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

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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
assessments, 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 \((14.0 \pm 7.6 \text{ vs. } 11.6 \pm 7.4, P = .002)\), and positive behaviors \((20.0 \pm 11.0 \text{ vs. } 17.4 \pm 11.8, P = .031)\). Serum NfL concentrations were higher in patients with f-FTD \((70.9 \pm 37.9 \text{ pg/mL})\) compared to s-FTD patients \((37.3 \pm 24.2 \text{ pg/mL}, P < .001)\), 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;\(^2\) 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.

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. 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.

2 | METHODS

2.1 | Participants

This retrospective study included a sample of patients diagnosed with FTD according to current clinical criteria 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.

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 (Aβ42) or positron emission tomography amyloid were measured in a subset of cases, to rule out Alzheimer’s disease, as previously reported. 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). Furthermore, in accordance with recent consensus recommendations, 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 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-amytrophic 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 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 GS 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).  

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).  

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.  

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.  

CSF total tau and p-tau concentrations were measured by sandwich ELISA (Innotest hTau Antigen kit, Innotest PHOSHO-TAU [181P], Fujirebio). CSF Aβ1-42 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. 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. CAT12 potentially provided more robust and accurate performances compared to other VBM pipelines.  

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.

In line with the original study, 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/), with neural network algorithm (Infomax) that attempts to minimize the mutual information of the network outputs; the component number was estimated to be 18, based on the minimum description length principle. The statistical reliability of the source decomposition was tested by using the ICASSO toolbox 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 pathogenic 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-tau181, and Aβ1-42, and serum p-tau181 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).

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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             | 63.2 ± 8.5 | 60.7 ± 8.6 | 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 comparisons 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; FTLD, 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     |         |           |           |         |
| CSF total tau, pg/mL   | 441.7 ± 292.0 | 433.2 ± 292.0 | 443.9 ± 296.5 | .808    |
| CSF p-tau181, pg/mL    | 62.7 ± 63.01  | 55.2 ± 65.0   | 64.6 ± 62.5  | .377    |
| CSF Aβ1-42, 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-tau181, 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 comparisons 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.

* Biological markers were performed in a subset of patients (for demographic 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.

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, 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, 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, potentially reflecting the unique impairment of different neurotransmitter systems in FTD.

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.

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

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, 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. 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, Pintech Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplett 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.
(BENUSI ET AL.), 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 contributed to revising the manuscript for intellectual content.

