Continuum of Frontal Lobe Impairment in Amyotrophic Lateral Sclerosis

Jennifer M. Murphy, PhD; Roland G. Henry, PhD; Susan Langmore, PhD; Joel H. Kramer, PsyD; Bruce L. Miller, MD; Catherine Lomen-Hoerth, MD, PhD

Objective: To identify the nature and prevalence of cognitive and behavioral abnormalities in patients with amyotrophic lateral sclerosis (ALS).

Main Outcome Measures: Neuropsychological tests, neurobehavioral interviews, and structured magnetic resonance imaging.

Design: Survey of clinical characteristics.

Setting: Multidisciplinary clinic within a university medical center.

Patients: A volunteer sample of 30 new patients with ALS were recruited consecutively. Of those invited, 23 participants (20 with sporadic ALS and 3 with familial ALS) enrolled. Participants ranged in age from 27 to 80 years (mean age, 56.5 years); the education level ranged from 12 to 21 years (mean education level, 3.5 years of college); and 17 participants (74%) were male.

Main Outcome Measures: Patients were classified into subtypes of frontotemporal lobar degeneration (n=5), suspected Alzheimer disease (n=1), and subthreshold variants of cognitive impairment (n=2), behavioral impairment (n=4), and cognitively and behaviorally normal (n=11). Five neuropsychological tests, 2 behavioral abnormalities, and right hemisphere gray matter reductions differentiated patients into normal and abnormal groups.

Conclusions: In this sample, a sizable proportion of patients with ALS possess a range of behavioral and cognitive changes that lie on a spectrum of frontotemporal impairment. Right hemisphere atrophy may be a biomarker for cognitive impairment in patients with ALS.

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A n association between dementia and amyotrophic lateral sclerosis (ALS) was first noted in the late 1800s, and studies dating back to the 1930s document dementia syndromes in ALS.1 In 1994, the Lund and Manchester groups2 first used the term frontotemporal dementia (FTD) with motor neuron disease, and a variety of reviews3-6 document the growing evidence of the link between FTD and motor neuron disease.

Incidence rates of ALS dementia vary owing to referral bias and differing diagnostic criteria. Historically, rates were documented as 3% in sporadic ALS and 15% in familial ALS,7 but recent studies8-11 using frontal lobe–based neuropsychological measures report rates as high as 28% to 48%. Rates of ALS dementia increase8,12,13 with the use of frontotemporal lobar degeneration (FTLD)–based dementia criteria13,14 and tools measuring behavioral, executive, and language change. Studies that define abnormality as the presence of frontal lobe dysfunction document dementia symptoms in 50% of all cases.11,13,16 The cerebral, neuropsychological, and pathological deficits associated with ALS are increasingly recognized as existing on a spectrum. Many nondemented patients with ALS exhibit cognitive deficits.17-22 Behaviorally, some patients with ALS meet full Neary criteria for FTLD,14,23,24 others have milder levels of behavioral changes, and still others appear normal.25

In this article, we address the following questions: (1) What percentage of patients with ALS meets Neary criteria for the 3 subtypes of FTLD? (2) How many patients possess cognitive or behavioral deficits that do not meet full criteria for FTLD? and (3) Are there neuroimaging differences between these groups?

METHODS

SUBJECTS

New patients were recruited consecutively from the ALS Center, University of California, San Francisco. Of approximately 30
patients with ALS invited into the study, 23 participants (20
with sporadic ALS and 3 with familial ALS) gave informed
consent and enrolled. Reasons given for refusal to participate
included inability to lie down in the magnetic resonance
imaging scanner and lengthy travel distance. No participant
had a history of other neurological or psychiatric disease, pre-
vious dementia diagnosis, head injury, or central nervous
system–related medical illness. All of the participants met cri-
teria for probable or definite ALS based on World Federation
of Neurology criteria.26 Participants ranged in age from 27 to
80 years (mean age, 56.5 years), the education level ranged
from 12 to 21 years (mean education level, 3.5 years of col-
lege), and 17 participants (74%) were male. Twenty partici-
pants were right-handed, 2 were left-handed, and 1 was ambi-
dextrous. The mean (range) duration of ALS symptom onset
was 23 (3–36) months. This study was approved by the insti-
tutional review board at the University of California, San
Francisco.

Measured clinical characteristics included age, sex, educa-
tional level, disease progression, bulbar vs limb onset, pres-
ence of pseudobulbar affect, and secondary effects of depres-
sion. A speech pathologist (S.L.) rated dysarthria levels as absent,
mild, moderate, or severe using operational definitions of each
level of severity. Pseudobulbar affect was defined by a score
higher than 13 on the Center for Neurologic Study–Lability
Scale.27 Forced vital capacity, a measure of breathing function,
was measured by a certified respiratory therapist (Colleen Meier,
BS) using standard techniques.

