Neurobehavioral Features in Frontotemporal Dementia With Amyotrophic Lateral Sclerosis

Patricia Lillo, MD; Beatrice Garcin, MD; Michael Hornberger, PhD; Thomas H. Bak, MD; John R. Hodges, MD, FRCP

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.
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.

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 ALS23,24; 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, 11 presented with bulbar motor onset, and 7 had limb motor onset present at diagnosis and death (independent-sample t test). 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). Mantel log-rank tests.

In addition, odds ratio analysis was used in the case of delusions and hallucinations. 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 delirium when behavioral changes, cognitive/language problems, and/or psychiatric 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 χ² 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.

There was a general male predominance that was more pronounced in the FTD/ALS group, but this difference did not reach significance (P=.33). No significant differences were found between the 2 groups with regard

---

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

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

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

<table>
<thead>
<tr>
<th>Symptom at Onset</th>
<th>bvFTD Group (n=43)</th>
<th>FTD/ALS Group (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory problems</td>
<td>27 (63)</td>
<td>3 (17)</td>
<td>.003</td>
</tr>
<tr>
<td>Word-finding problems</td>
<td>3 (7)</td>
<td>8 (44)</td>
<td>.002</td>
</tr>
<tr>
<td>Delusions</td>
<td>8 (19)</td>
<td>9 (50)</td>
<td>.03</td>
</tr>
<tr>
<td>Reduced speech output</td>
<td>10 (23)</td>
<td>9 (50)</td>
<td>.79</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>5 (12)</td>
<td>5 (28)</td>
<td>.12</td>
</tr>
<tr>
<td>Executive problems</td>
<td>21 (49)</td>
<td>12 (67)</td>
<td>.20</td>
</tr>
<tr>
<td>Behavioral changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of insight</td>
<td>40 (93)</td>
<td>18 (100)</td>
<td>.25</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>23 (53)</td>
<td>7 (39)</td>
<td>.29</td>
</tr>
<tr>
<td>Apathy</td>
<td>34 (79)</td>
<td>11 (61)</td>
<td>.14</td>
</tr>
<tr>
<td>Lack of empathy</td>
<td>17 (40)</td>
<td>3 (17)</td>
<td>.83</td>
</tr>
<tr>
<td>Stereotypical behavior</td>
<td>28 (65)</td>
<td>11 (61)</td>
<td>.77</td>
</tr>
<tr>
<td>Food preference/dietary</td>
<td>21 (49)</td>
<td>11 (61)</td>
<td>.38</td>
</tr>
</tbody>
</table>

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; FTD/ALS, FTD with amyotrophic lateral sclerosis.
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 ($\chi^2 = 9.03; P = .003; \varphi = -0.42$). In contrast, there was a significant association of word-finding problems with the diagnosis of FTD/ALS ($\chi^2 = 9.0; P = .002; \varphi = 0.44$). Also, anomia at the first medical visit showed a significant association with the FTD/ALS group (9 of 18 cases [50%]) ($\chi^2 = 3.9; P = .05; \varphi = 0.30$). 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 ($\chi^2 = 4.8; P = .03; \varphi = 0.31$). 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).

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

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

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 ($P < .001$).
lished literature, with the exception of high rates of psychot
cic and aphasic symptoms in those who developed ALS.

Several reports have highlighted the occurrence of
psychotic symptoms in patients with FTD who later de
developed ALS, often causing diagnostic challenges until mo
tor features were evident and led to a correct diagno
sis. A wide variety of delusions have been reported,
including the persecutory type (involving burglary and en
dangerment) and occasionally more complex types such as
thoughts of bodily invasion and the de Clérambault syn
drome, a type of erotomania. These symptoms tend to re
mit spontaneously with progression of the disease, and their
anatomic substrate remains unclear. Hallucinations and de
lusions have been regarded as relatively uncommon mani
festations of FTD, but recent studies have suggested that
particular subgroups of patients with FTD have a higher
rate of psychotic symptoms. Based on a review of 17 patho
logically confirmed cases of FTD, Velakoulis et al found
that younger people with FTD were particularly suscepti
ble to schizophrenialike psychosis and were associated
with FTLD-TDP pathologic features. Two of 4 young psy
chotic patients with FTD also developed motor neuron dis
ease (MND). Similarly, in a large pathological study that
included 17 cases of FTLD-MND, 5 presented with psy
chotic symptoms early in the disease, of whom 3 had con
current motor features and 2 presented with psychotic
symptoms before MND was clinically manifest. These
studies all indicate that patients with FTLD-MND/ALS are par
ticularly 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 patho
logical findings for FTLD-TDP. In those with bvFTD, the
pathological findings were available in only 4 of 8 patients
presenting with delusions, including 2 who presented with
FTLD-TDP, 1 with FTLD and tau-positive inclusions, and
1 with FTLD 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 estab
lished that PNFA associated with behavioral changes and bulbar motor onset is a distinctive form of present
ation in FTD/ALS.

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 be
havioral 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 un
able to comment because only those patients with clin
ical ALS underwent neurophysiological investigations.

This study confirms previous reports of a shorter sur
vival for FTD/ALS than for other forms of FTD. Moreover,
a neuropathological study comparing cases of FTLD/
MND and FTLD with ubiquitin inclusion showed that the
FTLD/MND group had a shorter survival despite the
fact that the 2 entities shared the same pathologic sub
strate with intraneuronal ubiquitin-positive inclu
sions. Patients with FTD/ALS show mild to moderate
bilateral frontal and temporal lobe atrophy with exten
sive microvacuolation of superficial cortical layers II and
III (spongiosis), neuronal loss and gliosis associated with
lower motor neuron loss, and corticospinal tract degen
eration. The TDP-43 proteinopathy pattern of FTD/ALS
differs from that of other subtypes of FTD such as se
mantic dementia, PNFA, and familial FTD associated with
progranulin mutations. Typically, FTD/ALS corre
sponds 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. 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 in
volving 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 symp
toms presents substantial challenges for the manage
ment of this disease and considerable caregiver distress.

Accepted for Publication: November 25, 2009.
Correspondence: John R. Hodges, MD, FRCP, Fronto
temporal Dementia Research Group, Prince of Wales
Medical Research Institute, Barker Street, Randwick, NSW
2031, Australia (j.hodges@powrmi.edu.au).

Author Contributions: Study concept and design: Lillo,
Garcin, Bak, and Hodges. Acquisition of data: Lillo, Gar
cin, Bak, and Hodges. Analysis and interpretation of data:
Lillo, Hornberger, and Hodges. Drafting of the manu
script: Lillo and Hodges. Critical revision of the manu
script for important intellectual content: Lillo, Garcin, Hor
nberger, Bak, and Hodges. Statistical analysis: Lillo, Gar
cin, and Hornberger. Obtained funding: Hodges. Study su
pervision: Bak and Hodges.

Financial Disclosure: Dr Hodges serves on the edi
torial board of Aphasiology, Cognitive Neuropsychiatry,
and Cognitive Neuropsychology and receives royalties
from Oxford University Press and Cambridge Univer
sity Press.

Funding/Support: This study was supported in part by
a program grant from the Medical Research Council (Dr
Hodges); by a CONICYT scholarship from the Comi
Sión Nacional de Investigación Científica y Tecnoló
gica, Government of Chile, and by the Faculty of Medi
cine, University of Chile (Dr Lillo); and by an Australian
Research Council Federation Fellowship (Dr Hodges).

Additional Contributions: David Foxe, BSc, assisted with
proofreading.

REFERENCES

1. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal


©2010 American Medical Association. All rights reserved.