Mendelian forms of disease and age at onset affect survival in Frontotemporal Dementia.

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Abstract

Introduction. Frontotemporal Dementia (FTD) is a common cause of young onset dementia. Very few reports on disease duration are currently available and predictors of survival are still undefined.

Objective. The aim of the present study was to assess the natural history of FTD and to define predictors of survival.

Methods: We considered 411 FTD patients consecutively enrolled in a tertiary referral centre for neurodegenerative disorders. Demographic and clinical variables were carefully recorded. Each patient underwent genetic screening for monogenic disease.

Results: The mean survival time from the onset of the symptoms was 7.8±4.0 years. The presence of a pathogenic mutation (*GRN*, *C9orf72* or *MAPT*) (Hazard ratio [HR] = 1.85, 95% CI: 1.04-3.31, p=0.037) and older age at disease onset (HR = 1.04, 95% CI: 1.02-1.07, Wald $\chi2$ = 9.86, p=0.002) were associated with shorter life expectancy. However, a significant negative interaction between age at onset and genetic mutation was found, suggesting that the effect of age is different in patients with and without a genetic mutation (p=0.028). Variables such as gender, clinical phenotype or education and occupation were not associated with survival risk.

Conclusion: Our findings suggest that monogenic disease and age at onset are independent predictors of survival and should be considered in future clinical intervention trials and in patients' and caregivers' counseling.

Introduction

Frontotemporal Dementia (FTD) is a common cause of young onset dementia [Ratnavalli et al., 2002, 12058088; Ikeda et al., 2004, 15178933] as consequence of focal frontal and temporal lobar atrophy, and is characterized by insidious and progressive personality changes, impairment of executive functions and language deficits [Seelaar et al., 2011, 20971753[.

Three clinical phenotypes have been described, namely the behavioral variant frontotemporal dementia (bvFTD) [Rascovsky et al., 2011, 21810890], the agrammatic variant of Primary Progressive Aphasia (avPPA) and the semantic variant of Primary Progressive Aphasia (svPPA) [Gorno-Tempini et al., 2011, 2132565]. A family history of dementia is found in 25–50% of cases of FTD and about 10% have a clear autosomal-dominant inheritance [Seelaar et al., 2008, 18703462] accounted predominantly by the *Microtubule-Associated Protein Tau* (*MAPT*) and *Granulin* (*GRN*) mutations, and the *Chromosome 9 open-reading-frame 72* (*C9orf72*) expansion [Borroni et al., 2013, 23609620].

The clinical course of FTD is for the most unpredictable. Average survival in clinical cohorts ranges from 3 to 14 years from initial symptom onset [Hodges et al., 2003, 12913196; Hodges et al., 2010, 19805492; Hu et al., 2009, 1990116; Roberson et al., 2005, 16157905; Rascovsky et al. 2005, 16087904; Chiu et al., 2010, 20360166; Le Rhun et al., 2005, 16186529] and, at present, only few variables have been associated with life expectancy in FTD with little replication.

It has been suggested that the best prognosis is associated with the svPPA phenotype [Roberson et al., 2005, 16157905], and among demographic variables, only higher occupation attainment was found to correlate with longer survival in autopsy-confirmed cases [Massimo et al., 2015, 25904687]. Furthermore, monogenic FTD due to pathogenic *GRN* mutations has been associated with poor prognosis [Borroni et al., 2011, 21311163].

Nevertheless, all these studies have been hindered by the relative small sample size, and by the lack of both extensive follow-up and comprehensive assessment of prognostic variables.

In this work, we took advantage of a large sample cohort of FTD patients, followed for more than fifteen years, and investigated the possible role of demographic characteristics, genetic background and clinical phenotype in predicting survival.

Methods

Subjects

Patients fulfilling current clinical criteria for probable or definite FTD [Rascovsky et al., 2011, 21810890; Gorno-Tempini et al., 2011, 21325651] were consecutively recruited from the Centre for Ageing Brain and Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Italy, from December 2001 to July 2016. All patients underwent somatic and neurological evaluation, routine laboratory examination, and a comprehensive neuropsychological and behavioral assessment.