DEFINING COGNITIVE
ABNORMALITIES IN ALS

Diagnoses of FTLD were based on the Neary criteria.21 Fronto-
temporal lobar degeneration includes 3 subtypes of fronto-
temporal abnormality: the frontal variant (FTD), progressive
nonfluent aphasia, and semantic dementia. Core Neary crite-
ria for FTD include early decline in social and personal con-
duct, emotional blunting, and loss of insight. Core Neary crite-
ria for semantic dementia include fluent speech with loss of
word meaning, and Neary criteria for progressive nonfluent
aphasia include nonfluent speech with agrammatism, para-
phrasias, or anomia. We used the NINCDS-ADRA (National
Institute of Neurological and Communicative Diseases and
Stroke/Alzheimer's Disease and Related Disorders Associ-
ation) criteria for Alzheimer disease (AD) as defined by
McKhann et al.28

Dementia diagnoses were made at a case conference atten-
ted by a team including a neurologist specializing in de-
mentia (B.L.M.), a neurologist specializing in ALS (C.L.-H.), a
neuropsychologist (J.M.M. or J.H.K.), and a nurse (Dallas
Forshey, BS) known to the patient. The Neary criteria for FTLD
were reviewed for each patient and diagnoses of the frontal vari-
ant of the disease were made when all 5 core criteria were met
by identifying clear examples of behavioral abnormalities (eg,
decline in social conduct, emotional blunting, or loss of in-
sight). The team gave deliberate consideration to avoid inclu-
sion of social and emotional behaviors resulting from the ALS
process itself to guard against bias toward overdiagnosing FTLD
(eg, social isolation due to embarrassment or emotional changes
due to pseudobulbar affect).

NEUROPSYCHOLOGICAL MEASURES

The neuropsychological battery was weighted toward execu-
tive functioning tests and has been detailed elsewhere.29 Each
neuropsychological measure has been shown to be effective in
identifying FTLD deficits. Neuropsychological evaluations were
completed in approximately 2 hours by an experienced neu-
ropsychologist (J.M.M.). Verbal fluency and motor test scores
were not analyzed for participants with moderate to severe dys-
arthria and upper limb motor impairment. Age- and sex-
corrected norms were used to generate standardized scores.

NEUROBEHAVIORAL MEASURES

The Neuropsychiatric Inventory30 was conducted with a care-
giver without the patient present. This scale measures 12 neu-
ropsychiatric behaviors common in dementia: delusions, hal-
lucinations, agitation, dysphoria, anxiety, apathy, irritability,
euphoria, disinhibition, aberrant motor behavior, nighttime
behavioral disturbances, and appetite and eating abnormalities.

NEUROIMAGING

Magnetic resonance imaging scans were obtained with whole-rain coverage. The scans included 3-dimensional T1-
weighted volumes. We used SIENAX software (Oxford Centre
for Functional Magnetic Resonance Imaging of the Brain, Ox-
ford, England) to estimate segmented gray and white matter
volumes. Lobar regions were defined from the parcellated Brod-
mann regions. Magnetic resonance imaging analyses were per-
formed for 20 normal controls and 22 patients with ALS.

STATISTICS

The single AD case was excluded from each analysis. Familial
and sporadic cases were not statistically separated owing to small
sample size.

RESULTS

SUBJECT COGNITIVE STATUS

Of the 23 patients with ALS who consented for the study, 6 met criteria for a dementia syndrome. One
patient met criteria for suspected AD and 5 met Neary re-
search criteria for the diagnosis of FTLD (2 with FTD, 2
with semantic dementia, and 1 with progressive nonfluent
aphasia).

IDENTIFYING A CONTINUUM
OF FRONTAL LOBE IMPAIRMENT

The incidence of neurobehavioral or cognitive disorder not meeting criteria for dementia was thus determined
for the 17 remaining patients. Of these 17 patients, 11
were cognitively and behaviorally normal and 6 had a
spectrum of cognitive or behavioral impairment (Figure 1). The team identified 4 patients who met only
partial Neary criteria for FTD or had conflicting infor-
mant reports of the severity of the behavioral changes.
Our group offers the term ALS with behavioral impair-
ment (ALSbi)31 to describe such patients with ALS who
display frontal lobe–based behavioral signs who do not
meet full criteria for FTD as defined by a Neuropsychi-
atric Inventory total domain score (severity × frequency)
of 3 or more on at least 2 behavioral domains (Table 1).

