

Neurobehavioral Features in Frontotemporal Dementia With Amyotrophic Lateral Sclerosis

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Objective: To compare the clinical features at presentation in patients with frontotemporal dementia (FTD) who develop amyotrophic lateral sclerosis (ALS) with those of patients with behavioral variant FTD (bvFTD) who do not develop ALS.

Design: Archival data analysis on 61 deceased patients with FTD. We reviewed the clinical features at presentation (behavioral changes, psychotic symptoms, language, and executive and memory problems) and survival.

Setting: Early Onset Dementia Clinic, Cambridge, England.

Patients: From a total of 156 patients with a clinical diagnosis of behavioral FTD, we selected 61 deceased patients with comprehensive medical records, including 43 with bvFTD and 18 with FTD/ALS.

Main Outcome Measures: Clinical features and survival.

Results: There was a significant association between the presence of delusions (50%; odds ratio, 4.4; 95% confidence interval, 1.3-14.5) and diagnosis of FTD/ALS (n=18), whereas the behavioral features were identical in both groups. The interval between the onset of behavioral changes and diagnosis of ALS was less than 2 years in 12 (67%) of the patients with FTD/ALS. The median survival from symptom onset was significantly shorter for the FTD/ALS group (2.4 years; 95% confidence interval, 1.8-3.0 years) than for the bvFTD group (6.6 years; 5.6-7.6 years).

Conclusions: Delusions are particularly common in patients who develop FTD/ALS. The occurrence of delusions in the context of behavioral FTD should lead to an early search for ALS features.

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F RONTOTEMPORAL DEMENTIA (FTD) is the second most common form of early-onset dementia in patients younger than 65 years.¹ Two major clinical presentations are recognized in FTD: the behavioral variant (bvFTD) and progressive aphasia, which in turn can be divided into semantic dementia and progressive nonfluent aphasia (PNFA).^{2,3}

During the past decade, there has been increasing awareness of the overlap between FTD and amyotrophic lateral sclerosis (ALS) at the clinical and pathological level. A proportion of patients presenting with classic ALS go on to manifest features of FTD and, likewise, some patients with FTD develop features of ALS.⁴⁻⁸ Pathologically, FTD/ALS is associated with underlying TAR DNA-binding protein (TDP-43) inclusions,^{9,10} which are also present in most patients with uncomplicated ALS.

Given the poor prognosis of those patients with FTD who develop ALS¹¹ and their need for additional care and medical services, it is important to identify such patients at an early stage. This study con-

cerns early predictors of FTD/ALS in patients presenting with bvFTD. To date, the clinical features reported in FTD/ALS¹¹ appear identical to those reported in other patients with bvFTD, notably changes in personality with apathy and/or disinhibition, irritability, loss of empathy, stereotyped behaviors, and alterations in appetite with an increased preference for sweet food.^{6,12} It has been suggested that the dementia progresses rapidly even before the onset of bulbar and limb features of ALS.⁶ A number of reports have suggested that delusions and hallucinations may be particularly common, but this has been based on small series.^{6,13-15} Some studies have reported language deficits, notably progressive aphasia preceding the appearance of motor features, predominantly in cases with bulbar motor onset.¹⁶⁻¹⁹

The interval between the onset of behavioral and motor features has typically ranged from 6 to 12 months, but the limits of this interval have not been explored. The prognosis appears to be even poorer in patients with FTD/ALS than for patients with others forms of FTD, and few patients survive longer than 3 years.^{11,20,21}

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Table 1. Demographic Data of bvFTD and FTD/ALS Groups

	Total (N=61)	bvFTD Group (n=43)	FTD/ALS Group (n=18)	P Value
Family history, No. (%)	13 (21)	9 (21)	4 (22)	.91
Male/female ratio	37/24	25/18	12/6	.53
Mean (SD) age, y				
At symptom onset	58.1 (8.0)	57.6 (7.9)	59.3 (8.6)	.44
At diagnosis	61.0 (8.2)	60.7 (8.2)	61.7 (8.2)	.68
At death	64.1 (8.1)	64.7 (8.0)	62.8 (8.5)	.42

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; FTD/ALS, FTD with amyotrophic lateral sclerosis.