Demographic characteristics including the estimated age at symptom onset and family history were carefully recorded. The age at symptoms onset was based on family reports of the earliest but persistent abnormal clinical feature in the domains of language, social function, personality change, or movement disorder. A positive family history was considered when patients had a first-degree relative with dementia, parkinsonism, or motor neuron disease. Educational attainment was measured by years of formal schooling, and occupational attainment was rated as previously published [Garibotto et al., 2008, 18936426].

Furthermore, each patient was screened for the most frequent causes of monogenic inherited disease in Italy [Borroni et al., 2009, 19730170]. Patients were tested for *GRN* mutations, by serum progranulin dosage and by direct sequencing [Ghidoni et al., 2012, 22123177], for *C9orf72* expansion and for *MAPT* P301L mutation. Given the evidence of low frequency of *MAPT* mutations in Italy [Binetti et al., 2003, 12565146] we considered only P301L mutation and we sequenced the entire *MAPT* gene in selected cases.

Information on the current status at censoring date (July 31st, 2016) was collected via reports from the regional Health Service or telephone interview.

Full written informed consent was obtained from all subjects according to the Declaration of

Helsinki. The study protocol was approved by the Brescia Hospital Ethics Committee.

Statistical analysis

Comparison between clinical subgroups was carried out using Pearson's χ2 test or one-way

ANOVA, as appropriate. Survival was calculated as time from symptom onset to time of death

from any cause (outcome=1) or censoring date (outcome=0). Survival analyses were carried out by

means of a Cox proportional-hazard regression analysis. This model was used to develop a

nomogram of patient risk. Hazard ratios (HR) are given with their respective 95% confidence

intervals (CIs), while statistical significance was assumed at $p<0.05$. Data analyses were carried out

using SPSS 21.0 (SPSS, Inc., Chicago, IL, USA) and SAS software 9.3 (SAS Institute Inc., Cary, NC,

USA).

Results

The present analysis was carried out on 411 FTD patients, including 294 patients with bvFTD, 77

with avPPA and 40 with svPPA. Demographic and clinical characteristics according to clinical

phenotype are reported in **Table 1**. The average age at symptom onset was 63.56±7.90 years,

while age at diagnosis was 66.24±7.91 years. Genetic screening revealed the presence of a

pathogenic mutation in 55 patients (13.4%) of the cohort, i.e. 46 *GRN* carriers (11.2%), 9 C9orf72

expansion carriers (2.2%) and 1 MAPT carrier (0.2%). One-hundred FTD (24.3%) were *APOE ε4*

allele carriers.

Out of the 411 patients, 120 died during the 15-year observation. In the entire cohort, the mean

survival time from symptom onset was 93.4±48.6 months (equal to 7.8±4.0 years).

As reported in **Table 2,** by means of multivariate cox proportional-hazard regression analysis,

patients with a genetic mutation (*GRN*, *C9orf72* or *MAPT*) showed shorter survival than those

without a genetic mutation (Hazard ratio [HR] = 1.85, 95% CI: 1.04-3.31, Wald χ2 = 4.34, p=0.037)

(**Figure 1A**), and there was an increased risk for age at disease onset (HR = 1.04, 95% CI: 1.02-1.07,

Wald χ2 = 9.86, p=0.002), equal to a 4.3% increase in the risk of death for every year of age (**Figure

1B**). We also observed a significant negative interaction between age and genetic mutation,

suggesting that the effect of age is different in patients with and without a genetic mutation

(p=0.028) (**Figure 1C**). Indeed, the change in the log hazard rate per year of age is 0.054 in patients

without a genetic mutation, while it is -0.035 in patients with a mutation.

A nomogram based on the multivariate cox proportional-hazard regression analysis is presented in

Figure 2 that can be used to calculate a prognostic score and to estimate the risk for death in

individual patients.

No association was found between gender, clinical phenotype (bvFTD, avPPA, svPPA), occupation

or education levels and survival probability.

