression. Serum neurofilament light concentrations were higher in patients with f-FTD compared to s-FTD patients, and f-FTD showed greater brain atrophy in the frontal and temporal regions and basal ganglia. Patients with f-FTD had significantly shorter survival than those with s-FTD.
3. **Future Directions**: The parallel characterization of both f-FTD and s-FTD will improve our understanding of the disease, and aid in designing future clinical trials for both genetic and sporadic forms of FTD.

2 | METHODS

2.1 | Participants

This retrospective study included a sample of patients diagnosed with FTD according to current clinical criteria,[2,3] consecutively recruited at the Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Italy, between July 2007 and July 2021.

Each participant underwent a neurological evaluation, routine laboratory examination, and a standardized neuropsychological and behavioral assessment, as previously reported.[10]

In all FTD cases, the diagnosis was supported by a routine brain structural imaging, while CSF concentrations of tau, phosphorylated tau (p-tau)$_{181}$, and amyloid beta (A$\beta_{1\text{-}42}$) or positron emission tomography amyloid were measured in a subset of cases, to rule out Alzheimer's disease, as previously reported.[11] Briefly, lumbar puncture was carried out in the outpatient clinic according to standard procedures, and CSF analysis was performed using enzyme-linked immunosorbent assay (ELISA).[12] Furthermore, in accordance with recent consensus recommendations,[13] genetic screening for *GRN*, *C9orf72*, and *MAPT P301L* mutations was performed in selected cases (i.e., for all bvFTD patients and PPA patients with a strong family history [GS < 3]). Given the low frequency of *MAPT* mutations in Italy[14] we considered only the P301L mutation and we sequenced the entire *MAPT* gene only in selected cases.

Patients with clinical signs or symptoms of motor involvement were all screened with electromyography for MND and were excluded from analysis if they had an overlap FTD-amyotrophic lateral sclerosis or FTD-MND syndrome.

A subgroup of FTD patients underwent blood sampling and a standardized magnetic resonance imaging (MRI) imaging for further group analyses. FTD patients were followed over time and data on survival recorded.

FTD cases were subgrouped according to the modified GS[15] and the presence of pathogenetic mutations. Cases with familial aggregation (f-FTD) were defined as GS 1 or 2 or carrying a pathogenic mutation, while s-FTD were defined as GCS 3 or 4. A GS of 1 corresponds to a family history consistent with the proband's clinical syndrome with an autosomal dominant inheritance pattern, with at least three people who are affected in two generations and who are linked by a first-degree relative; a GS of 2 indicates familial aggregation of three or more affected relatives but without meeting the criteria for a score of 1; a GS of 3 denotes one other affected relative; a GS of 4 signifies no known family history of neurodegenerative disease.

Full written informed consent was obtained from all subjects according to the Declaration of Helsinki. The Brescia Ethics Committee approved the study protocol.

2.2 | Neuropsychological and behavioral assessment

At baseline, patients underwent a standardized neuropsychological battery which included the Mini-Mental State Examination (MMSE), the Rey Auditory Verbal Learning Test (immediate and delayed recall),

the Rey Complex Figure (copy and recall), the Digit Span, Phonemic and Semantic Fluencies, the Token Test, the Clock-Drawing Test, and the Trail-Making Test (Part A and Part B).[16]

The level of functional independence was assessed with the Basic Activities of Daily Living (BADL) and the Instrumental Activities of Daily Living (IADL) questionnaires, whereas neuropsychiatric and behavioral disturbances were evaluated with the Frontal Behavioral Inventory (FBI).[17] The FBI was specifically developed to highlight the behavioral disturbances in FTD, in negative or deficient behaviors, such as apathy, aspontaneity, and indifference (FBI-A), and positive or disinhibited behaviors, such as irritability, impulsivity, and aggressiveness (FBI-B).[17] Disease severity was assessed using the global Clinical Dementia Rating (CDR) plus National Alzheimer's Coordinating Center (NACC) frontotemporal lobar degeneration (FTLD).[18,19]

2.3 | Serum neurofilament light and serum p-tau$_{181}$ measurements

A subgroup of patients (n = 199) underwent blood collection for serum neurofilament light (NfL) and serum p-tau$_{181}$ dosages by single molecule array (Simoa) technology, as previously described.[20,21] Briefly, NfL were measured on an HD-X Analyzer using the commercial NF-Light® assay according to the manufacturer's instructions (Quanterix=) with lower limit of quantitation of 0.174 pg/mL. Serum p-tau$_{181}$ was measured using an in-house Simoa assay developed at the University of Gothenburg with the lower limit of quantitation of 1 pg/mL. The measurements were performed in one round of experiments using the same batch of reagents, and the operators were blinded to all clinical information. Quality control samples had intra-assay and inter-assay coefficients of variation of less than 8% and 20%, respectively.