Two patients displayed executive dysfunction deficits on neuropsychological testing but had no behavioral defi-
cits. We suggest the term ALS with cognitive impairment
for those patients with ALS who score 1.5 SDs below the mean on at least 2 measures of executive function, semantic dementia, or primary progressive aphasia.

Although the subtypes identified here are not completely dissociable and the sample is small, the groups are distinct in interesting ways. The patients with ALS with comorbid FTD exhibited their first symptom of cognitive or behavioral decline, on average, 7 years and 7 months prior to their ALS diagnosis (range, 2-12 years), and the ALSbi group developed cognitive or behavioral symptoms concurrent with or after their ALS diagnosis.

**Clinical Comparisons**

The clinical characteristics of the cohort are shown in Table 2. The cognitively or behaviorally impaired ALS group includes patients with FTLD (n = 5), ALSbi (n = 4), and ALS with cognitive impairment (n = 2). A 1-way analysis of covariance revealed that the impaired ALS group did not differ from the cognitively intact ALS group in rates of pseudobulbar affect, level of depression, sex, education level, ALS disease state, or handedness. Significant group differences did occur for age. The ALS group with cognitive abnormalities was, on average, 16 years older (mean age, 64 years) than the cognitively intact patients with ALS (mean age, 48 years).

**Spectrum of Neuropsychological Abnormalities in Patients with ALS with Behavioral Abnormalities**

When the patients with ALS without behavioral deficits (n = 11) were compared with patients with ALS diagnosed with behavioral abnormalities (n = 9; 5 patients with FTLD and 4 with ALSbi), the patients with behavioral abnormalities demonstrated comorbid executive function abnormalities. The 2 patients with cognitive abnormalities were excluded from this analysis to avoid circularity, as the neuropsychological tests are used as a dependent variable. The behaviorally abnormal ALS group had significantly more impairment on 5 neuropsychological measures that tap into executive functioning: the Wisconsin Card Sort, the Boston Naming Test, California Designs, the Controlled Oral Word Association Test, and category fluency. On the Controlled Oral Word Association Test fluency test, the group with behavioral abnormalities scored only half the points (mean, 27.8 words) as those who were behaviorally intact (mean, 47.4 words). No group differences emerged for memory or spatial skills.

**Social disinhibition and irritability differentiate between groups**

Both the behaviorally and cognitively abnormal patients with ALS were grouped into an abnormal group (n = 11) and compared with the patients with ALS without cognitive and behavioral impairment (n = 11) to identify which neurobehavioral traits differentiate between them. The patients with ALS with cognitive and behavioral impairment showed more disinhibition (P = .005) and irritability (P = .04) than the cognitively and behaviorally intact ALS group. This difference is unlikely owing to depression because group differences in depression did not exist when compared using the Geriatric Depression Scale.

**Structural Magnetic Resonance Imaging**

Results from the nonparametric Kruskal-Wallis test with Bonferroni adjustment indicate that the ALS group with cognitive and behavioral deficits have reduced volumes as compared with the normal controls in all regions of interest (P = .004). The cognitively and behaviorally intact patients with ALS have larger right frontal, right parietal, and right limbic volumes as compared with the patients with ALS with cognitive and behavioral abnormalities. Cognitively and behaviorally intact patients with ALS have decreased right temporal volumes as compared with normal controls (Figure 2).

When taking every variable into account and controlling for the statistical effects of age, only right temporal

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**Table 1. Summary of Cognitive Subtypes**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>Pure motor system disorder as defined by the El Escorial criteria; no clinical evidence of frontotemporal dysfunction</td>
</tr>
<tr>
<td>ALS with cognitive impairment</td>
<td>Deficits (1.5 SDs below the age-matched mean) on ≥2 neuropsychological tests of executive functioning or tests measuring semantic or primary progressive aphasia, but insufficient to meet the Neary criteria for FTLD</td>
</tr>
<tr>
<td>ALS with behavioral impairment</td>
<td>NPI total domain score (severity × frequency) ≥3 on ≥2 domains</td>
</tr>
<tr>
<td>ALS with comorbid FTD</td>
<td>Patient with ALS meeting Neary criteria for FTD</td>
</tr>
</tbody>
</table>

Abbreviations: ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; NPI, Neuropsychiatric Inventory.
volume is most predictive of group membership. The 2 patients with semantic dementia had right temporal volumes within 1 SD of the mean. One of the 2 patients with semantic dementia was an outlier for left frontal atrophy, and this patient was ambidextrous.