Discussion

Several studies have assessed prognostic factors influencing survival in FTD, but only few variables have been reported as directly affecting life expectancy and mostly with contrasting results [Roberson et al., 2005, 16157905; Chiu et al., 2010, 20360166; Massimo et al., 2015, 25904687]. Indeed, one of the main limitations of such studies is represented by the relative small sample sizes [Massimo et al., 2015, 25904687; Hodges et al., 2003, 12913196; Rascovsky et al. 2005, 16087904; Nunnemann et al., 2011, 22056939] and by the lack of discrimination between mendelian and sporadic cases.

In the present study, we included a large cohort of patients affected with bvFTD, avPPA and svPPA with a probable or definite diagnosis (as determined by genetic screening for mutations in *MAPT*, *GRN* and *C9orf72* genes), and we considered a comprehensive number of possible predictors, including demographic variables, clinical phenotype and the most frequent causes of monogenic FTD. We excluded FTD with motor neuron disease cases as it has been clearly associated with a decreased survival [Josephs et al., 2005, 16116138; Hodges et al., 2003, 12913196; Lillo et al., 2010, 20625088].

The mean survival rate from symptom onset in our sample set is in line with previously reported data that is a mean of 7.8±4.0 years [Nunnemann et al., 2011, 22056939; Garcin et al., 2009, 19917988]. Even the timeframe from age at onset to diagnosis was similar to previous studies (2.67±2.35 years) [Garcin et al., 2009, 19917988; Rascovsky et al., 2005, 16087904; Le Rhun et al., 2005, 16186529; Coyle-Gilchrist et al., 2016, 27037234].

We identified that monogenic disease and older age at onset were inversely correlated with survival (HR 1.93 and 1.04, respectively).

The role of positive family history on survival is debated [Chiu et al., 2010, 20360166; Roberson et al., 2005, 16157905; Hodges et al., 2003, 12913196; Borroni et al., 2009, 19236162; Rascovsky et al. 2005, 16087904], but what seems clear is that monogenic FTD presents with a faster course [Borroni et al., 2011, 21311163; Chiu et al., 2010, 20360166; Beck et al., 2008, 18234697].

The effect of age at onset is again controversial, with reduced survival in older patients in the cohort by Chiu [Chiu et al., 2010, 20360166], whilst this was not confirmed in other cohorts [Hodges et al., 2010, 19805492; Roberson et al., 2005, 16157905; Nunnemann et al., 2011, 22056939].

To further elucidate the effect of pathogenic mutations on survival, we explored whether genetic and sporadic cases had a different correlation with the age at onset. Interestingly, an inverse correlation between age at onset and positive genetic status was found. This suggests that the effect of age is different in patients with and without a genetic mutation and is consistent with a model in which highly pathogenic mutations lead to faster pathological accumulation and earlier disease onset with rapid course, while a worse disease course in older, sporadic, FTD patients could be related to higher frailty and comorbidities, as hypothesized in autosomal dominant Alzheimer's disease [Ryman et al., 2014, 24928124].

We did not find significant effects on survival probability for the other considered variables, namely gender, clinical phenotype, education and occupational level. Indeed, in previously published literature data, two variables were found to be significantly associated with survival probability in FTD, namely the svFTD phenotype [Nunnemann et al., 2011, 22056939; Roberson et al., 2005, 16157905; Hodges et al., 2010, 19805492], and occupation attainment [Massimo et al., 2015, 25904687].

The svPPA phenotype seemed to have a longer clinical course [Nunnemann et al., 2011, 22056939; Roberson et al., 2005, 16157905; Hodges et al., 2010, 19805492] and we indeed found a trend,

even though non-significant, towards an increased survival in this cohort. With regards to occupational level, in a previous study by Massimo et al. [Massimo et al., 2015, 25904687], a higher occupational attainment was reported as a predictor of longer survival in autopsy-confirmed FTD, while we did not observe a significant influence of occupation on survival probability. This divergence could be explained by a different distribution of occupational levels in the two cohorts, with the majority of patients being unskilled laborers in our group, compared to a higher representation of professional and technical workers in the former study, and by the use of a different ranking scale in the two studies.

We acknowledge that this study entails some limitations, as we did not have autopsy confirmation in sporadic cases and we did not considered all the monogenic causes of FTD. However, included patients were evaluated by an extensive clinical and imaging work-up and followed longitudinally to ensure clinical diagnosis.