2.4 | CSF measurements

A subgroup of patients (n = 215) underwent lumbar puncture according to a standardized protocol, in the outpatient clinic, at fasting, after informed written consent had been obtained and according to standard procedures.[22] CSF total tau and p-tau concentrations were measured by sandwich ELISA (Innotest hTau Antigen kit, Innotest PHOSHO-TAU [181P], Fujirebio). CSF A$\beta_{1\text{-}42}$ levels were determined using a sandwich ELISA (Innotest β-amyloid [1–42], Fujirebio). Interassay variability was less than 7%.

2.5 | Imaging

A subgroup of patients (n = 239) was studied with three-dimensional T1-weighted magnetization prepared rapid gradient echo (MPRAGE) MRI. Three different scanners were considered, namely 1.5-Tesla Siemens Symphony, 1.5-tesla Siemens Avanto, and 3-Tesla Siemens Skyra. As the first step, the raw DICOM scans were converted into the Neuroimaging Informatics Technology Initiative format, using MRIcroGL software (https://www.nitrc.org/projects/mricrogl/). T1-weighted images were then processed and analyzed with the voxel-based morphometry (VBM) pipeline implemented in the Computational Anatomy Toolbox (CAT12 v.1742; http://www.neuro.uni-jena.de/cat/) for SPM12 (SPM12 v.7219; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running on MATLAB R2019b (the MathWorks, Inc.). The VBM pipeline consists of several stages (tissue segmentation, spatial normalization to a standard Montreal National Institute [MNI] template, modulation, and smoothing), as previously described.[23] CAT12 potentially provided more robust and accurate performances compared to other VBM pipelines.[24] The normalized and modulated gray matter images were then smoothed with 10-mm full width at half-maximum Gaussian kernel.

Source based morphometry (SBM) was consequently applied to study co-varying patterns of alterations. SBM leverages independent component analysis (ICA) to extract spatially independent patterns that occur in structural images. In contrast to mass-univariate testing (i.e., VBM analysis), SBM captures interrelationships between voxels to identify patterns of structural variation between different groups. Furthermore, as a multivariate approach, SBM can result in less-noisy sources of interest as well as a reduced number of multiple comparisons.[25]

In line with the original study,[25,26] to obtain a common set of sources, a group ICA (considering all subjects) was calculated by GIFT toolbox (GroupICAT v4.0c; https://trendscenter.org/software/gift/),[27] with neural network algorithm (Infomax) that attempts to minimize the mutual information of the network outputs;[28] the component number was estimated to be 18, based on the minimum description length principle.[27,29] The statistical reliability of the source decomposition was tested by using the ICASSO toolbox[30] by running Infomax 10 times with different initial conditions (RandInt option: algorithm started with different initial values) and bootstrapped (Bootstrap option) data sets. ICASSO estimation provided a very good reliability of the neural network algorithm (Infomax) with a very high mean stability index (I_q) across the considered sources (0.976 ± 0.005; good estimation: $I_q > 0.8$). Individual source maps were converted to Z scores before entering group statistics, to obtain voxel values comparable across subjects. Group analysis was run testing the differences between f-FTD and s-FTD, considering age, sex, scanner type, clinical phenotype (bvFTD and PPA), disease severity (CDR plus NACC FTLD score), and total gray matter volume (GMV) as nuisance variables. The statistical threshold was set at $P < .05$ corrected for multiple comparisons. Source matrix was used for visualization, scaling each map to unit standard deviation (SBM Z-map), and threshold at $|Z| > 2.0$. The maps of significant sources were then superimposed onto the MNI normalized template brain.

