Continuum of Frontal Lobe Impairment in Amyotrophic Lateral Sclerosis

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

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

Results: 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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An 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. In 1994, the Lund and Manchester groups first used the term frontotemporal dementia (FTD) with motor neuron disease, and a variety of reviews 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, but recent studies using frontotemporal lobar degeneration (FTLD)–based dementia criteria 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. 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. Behaviorally, some patients with ALS meet full Neary criteria for FTLD, others have milder levels of behavioral changes, and still others appear normal.

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, previous dementia diagnosis, head injury, or central nervous system–related medical illness. All of the participants met criteria for probable or definite ALS based on World Federation of Neurology criteria. 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. Twenty participants were right-handed, 2 were left-handed, and 1 was ambidextrous. The mean (range) duration of ALS symptom onset was 23 (1-36) months. This study was approved by the institutional review board at the University of California, San Francisco.

Measured clinical characteristics included age, sex, educational level, disease progression, bulbar vs limb onset, presence of pseudobulbar affect, and secondary effects of depression. 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. Forced vital capacity, a measure of breathing function, was measured by a certified respiratory therapist (Colleen Meier, BS) using standard techniques.

NEUROPSYCHOLOGICAL MEASURES

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

DEFINING COGNITIVE ABNORMALITIES IN ALS

Diagnoses of FTLD were based on the Neary criteria. Fron	otemporal lobar degeneration includes 3 subtypes of fronto
temporal abnormality: the frontal variant (FTD), progressive nonfluent aphasia, and semantic dementia. Core Neary criteria for FTD include early decline in social and personal conduct, emotional blunting, and loss of insight. Core Neary criteria for semantic dementia include fluent speech with loss of word meaning, and Neary criteria for progressive nonfluent aphasia include nonfluent speech with agrammatism, paraphasias, or anomia. We used the NINCDS-ADRA (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association) criteria for Alzheimer disease (AD) as defined by McKhann et al. Dementia diagnoses were made at a case conference attended by a team including a neurologist specializing in dementia (B.L.M.), a neurologist specializing in ALS (C.L.-H.), a neuropsychologist (J.M.M. or J.H.K.), and a nurse (Dallas Forshew, BS) known to the patient. The Neary criteria for FTLD were reviewed for each patient and diagnoses of the frontal variant 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 insight). The team gave deliberate consideration to avoid inclusion 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).

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 research 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 informant reports of the severity of the behavioral changes. Our group offers the term ALS with behavioral impairment (ALSbi) 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 Neuropsychiatric 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 deficits. 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>
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<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>
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Abbreviations: ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; NPI, Neuropsychiatric Inventory.
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 ≥2) 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.30

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, parti-
particularly when combined with bulbar-onset ALS. 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.

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. Patients with right-hemisphere deficits exhibit an indifference reaction, tending to deny the extent of their disabilities; 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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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. Statistical analysis: Murphy, Henry, and Kramer. Obtained funding: Kramer, Miller, and Lomen-Hoerth. Administrative, technical, and material support: Murphy, Langmore, and Kramer. Study supervision: Lomen-Hoerth.

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REFERENCES