REFERENCES
1. Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet. 2015; 386(10004):1672-1682. http://linkinghub.elsevier.com/retrieve/pii/S0140673615004614
2. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76(11):1001-1014. http://eutils.ncbi.nlm.nih.gov/entrez/eutils/efetch.fcgi?dbfrom=pubmed&id=21325651&retmode=ref&cmd=prlinks
3. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134(Pt 9):2456-2477. https://doi.org/10.1093/Brain/awr179
4. Borroni B, Benussi A. Recent advances in understanding frontotemporal degeneration. F1000Res. 2019;8:2098. https://doi.org/10.12688/f1000research.20330.1
5. Rohrer JD, Guerreiro R, Vandrovcova J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009;73(18):1451-1456. http://eutils.ncbi.nlm.nih.gov/entrez/eutils/efetch.fcgi?dbfrom=pubmed&id=19884572&retmode=ref&cmd=prlinks
6. Borroni B, Padovani A. Dementia: a new algorithm for molecular diagnostics in FTLD. Nat Rev Neurol. 2013;9(5):241-242. http://doi.org/10.1038/nrneurol.2013.72
7. Benussi A, Padovani A, Borroni B. Phenotypic heterogeneity of monogenic frontotemporal dementia. Front Aging Neurosci. 2015;7(SEP):171. https://doi.org/10.3389/fagi.2015.00171
8. Heuer HW, Wang P, Rascovsky K, et al. Comparison of sporadic and familial behavioral variant frontotemporal dementia (FTD) in a North American cohort. Alzheimer’s Dement. 2020;16(1):60-70. https://doi.org/10.1016/j.jalz.2020.04.011
9. Capozzo R, Sassi C, Hammer MB, et al. Clinical and genetic analyses of familial and sporadic frontotemporal dementia patients in Southern Italy. Alzheimer’s Dement. 2017;13(8):858-869. https://doi.org/10.1016/j.jalz.2017.01.011
10. Benussi A, Gazzina S, Premi E, et al. Clinical and biomarker changes in presymptomatic genetic frontotemporal dementia. Neurobiol Aging. 2019;76:133-140. https://doi.org/10.1016/j.neurobiolaging.2018.12.018
11. Borroni B, Benussi A, Archetti S, et al. Csf p-tau181/tau ratio as biomarker for TDP pathology in frontotemporal dementia. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(1-2):86-91. https://doi.org/10.3109/21678421.2014.971812
12. Padovani A, Benussi A, Cotelli MS, et al. Transcranial magnetic stimulation and amyloid markers in mild cognitive impairment: impact on diagnostic confidence and diagnostic accuracy. Alzheimers Res Ther. 2019;11(1):95. https://doi.org/10.1186/s13195-019-0555-3
13. Koriath CAM, Kenny J, Ryan NS, et al. Genetic testing in dementia – utility and clinical strategies. Nat Rev Neurol. 2021;17(1):23-36. https://doi.org/10.1038/s41582-020-00416-1. Published online 2020.
14. Fostinelli S, Ciani M, Zanardini R, et al. The heritability of frontotemporal lobar degeneration: validation of pedigree classification criteria in a Northern Italy cohort. J Alzheimers Dis. 2018;61(2):753-760. https://doi.org/10.3233/JAD-170661
15. Goldman JS, Farmer JM, Wood EM, et al. Comparison of family histories in FTLD subtypes and related tauopathies. Neurology. 2005; 65(11):1817-1819. http://eutils.ncbi.nlm.nih.gov/entrez/eutils/efetch.fcgi?dbfrom=pubmed&id=16344531&retmode=ref&cmd=prlinks
16. Cosseidu M, Benussi A, Gazzina S, et al. Mendelian forms of disease and age at onset affect survival in frontotemporal dementia. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19(1-2):87-92. https://doi.org/10.1080/21678421.2017.1384020
17. Cosseidu M, Benussi A, Gazzina S, et al. Progression of behavioural disturbances in frontotemporal dementia: a longitudinal observational study. Eur J Neurol. 2020;27(2):265-272. https://doi.org/10.1111/ene.14071
18. Knopman DS, Kramer JH, Boeve BF, et al. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. Brain. 2008;131(11):2957-2968. https://doi.org/10.1093/brain/awn234
19. Miyagawa T, Brushaber D, Syrjanen J, et al. Utility of the global CDR® plus NACC FTLD rating and development of scoring rules: data from the ARTFL/LEFFTDS Consortium. Alzheimer’s Dement. 2020;16(1):106-117. https://doi.org/10.1016/j.alz.12033
20. Benussi A, Karikari TK, Ashton N, et al. Diagnostic and prognostic value of serum NfL and p-Tau181 in frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry. 2020;91(9):960-967. https://doi.org/10.1136/jnnp-2020-332487
21. Karikari T, Pascoal T, Ashton N, et al. Plasma phospho-tau181 as a biomarker for Alzheimer’s disease: development and validation of a prediction model using data from four prospective cohorts. Lancet Neurol. 2020;19(5):422-433.
22. Borroni B, Malinverno M, Gardoni F, et al. Tau forms in CSF as a reliable biomarker for progressive supranuclear palsy. Neurology. 2008;71(22):1796-1803. https://doi.org/10.1212/01.wnl.0000335941.68602.39
23. Kurth F, Gaser C, Luders E. A 12-step user guide for analyzing voxel-wise gray matter asymmetries in statistical parametric mapping (SPM). Nat Protoc. 2015;10(2):293-304. https://doi.org/10.1038/nprot.2015.014
24. Farokhian F, Beheshti I, Sone D, Matsuda H, Comparing CAT12 and VBM8 for detecting brain morphological abnormalities in temporal lobe epilepsy. Front Neurol. 2017;8(AUG):428. https://doi.org/10.3389/fneur.2017.00428
25. Xu L, Groth KM, Pearlson G, Schretlen DJ, Calhoun VD. Source-based morphometry: the use of independent component analysis to identify gray matter differences with application to schizophrenia. Hum Brain Mapp. 2009;30(3):711-724. https://doi.org/10.1002/hbm.20540
26. Gupta CN, Calhoun VD, Rachakonda S, et al. Patterns of gray matter abnormalities in schizophrenia based on an international mega-analysis. Schizophr Bull. 2015;41(5):1133-1142. https://doi.org/10.1093/schbul/sbu177
27. Calhoun VD, Adali T, Pearlson GD, Pekar JJ. A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp. 2002;16(2):131-131. https://doi.org/10.1002/hbm.10044
28. Mckeown MJ, Makeig S, Brown GG, et al. Analysis of fMRI data by blind separation into independent spatial components. Hum Brain Mapp. 1998;6(3):160-188. https://doi.org/10.1002/(sic)1097-0193(1998)6:3<160::aid-hbmm5>3.0.co;2-r  

29. Li Y-O, Adali T, Calhoun VD, Estimating the number of independent components for functional magnetic resonance imaging data. Hum Brain Mapp. 2007;28(11):1251-1266. https://doi.org/10.1002/hbm.20359  

30. Himberg J, Hyvärinen A. Icasso: software for investigating the reliability of ICA estimates by clustering and visualization. http://www.cis.hut.fi/projects/ica/icasso/  

31. Benussi A, Dell’Era V, Cantoni V, et al. Neurophysiological correlates of positive and negative symptoms in frontotemporal dementia. J Alzheimers Dis. 2020;73(3):1133-1142. https://doi.org/10.3233/JAD-190986. Arighi A, ed.  