2.6 | Statistical analysis

Continuous and categorical variables are reported as mean (± standard deviation) and n (%), respectively. Baseline demographic and

clinical variables were compared across groups using Student's t-test or Fisher's tests, as appropriate. Differences in cognitive or behavioral scores were compared with analysis of covariance (ANCOVA), with phenotype (i.e., bvFTD, nonfluent variant of PPA, and svPPA), disease severity (CDR plus NAAC FTLD), and disease duration as covariates. Disease duration was defined as the difference between age at enrollment and age at onset. Differences in serum NfL levels or CSF parameters between groups were compared with ANCOVA, with age and phenotype as covariates.

Survival was calculated as time from symptom onset to time of death from any cause (outcome = 0) or censoring date (outcome = 1). Information on the current status at censoring date was collected by reports from the regional Health Service or from a telephone interview. Survival analysis was carried out by the Kaplan-Meier method with log rank post hoc testing and by means of univariate and multivariate stepwise Cox proportional-hazard regression analysis; hazard ratios (HR) are provided with their respective 95% confidence intervals (CIs).

A two-sided *P*-value < .05 was considered significant. Statistical analyses were performed using SPSS (v.24; SPSS, IBM).

3 | RESULTS

3.1 | Participant characteristics

In total, 570 participants (mean age = 65.8 ± 8.3 years; 277 females [48.6%]) were included in the present study. Of these, 123 were classified as f-FTD (95 with pathogenetic mutations, namely 66 *GRN*, 26 *C9orf72*, and 3 *MAPT* mutations, and 28 with either GS = 1 or 2) and 447 as s-FTD (133 with GS = 3 and 314 with GS = 4). Demographic and neuropsychological characteristics of included patients are reported in Table 1. f-FTD and s-FTD cases showed comparable demographic features, except for younger age at disease onset, age at diagnosis, and higher years of education in the f-FTD group (all $P < .05$, see Table 1). Disease duration was similar between groups: 2.7 ± 2.1 years in f-FTD and mean 2.6 ± 2.3 in s-FTD, $P = .913$.

3.2 | Clinical and behavioral differences between f-FTD and s-FTD

Clinical and behavioral scores according to f-FTD and s-FTD groups are reported in Table 1. No significant differences in global cognitive performances between f-FTD and s-FTD were found. f-FTD showed worse behavioral disturbances as measured with FBI-A (14.0 ± 7.6 vs. 11.6 ± 7.4, $P = .001$), and FBI-B (20.0 ± 11.0 vs. 17.4 ± 11.8, $P = .009$).

In particular, when FBI-A subitems were analyzed, f-FTD showed worse scores in personal neglect (53.5% vs. 37.4%, $P < .05$), disorganization (75.6% vs. 60.7%, $P < .05$), and alien hand phenomenon and/or apraxia (24.4% vs. 10.5%, $P = .03$), after adjusting for phenotype.

f-FTD and s-FTD were similar across standard neuropsychological tests, and only a tendency in letter fluency differences were observed, with f-FTD showing greater impairment compared to s-FTD (15.8 ± 11.4 vs. 19.4 ± 10.7, $P = .064$). No other significant differences in cognitive domains were detected.

3.3 | Biological differences between f-FTD and s-FTD

Serum NfL concentrations were higher in patients with f-FTD (70.9 ± 37.9 pg/mL) compared to s-FTD patients (37.3 ± 24.2 pg/mL, $P < .001$). CSF total tau, p-tau$_{181}$, and A$\beta_{1\text{-}42}$, and serum p-tau$_{181}$ levels did not show significant differences between groups (all $P > .05$) (see Table 2 and Table S1 in supporting information).

3.4 | Imaging

Twelve of the 18 estimated sources were considered, after excluding seven sources for artifacts (i.e., signal near the external boundary of the brain or appearing primarily in ventricles or white matter areas). The 12 sources included frontoparietal (right and left), basal ganglia, visual, default mode network (posterior and anterior), auditory, and frontal pathway. Among them, four sources presented loading scores (as index of gray matter density) significant differences between f-FTD and s-FTD, considering comparable disease stage ($P < .01$ corrected for multiple comparisons using the false discovery rate [FDR]). As shown in Figure 1, f-FTD showed greater brain atrophy in the basal ganglia (putamen, caudate, thalamus; source 3); in the medial and inferior frontal gyri (source 11); in the middle frontal gyri, thalamus, and inferior parietal lobule (source 16); and in the temporal regions (source 17). Clinical and demographical characteristics of the subset of patients that underwent MRI imaging is reported in Table S1.