At present, it is uncertain whether there are differences in the clinical presentation of patients with FTD/ALS vs those with bvFTD who do not manifest ALS. Few systematic studies have been conducted, and none have explicitly explored predictors of subsequent ALS in patients presenting with bvFTD. The aims of this study were to compare the clinical symptoms at presentation in FTD/ALS vs bvFTD cases and to report on the survival of these groups.

METHODS

CASE SELECTION

A review of the database of the Cambridge Early Onset Dementia Clinic identified all cases with a clinical diagnosis of FTD from January 1, 1990, through December 31, 2007. Cases with a diagnosis of semantic dementia and PNFA were excluded.²

From a total cohort of 156 cases that met criteria for behavioral FTD,² we selected all 61 deceased patients with comprehensive medical records. Eighteen cases designated as FTD/ALS presented with behavioral and cognitive changes,^{2,22} followed by the development motor symptoms that fulfilled revised El Escorial Criteria for clinically definite ALS^{23,24}; diagnoses were confirmed by electromyography. Of these 18 cases, 11 presented with bulbar motor onset, and 7 had limb motor onset. For those 43 FTD cases that did not develop clinical ALS, we prefer the designation bvFTD.^{3,22} All patients had been followed up in a specialist multidisciplinary clinic with neurological, psychiatric, and cognitive evaluations. Psychotic symptoms were evaluated and recorded by a senior psychiatrist in all cases. Delusions and hallucinations were defined as follows according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) glossary.²⁵ Delusion was "a false belief based on incorrect inference about external reality that is firmly sustained despite what almost everyone also believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary. The belief is not one ordinarily accepted by other members of the person's culture."⁷ Hallucination was "a sensory perception that has the compelling sense of reality of true perception but that occurs without external stimulation of the relevant sensory organ."⁷

Pathological confirmation was available in 25 of the bvFTD cases (58%). All of them presented with frontotemporal lobar degeneration (FTLD); of these, 13 had tau-positive inclusions, 11 had ubiquitinated and TDP-43 inclusions (FTLD-TDP), and 1 had no inclusions. Of the 18 FTD/ALS cases, post-mortem pathological examination in 12 (67%) showed FTLD with ubiquitinated inclusions. Tissue for additional TDP-43 staining was available in 10 cases, and results confirmed all to be FTLD-TDP.²⁶

Table 2. Summary of Onset Symptoms in bvFTD vs FTD/ALS Groups

Symptom at Onset	No. (%) of Patients		P Value
	bvFTD Group (n=43)	FTD/ALS Group (n=18)	
Memory problems	27 (63)	3 (17)	.003
Word-finding problems	3 (7)	8 (44)	.002
Delusions	8 (19)	9 (50)	.03
Reduced speech output	10 (23)	9 (50)	.79
Hallucinations	5 (12)	5 (28)	.12
Executive problems	21 (49)	12 (67)	.20
Behavioral changes			
Loss of insight	40 (93)	18 (100)	.25
Disinhibition	23 (53)	7 (39)	.29
Apathy	34 (79)	11 (61)	.14
Lack of empathy	17 (40)	3 (17)	.83
Stereotypical behavior	28 (65)	11 (61)	.77
Food preference/ dietary change	21 (49)	11 (61)	.38

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; FTD/ALS, FTD with amyotrophic lateral sclerosis.

Patients with simultaneous onset of behavioral and ALS features were not included; neither were those with ALS who later developed behavioral and/or cognitive changes.

