Establishing Subtypes of the Continuum of Frontal Lobe Impairment in Amyotrophic Lateral Sclerosis

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This review summarizes recent advances in our understanding of the cognitive changes seen in patients with amyotrophic lateral sclerosis (ALS). Emphasis is placed on identifying and diagnosing subtypes of ALS patients with a continuum of frontotemporal impairment. The reviewed literature focuses on progress made in the past 20 years, with an emphasis on studies measuring abnormalities in ALS patients without dementia. We describe peer-reviewed journal articles using neuropsychological batteries and imaging techniques. We also discuss debates raised in recent meetings. In the past 2 decades, the field of ALS has been transformed in terms of its understanding of extramotor cerebral changes. Particularly in the past 10 years, investigators have invalidated the theory that cognitive abnormality in ALS patients is simply a rarely occurring, frank frontotemporal lobar degeneration syndrome. Instead, a growing body of evidence suggests that ALS patients with comorbid frontotemporal lobar degeneration lie on a spectrum of frontotemporal abnormality, with a large proportion of ALS patients possessing a range of behavioral and cognitive changes. As more investigations use standardized tools measuring behavior and cognition, distinct subtypes may be diagnosed.

Arch Neurol. 2007;64:330-334

Amyotrophic lateral sclerosis (ALS), the most common adult-onset motor neuron disease, is characterized pathologically by progressive loss of upper motor neurons in layer 5 of the cortex and by progressive loss of lower motor neurons in brainstem motor nuclei and the anterior horn of the spinal cord. This pattern of neurodegeneration produces a well-defined clinical syndrome that is usually distinct from other neurologic diseases. Amyotrophic lateral sclerosis produces progressive weakness, muscular wasting, and spasticity, starting segmentally before becoming widespread and producing death from respiratory failure a median of 3 years after onset.

Frontotemporal lobar degeneration (FTLD), a syndrome far less common than Alzheimer disease, is characterized pathologically by progressive degeneration of frontal or anterior temporal lobe neurons. In contrast to Alzheimer disease, FTLD produces early changes in behavior, executive function, and language, with relatively intact memory and praxis. Current research criteria divide FTLD into 3 categories: frontotemporal dementia (FTD) (by far the most common form), nonfluent progressive aphasia, and semantic dementia. The first disorder manifests primarily with personality changes, the second with nonfluent aphasia, and the last with fluent aphasia with significant loss of word meaning.

An association between dementia and ALS was first noted in the late 1800s and has subsequently been reported by many investigators. Patients with familial and sporadic ALS exhibit signs of frontotemporal lobe deterioration, including personality, behavior, planning, organization, and language dysfunction. Of patients with FTLD seen in a dementia clinic, 15% met the cri...
teria for a definitive ALS diagnosis, and an additional 30% had more subtle signs suggesting possible ALS. Conversely, a percentage of ALS patients possess comorbid FTLD, most often emerging before their motor neuron symptoms. It is yet unknown what common mechanism may underlie the co-occurrence of ALS and FTLD, but the field exploring this question has become an active and exciting area of research in the past decade. Two recent advances have emerged in this field, and these observations are the focus of this review: (1) the frontotemporal impairment seen in ALS patients is not a rare event consisting of full-blown dementia as was once thought but seems to lie on a spectrum, with a wide percentage of patients showing varying signs of pathologic abnormality and (2) a useful tool to study the spectrum may be to categorize patients into subtypes of cognitive and behavioral impairment.

Evidence from fields as broad as pathology, structural imaging, positron emission tomography, single-photon emission computed tomography, and neuropsychology suggest that the frontotemporal impairment in ALS patients lies on a broad spectrum, with approximately half of the patients displaying at least mild abnormalities. A consistent finding has emerged: the pathologic signs, cerebral atrophy, blood flow decrements, neurotransmitter decrease, and neuropsychologic impairment reveal the same pattern of abnormalities whether the patient shows very mild subclinical changes, moderate change that is perceived by the patient and the family, or full-blown dementia, suggesting that a frontotemporal degenerative process in ALS patients is not the rare event it was once thought to be.