3.5 | Survival in f-FTD versus s-FTD

Survival analysis was available for 567 participants (447 sporadic and 123 familial FTD). Overall, 149 deaths occurred in the whole sample, with 115 (26.0%) in s-FTD and 34 (27.6%) in f-FTD. The univariate Cox regression analysis showed a significant association between survival and f-FTD (HR 1.76, 95% CI 1.20–2.60, $P = .004$). Patients with f-FTD had significantly shorter survival than those with s-FTD at the Kaplan-Meier survival curves ($P = .004$; see Figure 2). The mean estimated survival in the whole sample was of 175.0 (95% CI 162.6–187.4) months, with 181.2 (95% CI 167.7–194.6) months in s-FTD and 122.8 (95% CI 108.8–136.8) months in f-FTD.

When predictors of survivals were considered, namely familial aggregation (f-FTD and s-FTD), serum NfL levels and behavioral disturbances (FBI-A), the multivariate Cox regression analysis showed that only serum NfL was significantly associated to survival (HR 1.02, 95% CI 1.01–1.02, $P < .001$).

TABLE 1 Demographic characteristics and biomarkers of familial and sporadic FTD patients

Variable	All FTD	f-FTD	s-FTD	*P*-value
Number	570	123	447	
Age, years	65.9 ± 8.3	63.2 ± 8.6	66.7 ± 8.0	**<.001**
Sex, female % (n)	48.6 (277)	48.8 (60)	48.5 (217)	.928
Age at onset, years	63.3 ± 8.3	60.7 ± 8.5	63.9 ± 8.1	**<.001**
Disease duration, years	2.6 (2.2)	2.7 (2.1)	2.6 (2.3)	.913
Education, years	9.0 ± 4.3	9.7 ± 4.2	8.8 ± 4.3	**.031**
Phenotype, % (n)				**.004**
bvFTD	66.8 (381)	64.2 (302)	67.6 (302)	
nfPPA	21.2 (121)	30.1 (37)	18.8 (84)	
svPPA	11.9 (68)	5.7 (7)	13.6 (61)	
Global cognitive functions				
CDR plus NACC FTLD	1.6 ± 0.9	1.7 ± 0.9	1.6 ± 0.9	.065
MMSE	19.9 ± 7.6	18.4 ± 8.6	20.4 ± 7.2	.194
Behavioral disturbances				
FBI-A	12.2 ± 7.5	14.0 ± 7.6	11.6 ± 7.4	**.001**
FBI-B	5.9 ± 5.7	6.0 ± 5.2	5.8 ± 5.9	.628
FBI-AB	18.0 ± 11.7	20.0 ± 11.0	17.4 ± 11.8	**.009**
Cognitive domains				
RAVL, immediate recall	29.3 ± 12.4	28.8 ± 15.2	29.5 ± 11.0	.609
RAVL, delayed recall	4.9 ± 3.8	5.1 ± 4.0	4.8 ± 3.7	.228
Rey complex figure, copy	23.8 ± 13.2	22.8 ± 10.0	24.1 ± 13.9	.590
Rey complex figure, recall	9.6 ± 7.8	9.9 ± 6.0	9.5 ± 8.2	.487
Digit span forward	4.8 ± 1.3	4.6 ± 1.2	4.8 ± 1.4	.291
Fluency, letter	18.6 ± 10.9	15.8 ± 11.4	19.4 ± 10.7	.064
Fluency, semantic	23.6 ± 12.2	22.4 ± 11.9	23.9 ± 12.2	.784
Token test	25.4 ± 8.2	24.2 ± 8.6	25.8 ± 8.1	.212
Clock Drawing Test	5.5 ± 3.1	5.2 ± 3.1	5.7 ± 3.1	.925
Trail making Test, Part A (sec)	122.8 ± 143.8	124.2 ± 136.7	122.5 ± 146.0	.785
Trail Making Test, Part B (sec)	275.5 ± 156.0	280.7 ± 164.4	274.1 ± 154.1	.852