Case files were reviewed by 2 behavioral neurologists who had not been involved in the initial clinical evaluation of the cases (P.L. and B.G.). A positive family history was defined as a first-degree relative with a history of dementia compatible with FTD or ALS. Particular attention was paid to the symptom profile at onset, notably behavioral changes (loss of insight, apathy, disinhibition, lack of empathy, stereotypical behaviors, and change of eating pattern), reduced speech output, word finding problems, impaired attention and executive function, everyday memory problems, and psychotic symptoms (hallucinations and delusions). None of the patients presented with delirium²⁵ when behavioral changes, cognitive/language problems, and/or psychotic symptoms appeared. Ethical written consent was obtained from all patients in this study according to the Ethical Standard Committee of Addenbrooke's Hospital.

STATISTICAL ANALYSIS

We used commercially available software (SPSS statistics release 17.0; SPSS Inc, Chicago, Illinois) to analyze age at symptom onset, diagnosis, and death (independent-sample *t* test). Demographic variables (sex and family history) and the distribution of symptoms across groups was compared using Pearson χ^2 tests with the correction for continuity. The Fisher exact test was used in cases with an expected count of less than 5. Strength of association was measured by the ϕ coefficient. In addition, odds ratio analysis was used in the case of delusions. Survival analyses were conducted using Kaplan-Meier estimates (95% confidence interval [CI]) followed by Cox-Mantel log-rank tests.

RESULTS

There was a general male predominance that was more pronounced in the FTD/ALS group, but this difference did not reach significance ($P=.53$). No significant differences were found between the 2 groups with regard

Table 3. Psychotic Symptoms in 9 Patients With FTD/ALS

Sex/ Age, y	Hallucinations	Delusions	Pathological Diagnosis
M/53	No	Persecutory delusions of endangerment (people of his town were racist and were against him)	NA
M/48	No	Persecutory delusions of endangerment (someone was following him, particularly when driving)	FTLD-TDP
M/48	No	Persecutory delusions of endangerment	FTLD-TDP
M/73	No	Delusions of theft, burglary (people breaking into his house to steal things)	NA
M/60	Visual (insects, spies, and witches)	Delusions of theft, burglary	NA
F/59	Visual (2 gorillas behind the door)	Persecutory delusions of endangerment (animals and people trying to hurt her)	FTLD-TDP
F/50	Visual (demons, her dead father, and another father looking out of window)	Somatic delusions, broken arms, delusions of theft and burglary, phantom boarder syndrome, persecutory delusions of endangerment (a man followed her from Brazil and put demons around her house)	FTLD-TDP
F/51	Visual (seeing an old boyfriend)	Erotomania (kissing her old boyfriend and making tea for him)	FTLD-TDP
F/59	Visual (seeing spiders and a lion)	Persecutory delusions of endangerment (a tradesman attacked her; the husband attempted to strangle her)	FTLD-TDP

Abbreviations: FTD/ALS, frontotemporal dementia with amyotrophic lateral sclerosis; FTLD-TDP, frontotemporal lobar degeneration with TDP-43 inclusions; NA, not available.