Comment

In an unselected ALS cohort, we found a spectrum of frontal lobe dysfunction in half of our patients. The cognitive and behavioral abnormalities varied in severity, with 5 patients (22%) meeting Neary criteria for FTLD, 4 (17%) demonstrating more subtle behavioral disturbances, and 2 (9%) exhibiting subtle cognitive dysfunction. When these patients with ALS with abnormalities were grouped together into a broad category, they were found to have reduced volumes in right frontal, right parietal, and right limbic lobes as compared with patients with ALS without cognitive or behavioral disturbance. The ALS group with moderate or severe behavioral disturbance had comorbid executive dysfunction as compared with the ALS group without behavioral impairment, despite the groups’ similarity in memory, spatial skills, level of depression, and disease progression. The continuum hypothesis is supported by the evidence that both the ALSbi group and the ALS-FTD group show the same abnormalities on executive function tests.

Although a cutoff of 2 SDs would provide a more conservative criterion when classifying patients with cognitive abnormalities, the 1.5-SD cutoff allows for a more sensitive indicator of the moderate executive function changes typically seen in the ALS population. Although our Neuropsychiatric Inventory cutoff for ALSbi (domain score ≥ 3 on ≥ 2 domains) requires validation, to our knowledge, there is no evidence to date that patients with terminal illness possess elevated Neuropsychiatric Inventory scores and it is known that nondemented elderly patients earn scores well below 0.5 on each domain.

Advanced age did not account for group differences in cognitive deficits, but it appears to be an indicator of heightened risk for cognitive and behavioral deficits, par-

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<tr>
<th>Clinical Characteristics</th>
<th>Patients With Cognitive or Behavioral Dysfunction (n = 11)</th>
<th>Cognitively and Behaviorally Normal Patients (n = 11)</th>
<th>F Score</th>
<th>P Value</th>
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<td>Pseudobulbar affect, No. (%) affected</td>
<td>7 (64)</td>
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<td>0.441</td>
<td>.52</td>
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<td>Bulbar onset, No.</td>
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<td>2</td>
<td>NA</td>
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<tr>
<td>Dysarthria scale score, mean</td>
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<td>Familial cases, No.</td>
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Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale; FVC, forced vital capacity; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State examination; NA, not applicable.

*The scores were rated as follows: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe.

Figure 2. Structural magnetic resonance image comparisons across 3 groups. Coronal, axial, and sagittal views of a 61-year-old neurologically normal control subject (A), a 57-year-old cognitively normal patient with amyotrophic lateral sclerosis (B), and a 54-year-old patient with amyotrophic lateral sclerosis with cognitive abnormalities (C). R indicates right; L, left.
ticularly when combined with bulbar-onset ALS. 20 Disinhibition and irritability stood out as 2 traits that most distinguished between those patients who met criteria for behavioral disturbance and those who did not, independent of depression rates. The single AD diagnosis may be explained as having a separate cause that is consistent with customary AD, as has been described in other ALS samples.22,23

Among the patients with ALS, those with full-blown dementia or subthreshold abnormalities in cognition or behavior had gray matter reductions in right frontal, right parietal, and right limbic lobes as compared with the patients with ALS without abnormalities. This anatomical distinction between the 2 ALS groups suggests that right hemisphere atrophy among patients with ALS may be a type of biomarker linked to behavioral and cognitive abnormalities. Such right hemisphere deficits have been linked to inappropriate range and intensity of affect as well as impaired ability to perceive facial expression.24 Patients with right-hemisphere deficits exhibit an indifference reaction, tending to deny the extent of their disabilities;25 this is a common trait observed in patients with ALS with behavioral disturbance.

Patients with ALS with cognitive abnormalities have poorer compliance and reduced survival rates, suggesting that identification of these traits is clinically important, and the ALS field of research may be advanced with a more detailed categorization of ALS phenotypes.

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Correspondence: Jennifer M. Murphy, PhD, Department of Neurology, ALS Center, University of California, San Francisco, 350 Parnassus Ave, Suite 500, San Francisco, CA 94117 (jennifer.murphy@ucsf.edu).

Author Contributions: Dr Murphy had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Murphy, Henry, Kramer, Miller, and Lomen-Hoerth. Acquisition of data: Murphy, Henry, and Langmore. Analysis and interpretation of data: Murphy, Henry, and Lomen-Hoerth. Drafting of the manuscript: Murphy and Henry. Critical revision of the manuscript for important intellectual content: Murphy, Henry, Langmore, Kramer, Miller, and Lomen-Hoerth. Administrative, technical, and material support: Murphy, Langmore, and Kramer. Study supervision: Lomen-Hoerth.

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REFERENCES