Note: Categorical variables were compared with chi-square test while continuous variables were compared with one-way ANOVA; for clinical and behavioral measures, result were corrected for phenotype, disease severity, and disease duration; cognitive tests were corrected for age and education, according to Italian normative data.
Significant comaprisons are reported in boldface.
Abbreviations: ANOVA, analysis of variance; bvFTD, behavioral variant frontotemporal dementia; CDR plus NACC FTLD, CDR Dementia Staging Instrument plus behavior and language domains from the National Alzheimer's Coordinating Center and Frontotemporal Lobar Degeneration modules; FBI, Frontal Behavioral Inventory; f-FTD, familial FTD; FTD, frontotemporal dementia patients; MMSE, Mini-Mental State Examination; nfPPA, non-fluent variant of primary progressive aphasia; NPI, Neuropsychiatric Inventory; RAVL, Rey Auditory Verbal Learning test; s-FTD, sporadic FTD; svPPA, semantic variant of primary progressive aphasia.

3.6 | f-FTD and s-FTD subgroups comparisons

When f-FTD subgroups were considered, that is, pathogenetic mutations carriers versus GS = 1 or 2 patients without pathogenetic mutations, the former group presented earlier age at disease onset and earlier age at diagnosis (see Table S2 in supporting information). No significant differences in clinical presentation or biological markers, except for increased CSF total tau (491.1 ± 290.7 vs. 294.9 ± 183.4, $P = .015$) and serum NfL, even though not significant (78.2 ± 36.9 vs. 49.2 ± 31.9, $P = .067$) in patients carrying pathogenetic mutations, were reported (Table S2). When s-FTD subgroups were considered, that is, GS = 3 versus GS = 4, comparable findings between groups were found.

When only bvFTD patients were considered (n = 351), comparable results were shown, with f-FTD showing earlier age at disease onset and earlier age at diagnosis and significantly higher serum NfL compared to s-FTD (see Table S3 in supporting information). The univariate Cox regression analysis showed a significant association between

TABLE 2 Biological markers of familial and sporadic FTD patients

Variable	All FTD	f-FTD	s-FTD	*P*-value
Number	215	43	172	
Biological markers[a]				
CSF total tau, pg/mL	441.7 ± 292.0	433.2 ± 292.0	443.9 ± 296.5	.808
CSF p-tau$_{181}$, pg/mL	62.7 ± 63.01	55.2 ± 65.0	64.6 ± 62.5	.377
CSF A$\beta_{1\text{-}42}$, pg/mL	765.7 ± 383.7	804.1 ± 344.3	756.1 ± 393.3	.390
Serum NfL, pg/mL	44.0 ± 30.6	70.9 ± 37.9	37.3 ± 24.2	**<.001**
Serum p-tau$_{181}$, pg/mL	3.0 ± 6.3	2.4 ± 9.8	3.2 ± 5.0	.454

Note: Continuous variables were compared with one-way ANCOVA, corrected for age and phenotype.
Significant comaprisons are reported in boldface.
Abbreviations: Aβ, amyloid beta; ANCOVA, analyses of covariance; CSF, cerebrospinal fluid; FTD, frontotemporal dementia patients; f-FTD, familial FTD; NfL, neurofilament light; p-tau, phosphorylated tau; s-FTD, sporadic FTD.
[a]Biological markers were performed in a subset of patients (for demographical and clinical characteristics see Table S1).