32. Benussi A, Alberici A, Buratti E, et al. Toward a glutamate hypothesis of frontotemporal dementia. Front Neurosci. 2019;13(March):304. https://doi.org/10.3389/fnins.2019.00304  

33. Borroni B, Benussi A, Premi E, et al. Biological, neuroimaging, and neurophysiological markers in frontotemporal dementia: three faces of the same coin. J Alzheimers Dis. 2018;62(3):1113-1123. https://doi.org/10.3233/JAD-170584  

34. Palese F, Bonomi E, Nuzzo T, et al. Anti-GluA3 antibodies in frontotemporal dementia: effects on glutamatergic neurotransmission and synaptic failure. Neurobiol Aging. 2020;86:143-155. https://doi.org/10.1016/j.neurobiaging.2019.10.015  

35. Murley AG, Rowe JB. Neurotransmitter deficits from frontotemporal lobar degeneration. Brain. 2018;141(5):1263-1285. https://doi.org/10.1093/brain/awx327  

36. Hodges JR, Davies R, Xuereb J, Kril J, Halliday G. Survival in frontotemporal dementia: clinical features and predictors of progression. J Neurol Neurosurg Psychiatry. 2021;11(5):188. https://doi.org/10.1186/s13195-021-00932-2  

37. Chiu WZ, Kaat LD, Seelaar H, et al. Survival in progressive supranuclear palsy and frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2010;81(4):441-445. http://jnnp.bmj.com/cgi/doi/10.1136/jnnp.2009.195719  

38. Borroni B, Grassi M, Archetti S, et al. Genetic background predicts poor prognosis in frontotemporal lobar degeneration. Neurodegener Dis. 2011;8(5):289-295. https://doi.org/10.1159/000322790  

39. Rohrer JD, Woollacott IOC, Dick KM, et al. Serum neurofilament light chain protein is a measure of disease intensity in frontotemporal dementia. Neurology. 2016;87(13):1329-1336. https://doi.org/10.1212/WNL.0000000000003154  

40. Panman JL, Venkatraghavan V, Van Der Ende EL, et al. Modelling the cascade of biomarker changes in GRN-related frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2021;92(5):494-501. https://doi.org/10.1136/jnnp-2020-323541  

41. Gaetani L, Blenow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry. 2019;90(8):870-881. https://doi.org/10.1136/jnnp-2018-320106  

42. Steiner J, Anderl-Straub S, Diehl-Schmid J, et al. Serum neurofilament light chain in behavioral variant frontotemporal dementia. Neurology. 2018;91(15):e1390-e1401. http://www.neurology.org/lookup/doi/10.1212/WNL.0000000000006318  

43. Benussi A, Karikari TK, Ashton N, et al. Diagnostic and prognostic value of serum NfL and p-Tau 181 in frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry. 2020;91(9):960-967. https://doi.org/10.1136/jnnp-2020-323487  

44. van der Ende EL, Xiao M, Xu D, et al. Neuronal pentraxin 2: a synapse-derived CSF biomarker in genetic frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2020;91(6):612-621. https://doi.org/10.1136/jnnp-2019-322493  

45. Heller C, Foiani MS, Moore K, et al. Plasma glial fibrillary acidic protein is raised in progranulin-associated frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2020;91(3):263-270. https://doi.org/10.1136/jnnp-2019-321954  

46. Solje E, Benussi A, Buratti E, Remes AM, Haapasalo A, Borroni B. State-of-the-art methods and emerging fluid biomarkers in the diagnostics of dementia—a short review and diagnostic algorithm. Diagnostics. 2021;11(5):788. https://doi.org/10.3390/diagnostics11050788  

47. Benussi A, Ashton NJ, Karikari TK, et al. Prodomal frontotemporal dementia clinical features and predictors of progression. Alzheimers Res Ther. 2021;13(1):188. https://doi.org/10.1186/s13195-021-00932-2  

48. Giunta M, Solje E, Gardoni F, Borroni B, Benussi A. Experimental disease-modifying agents for frontotemporal lobar degeneration. J Exp Pharmacol. 2021;13:359-376. https://doi.org/10.2147/JEPS262352

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