A CONTINUUM OF COGNITIVE AND BEHAVIORAL IMPAIRMENT IN ALS

Executive functioning is a term used to describe the complex cognitive process that requires the frontal lobe to integrate input from multiple cortical systems. Planning, organizing information mentally, shifting attention, inhibiting behavior, and negotiating social mores are all examples of executive functioning. Historically it was thought that only 3% of ALS patients possessed such frontal lobe deficits, as caused by full-blown FTD. In the past 20 years, however, dozens of studies have documented the presence of executive functioning deficits in many ALS patients. Frequently, these data reveal that patients without dementia possess the same executive function deficits seen in ALS patients with associated FTLD but simply to a milder degree, suggesting a continuum of involvement.

Rates of executive function deficits in ALS patients without dementia range from 22% to 35%. Specific deficits consist of verbal and design fluency loss, poor sustained attention, poor verbal reasoning, impaired set shifting, poor response inhibition, loss of visual attention, decreased initiation of random movements on a joystick task, and poor problem solving and judgment on tests such as the Wisconsin Card Sorting Test. The most common deficit documented in ALS patients is a deficit in verbal fluency, and this pattern is seen in patients with and without dementia.

Neurobehaviorally, ALS patients also vary in frontotemporal lobar impairment. A proportion of patients meet the primary and supporting criteria of Neary et al for FTLD, others have mild or moderate levels of frontal lobe–based behavioral changes, and still others seem normal. Few studies have systematically measured the neurobehavioral changes in an unselected sample of ALS patients, but the ALS Center at the University of California at San Francisco has conducted structured interviews with caregivers using the Neuropsychiatric Inventory. In a cohort of 24 confirmed ALS patients, caregivers reported a range of mild to moderate symptoms of irritability, disinhibition, depression, apathy, and agitation (in that order) as the most common complaints that were not related to motor neuron disease.

These cognitive and behavioral deficits play an important role in clinical management and patient survival rates. During a 2-year period Olney et al carefully tracked a 100-patient ALS cohort, collecting clinical information and survival data, and results suggest that co-morbid diagnosis of FTLD may be associated with an adverse effect on survival. The median survival from symptom onset of ALS was 2 years 4 months for those with FTLD and 3 years 3 months for the 53 ALS patients with normal executive and behavioral function.

A CONTINUUM OF EXTRAMOTOR CEREBRAL ANOMALY IN ALS

Imaging studies provide support for the neural mechanisms for these cognitive and behavioral abnormalities, documenting cerebral abnormalities that extend well beyond the primary, secondary, and sensorimotor cortices. Structural imaging, positron emission tomography, functional magnetic resonance imaging (MRI), and single-photon emission computed tomography data reveal a pattern of widespread cortical involvement in ALS, with a worsening of this pattern in cognitively or behaviorally abnormal ALS patients. Mild to moderate cerebral atrophy has been documented in ALS patients with unknown cognitive status, with 50% of the sample having parietal atrophy, 38% having insula atrophy, 32% having frontal atrophy, 20% having temporal atrophy, and 12% having occipital atrophy. In addition, white matter degeneration has also been identified, suggesting a loss of fibers from the temporal and parietal lobes. An investigation using voxel-based morphometry identified left middle and inferior frontal gyri, the anterior portion of the superior frontal gyrus, the superior temporal gyrus, the temporal poles, and the left posterior thalamus as areas of brain atrophy in ALS patients, with patients with co-morbid FTLD having more severe frontal atrophy.

Patients with ALS without dementia have pronounced reductions in regional cerebral blood flow in the frontal and anterior temporal cortices on positron emission tomography, and patients without dementia with decreased verbal fluency scores have impaired activation of the dorsolateral prefrontal cortex, premotor cortex, bilateral insular cortex, and thalamus compared with ALS patients, who perform well on fluency measures. Patients with ALS and diagnosed dementia have decreased uptake in the frontal lobe, and some have additional ab-
neuralities in the temporal, parietal, and right thalamic regions on positron emission tomography. Functional MRI data reveal that when ALS patients without dementia perform a verbal fluency task they exhibit reduced activation in the middle and inferior frontal gyri and the anterior cingulate gyrus, in addition to regions of the parietal and temporal lobes.11 Investigations using single-photon emission computed tomography reveal that patients without significant dementia signs have metabolic reduction in the frontal lobe, and those with neuropsychologic dysfunction have abnormal anterior cingulate metabolism and frontal hypoperfusion.