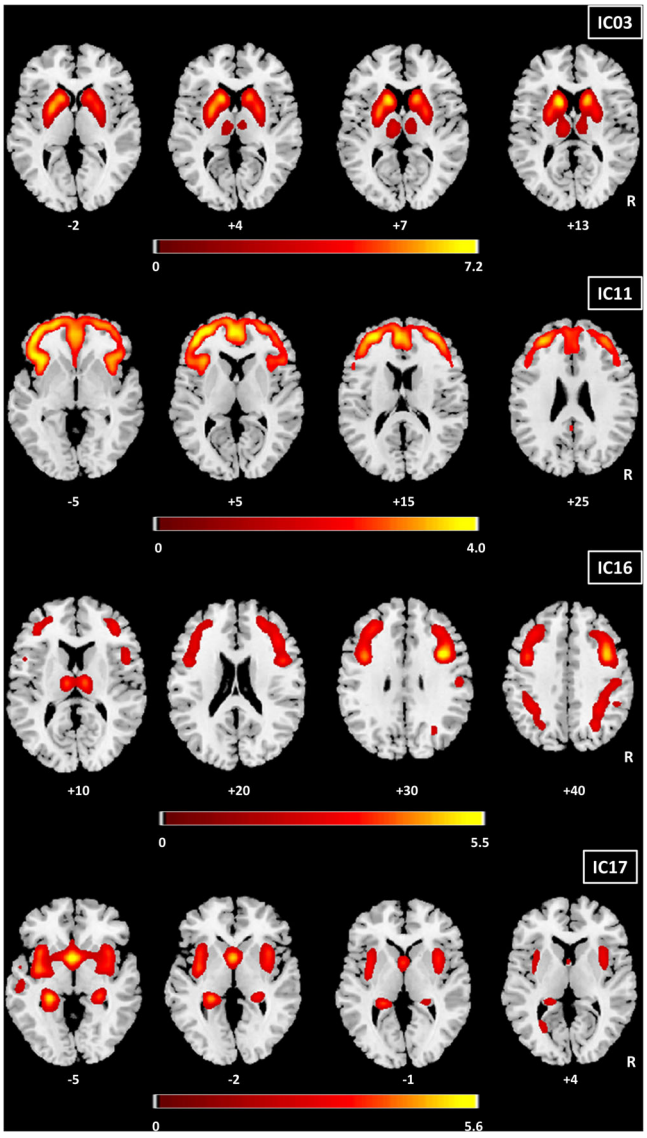

FIGURE 1 Source based morphometry (SBM) analyses showing greater brain damage in f-FTD compared to s-FTD. See text for details. f-FTD, familial frontotemporal dementia; IC, independent component

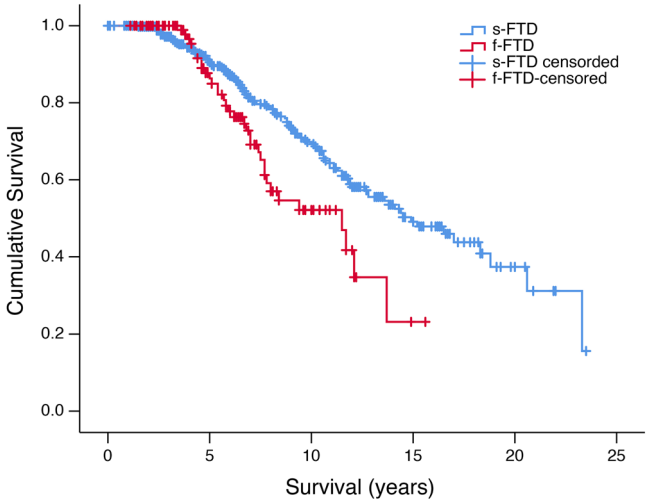

FIGURE 2 Survival curves in f-FTD and s-FTD. Kaplan-Meier survival curves in f-FTD (red line) and s-FTD (blue line). f-FTD, familial frontotemporal dementia; s-FTD, sporadic frontotemporal dementia

survival and f-bvFTD (HR 1.72, 95% CI 1.06–2.81, $P = .03$). Patients with f-bvFTD had significantly shorter survival than those with s-FTD at the Kaplan-Meier survival curves ($P = .028$).

4 | DISCUSSION

The possibility to generalize our understandings on treatments and assessments to both f-FTD and s-FTD is a fundamental perspective for the near future, considering the constant advancement in potential disease-modifying therapies that target particular genetic forms of FTD. However, this is currently a difficult task, considering the absence of a clear understanding of the differences and similarities that characterize f-FTD and s-FTD.

In the present study, we observed that f-FTD and s-FTD share similar demographic features, including sex and phenotype distribution, but with younger age at disease onset and diagnosis in the f-FTD group,

and marginally lower years of education in the s-FTD group. This is in line with a previous study in bvFTD,[8] with f-FTD being on average 4.8 years younger than s-FTD, and as previously reported this was mainly driven by pathogenetic mutations (see Tables S2 and S3). Moreover, this could be also partially explained by an ascertainment bias, considering that patients with a known family history for the disease may seek diagnosis sooner and may be more vigilant regarding the onset of subtle cognitive or behavioral symptoms.