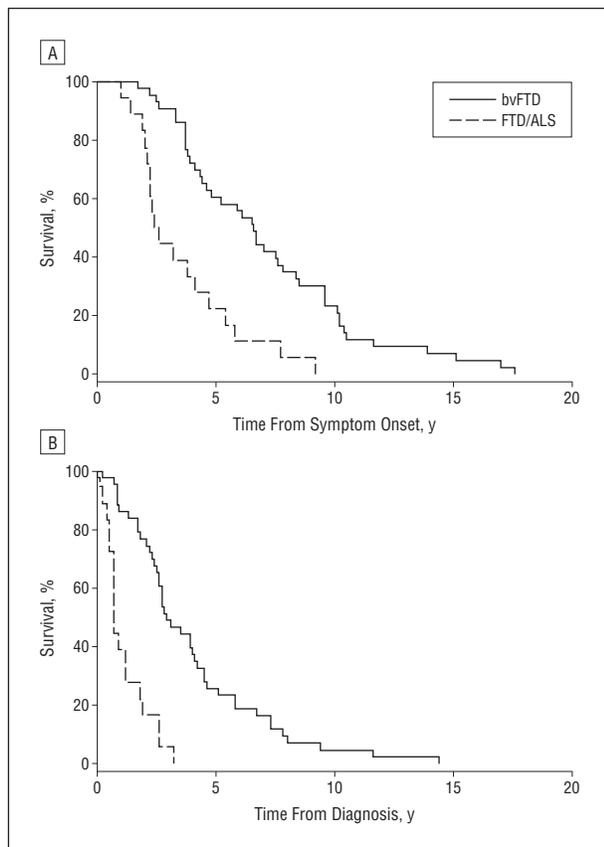


Figure. Survival curves in patients with behavioral variant frontotemporal dementia (bvFTD group) and patients with FTD who developed amyotrophic lateral sclerosis (FTD/ALS group). A, Kaplan-Meier survival curve from symptom onset to death in the bvFTD and FTD/ALS groups ($P < .001$). B, Kaplan-Meier survival curve from diagnosis to death in the bvFTD and FTD/ALS groups ($P < .001$).

to age at onset of symptoms, diagnosis, or death. The rate of a positive family history was almost identical in the 2 subgroups at more than 20% each (**Table 1**).

A summary of key symptoms at presentation is given in **Table 2**. Of note was the finding of a greater rate of

memory problems associated with the bvFTD group ($\chi^2=9.03$; $P=.003$; $\phi=-0.42$). In contrast, there was a significant association of word-finding problems with the diagnosis of FTD/ALS ($\chi^2=9.0$; $P=.002$; $\phi=0.44$). Also, anomia at the first medical visit showed a significant association with the FTD/ALS group (9 of 18 cases [50%]) ($\chi^2=3.9$; $P=.05$; $\phi=0.30$). One of the most striking findings pertained to psychotic symptoms. Half of the FTD/ALS cases had delusions compared with only 19% in the bvFTD group ($\chi^2=4.8$; $P=.03$; $\phi=0.31$). Based on the odds ratio, the odds of presenting with delusions in the FTD/ALS group was 4.4 times the odds of presenting with delusions in the bvFTD group (95% CI, 1.3-14.5). By contrast, there was no significant association between the rate of hallucinations and any particular phenotype. The profile of psychotic symptoms in patients with FTD/ALS and their corresponding pathological findings is shown in **Table 3**. When we compared the subgroups of FTD/ALS according to motor onset (limb vs bulbar), there was not a significant association between motor onset and profile of clinical symptoms at onset.

In the FTD/ALS group, the time from the onset of behavioral changes to manifestations of ALS varied from 0.3 to 7.3 years, with a mean (SD) of 2.1 (2.0) years. In 12 of 18 patients with FTD/ALS (67%), the interval was less than 2 years.

Kaplan-Meier survival analysis confirmed that the FTD/ALS group had a significantly shorter evolution from symptom onset to death, with a median survival of 2.4 (95% CI, 1.8-3.0) years compared with 6.6 (5.6-7.6) years for the bvFTD group ($P < .001$) (**Figure, A**). The difference in median survival from diagnosis was even more evident, with 0.7 (95% CI, 0.5-0.9) years for the FTD/ALS group vs 2.9 (2.1-3.7) years for the bvFTD group ($P < .001$) (**Figure, B**).

COMMENT

The profile of behavioral symptoms in FTD/ALS was identical to that seen in typical bvFTD, in keeping with the pub-

lished literature,^{11,12} with the exception of high rates of psychotic and aphasic symptoms in those who developed ALS.