In conclusion, we here provide evidence for independent correlation between survival rates and mendelian or age of onset driven FTD patients. The current work helps defining patients with worse prognosis is crucial for counselling patients and caregivers, for testing potential modifier treatments reducing the patients' number needed in clinical trials, and in establishing the effects of a disease-modifying drug within a reasonable timeframe. Confirmation on larger cohorts of neuropathologically proven cases is warranted.

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Table 1. Demographic and clinical characteristics of included patients

Patients	All FTD (n=411)	bvFTD (n=294)	avPPA (n=77)	svPPA (n=40)
Sex, male, % (number)	51.6 (212)	56.8 (167)^°	41.6 (32)*	32.5 (13)*
Age at diagnosis, years	66.24±7.91	65.94±7.56	66.90±8.84	67.25±8.57
Age at disease onset, years	63.56±7.90	63.26±7.48	64.14±8.91	64.70±8.80
Time from onset to diagnosis, years	2.67±2.35	2.65±2.47	2.76±2.03	2.68±2.06
Survival[a], months	93.41±48.58	90.43±52.25	98.25±39.96	111.63±19.61
Education, years	8.34±4.25	7.99±4.06°	9.01±4.45	9.63±4.95*
Occupational level				
level 2, %	43.3 (178)	47.6 (140)	32.5 (25)	32.5 (13)
level 3, %	16.5 (68)	15.6 (46)	18.2 (14)	20 (8)
level 4, %	20.4 (84)	19.7 (58)	24.7 (19)	17.5 (7)
level 5, %	13.9 (57)	12.2 (36)	18.2 (14)	17.5 (7)
level 6, %	5.8 (24)	4.8 (14)	6.5 (5)	12.5 (5)
Positive family history, % (number)	41.1 (169)	41.5 (122)	46.8 (36)	27.5 (11)
Pathogenic mutations, % (number)	13.6 (56)	12.2 (36)^	24.7 (19)*°	2.5 (1)^
ApoE-ε4 alleles, % (number)	24.3 (100)	26.5 (78)	15.6 (12)	25 (10)
FTLD-CDR at diagnosis	6.39±4.42	6.33±4.40	6.50±4.49	6.70±4.45
MMSE at diagnosis	20.43±8.25	21.62±7.30^	16.08±9.89*°	20.05±8.80^

Results are sown as mean ± standard deviation. Gender, occupational level, positive family history, presence of pathogenic mutation and frequency of ApoE-ε4 carrier are indicated as percentage, number of subjects between brackets. [a]Survival considered only for truncated cases (death). One-way ANOVA interaction or χ^2-square test, as appropriate. *vs bvFTD; ^vs avPPA; °vs svPPA with *post hoc* tests with Bonferroni correction for multiple comparisons ($p<0.05$).

FTLD-CDR = FTLD-modified Clinical Dementia Rating scale; MMSE = Mini-Mental State Examination; bvFTD = behavioral variant frontotemporal dementia; avPPA = agrammatic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia

Table 2. Multivariate Cox proportional-hazard regression analysis

	Hazard Ratio (95% CI)	p value
Sex (male)	0.89 (0.61-1.31)	0.561
Genetic mutation	1.89 (1.04-3.31)	**0.037**
Age at disease onset	1.04 (1.02-1.07)	**0.002**
Clinical Phenotype		
bvFTD	1 (reference)	
avPPA	1.28 (0.81-2.07)	0.416
svPPA	0.73 (0.35-1.55)	0.284
Occupation level	0.86 (0.71-1.04)	0.182
Education (years)	1.04 (0.98-1.11)	0.255

Significant values are reported in bold; bvFTD = behavioral variant frontotemporal dementia; avPPA = agrammatic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia

Legend to figures.

Fig. 1. Survival curves for genetic mutation **(A)** and age at disease onset **(B)**, and the combination of both **(C)**, adjusted for gender, clinical phenotype (bvFTD, avPPA, svPPA), occupation level and education.

Fig. 2. Frontotemporal Dementia risk model nomogram.