According to previous studies,[8] patients' subgroups were highly similar across behavioral and cognitive measures, with only slight differences in the FBI-A and in the letter fluency scores, despite arising from different underlying pathologies and genetic factors. The FBI-A evaluates negative or deficient behaviors, such as apathy, aspontaneity, and indifference, which may depend on a deficit of glutamatergic transmission, while positive symptoms, evaluated with the FBI-B, may be the consequence of a lack of GABAergic inhibition,[31,32] potentially reflecting the unique impairment of different neurotransmitter systems in FTD.[33–35]

Despite a comparable clinical picture, f-FTD showed higher serum NfL concentrations by an average of 37.3 pg/mL and greater brain damage, compared to s-FTD. Moreover, f-FTD showed a shorter survival rate than s-FTD, and this finding is supported by several studies showing that disease survival is generally shorter in the genetic forms of FTD.[16,36–38]

Serum NfL levels have already been shown to be a consistent and reliable marker of disease severity in both genetic and sporadic FTD,[39–46] with levels increasing already in the prodromal phases of disease,[47] and correlating with disease survival.[43] Also in this study, serum NfL levels were the most significant predictors of survival.[43]

These findings raise important issues, suggesting that there were no demographic or clinical features that may reliably distinguish f-FTD from s-FTD, providing empirical support for the applicability of clinical scores developed for s-FTD to f-FTD. Conversely, different rates of progression between groups have fundamental implications when considering potential generalizability in future pharmacological and non-pharmacological clinical trials. In view of recent advances in disease-modifying therapies that target specific pathogenic routes,[48] f-FTD and s-FTD should be considered separately to measure the effects of treatment interventions, given the different disease trajectories.

We acknowledge that the present study entails several limitations. First, we did not evaluate motor features of parkinsonisms, which characterize PSP or CBS-like phenotypes; previous studies have indeed shown that f-FTD may present with more severe motor symptoms, mainly driven by *MAPT* mutations that present greater involvement of basal ganglia with tau disease pathology.[8] Second, not all patients with s-FTD underwent genetic screening, so we may not entirely exclude the presence of pathogenic variants in this group. Third, only a subset of patients underwent biological measurements or imaging analyses, but still significant differences could be observed between groups. Fourth, the lack of pathological confirmation in the s-FTD cases prevented evaluation of significant differences and distributions between proteinopathies. Finally, we considered both bvFTD and PPA together, even though clinical phenotype was included as covariate in the statistical analyses.

Major strengths of our study are the large series of FTD patients and the comprehensive approach in extensively evaluating demographic, clinical, fluid biomarker, and imaging data, carried out at the same study site to minimize variability.

In conclusion, our results suggest that f-FTD and s-FTD are very similar clinical entities, but with different rates of progression. The parallel characterization of both f-FTD and s-FTD will improve our understanding of the disease, and aid in designing future clinical trials through both genetic and sporadic forms of FTD.

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CONFLICTS OF INTEREST

H.Z. has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). K.B. has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu; Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB

(BBS), which is a part of the GU Ventures Incubator Program. Author disclosures are available in the supporting information.

AUTHOR CONTRIBUTIONS

Alberto Benussi and Barbara Borroni designed the study. Alberto Benussi, Antonella Alberici, Alessandro Padovani, and Barbara Borroni recruited patients. Alberto Benussi, Ilenia Libri, Enrico Premi, Antonella Alberici, Valentina Cantoni, Yasmine Gadola, Jasmine Rivolta, Marta Pengo, Stefano Gazzina, Vince D. Calhoun, Roberto Gasparotti, Henrik Zetterberg, Nicholas J. Ashton, Kaj Blennow, Alessandro Padovani, and Barbara Borroni performed experiments and analyzed the data. Alberto Benussi, Ilenia Libri, Enrico Premi, and Barbara Borroni evaluated the data and co-wrote the manuscript. Alberto Benussi, Ilenia Libri, Enrico Premi, Antonella Alberici, Valentina Cantoni, Yasmine Gadola, Jasmine Rivolta, Marta Pengo, Stefano Gazzina, Vince D. Calhoun, Roberto Gasparotti, Henrik Zetterberg, Nicholas J. Ashton, Kaj Blennow, Alessandro Padovani, and Barbara Borroni contributed to revising the manuscript for intellectual content.

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SUPPORTING INFORMATION

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