Several reports have highlighted the occurrence of psychotic symptoms in patients with FTD who later developed ALS, often causing diagnostic challenges until motor features were evident and led to a correct diagnosis.^{13,14,27,28} A wide variety of delusions have been reported, including the persecutory type (involving burglary and endangerment) and occasionally more complex types such as thoughts of bodily invasion and the de Clérambault syndrome, a type of erotomania.²⁸ These symptoms tend to remit spontaneously with progression of the disease, and their anatomic substrate remains unclear. Hallucinations and delusions have been regarded as relatively uncommon manifestations of FTD,^{29,30} but recent studies have suggested that particular subgroups of patients with FTD have a higher rate of psychotic symptoms.³¹ Based on a review of 17 pathologically confirmed cases of FTD, Velakoulis et al³² found that younger people with FTD were particularly susceptible to schizophrenialike psychosis and were associated with FTLTDP pathologic features. Two of 4 young psychotic patients with FTD also developed motor neuron disease (MND). Similarly, in a large pathological study that included 17 cases of FTLTDP-MND, 5 presented with psychotic symptoms early in the disease, of whom 3 had concurrent motor features and 2 presented with psychotic symptoms before MND was clinically manifest.³³ These studies all indicate that patients with FTLTDP-MND/ALS are particularly prone to present with psychotic symptoms in the prodromic behavioral phase of the illness before the onset of motor features. This report showed that 6 of 9 patients with FTD/ALS who presented with delusions had pathological findings for FTLTDP. In those with bvFTD, the pathological findings were available in only 4 of 8 patients presenting with delusions, including 2 who presented with FTLTDP, 1 with FTLTDP and tau-positive inclusions, and 1 with FTLTDP but no inclusions.

Word-finding problems and reduced speech output were also significantly more prominent in the FTD/ALS group, although this difference may have been due to the selection of exclusively behavioral variant cases in which the language impairment is less common than in semantic dementia and PNFA. It has been well established that PNFA associated with behavioral changes and bulbar motor onset is a distinctive form of presentation in FTD/ALS.¹⁵⁻¹⁹

Twelve of the 18 patients with FTD/ALS manifested motor symptoms and signs within 2 years of the onset of behavioral changes, although this interval in 1 case was as long as 7 years. This suggests that patients with behavioral and psychotic features should be monitored for the onset of ALS. It is, of course, possible that the rate of subclinical motor features is even higher, but we are unable to comment because only those patients with clinical ALS underwent neurophysiological investigations.

This study confirms previous reports of a shorter survival for FTD/ALS than for other forms of FTD.^{11,20,21} Moreover, a neuropathological study comparing cases of FTLTDP/MND and FTLTDP with ubiquitin inclusion showed that the FTLTDP/MND group had a shorter survival despite the fact that the 2 entities shared the same pathologic substrate with intraneuronal ubiquitin-positive inclu-

sions.³⁴ Patients with FTD/ALS show mild to moderate bilateral frontal and temporal lobe atrophy with extensive microvacuolation of superficial cortical layers II and III (spongiosis), neuronal loss and gliosis¹³ associated with lower motor neuron loss, and corticospinal tract degeneration. The TDP-43 proteinopathy pattern of FTD/ALS differs from that of other subtypes of FTD such as semantic dementia, PNFA, and familial FTD associated with progranulin mutations. Typically, FTD/ALS corresponds to Mackenzie type 3 and Sampathu-Neumann type 2 classifications, with numerous neuronal cytoplasmic TDP-43-positive inclusions in both the superficial and the deep laminae of the frontal and temporal neocortex and the dentate gyrus, with few dystrophic neuritis and sparse intranuclear inclusions.³⁵ These factors suggest that the evolution of the neurodegenerative process may be fundamentally different in FTD/ALS than in other forms of FTD associated with TDP-43. A prospective study involving a larger number of patients is needed as a next step to confirm these findings.

In conclusion, the early presence of delusion should lead to a search for ALS features in patients presenting with bvFTD. The short evolution of FTD/ALS and the combination of physical, cognitive, and behavioral symptoms presents substantial challenges for the management of this disease and considerable caregiver distress.

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