Because neuroimaging is a sensitive way to understand anatomically the regions affected in ALS, we studied whether cognitively and behaviorally abnormal ALS patients had patterns of atrophy similar to cognitively and behaviorally intact ALS patients, and particularly whether ALS patients with subthreshold signs of dementia demonstrated subclinical disease on MRI. We evaluated 20 nonneurologic controls and 22 consecutive patients visiting the ALS Center at the University of California at San Francisco using neuroimaging to assess lobal atrophy and neuropsychologic and neurobehavioral interviews to determine cognitive and behavioral functioning. We obtained MRIs with whole-brain coverage. The scans included 3-dimensional T1-weighted volumes, and we used SIENAX software to estimate segmented gray and white matter volumes and transformations to standard templates to segment individual lobar regions.

Lobar gray matter volumes were determined for the frontal, temporal, parietal, occipital, limbic, and insular regions of the right and left hemispheres. We found that ALS patients with comorbid behavioral or cognitive abnormalities possessed significant reductions in gray matter volume across 11 of the 12 regions of interest. Perhaps more striking was the finding that the 11 patients with either full-blown dementia or subthreshold abnormalities in cognition or behavior also had significant reductions in gray matter in the right frontal, right parietal, and right limbic lobes compared with the 11 ALS patients without abnormalities. This anatomical distinction between the 2 ALS groups suggests that right hemisphere atrophy in ALS patients may represent a biomarker associated with behavioral and cognitive abnormalities. Such right hemisphere deficits have been linked to inappropriate range and intensity of affect and impaired ability to perceive facial expression and voice quality in others. Patients with right hemisphere deficits also have been described as having an “indifference reaction,” tending to deny or make light of the extent of their disabilities. As a result, right hemisphere patients tend to set unrealistic goals for themselves, fail to take limitations into account, and seem to be unconcerned about their problems, common traits described by family members of ALS patients with behavioral disturbance.

Regarding the hypothesis that atrophy would be identifiable in ALS patients with subthreshold dementia characteristics, we observed atrophy in patients with executive function deficits yet normal behavior and even in patients who were normal at baseline evaluation but who developed executive function problems 1 year later. Although this study used a small number of patients (N = 24) and the results should be interpreted cautiously, comparisons of individuals illustrate a continuum of frontal lobe impairment that mirrors the spectrum of cognitive and behavioral impairment on testing.

The Figure demonstrates the cerebral atrophy differences in 5 different patients in this study. The right frontal lobe, a region shown to be correlated with cognitive and behavioral deficits, was found to have associated atrophy in each of the 5 patients. The patient with FTLD (Figure E) was diagnosed as having the frontal variant of FTLD as defined by the criteria of Neary et al13, with significant disinhibition as measured using the Neuropsychiatric Inventory. Included is a patient with normal cognition and normal verbal fluency at the time of baseline MRI who had reduced gray matter lobar volumes similar to patients with low verbal fluency and executive dysfunction (Figure C). At 1-year follow-up this patient had a dramatic decline in her verbal fluency score, suggesting that her pattern of frontal lobe atrophy preceded her executive dysfunction and could be thought of as a type of biomarker.

**SUBTYPING THE SPECTRUM OF FRONTOTEMPORAL CHANGE IN ALS**

We suggested that explicit distinctions can be made between subgroups of abnormal ALS patients to more accurately characterize the frequency and nature of cognitive and behavioral abnormalities in ALS patients. The imaging data described previously herein suggest that patients with subthreshold cognitive and behavioral abnormalities have corresponding cerebral atrophy, indicating that ALS patients without dementia who have abnormalities have more than simple hypoxia, depression, or fatigue-related problems. By attempting to group patients into unique subtypes we may advance the field by distinguishing among different etiologies.

A helpful nomenclature may be *ALS with cognitive impairment* (ALSci) for ALS patients who perform 1.5 SD below the mean on at least 2 executive function neuropsychologic measures. A recent review1 offers the term *behaviorally impaired* (ALSbi) to describe ALS patients who display frontal lobe–based behavioral signs and do not meet the full criteria for FTD. The Neuropsychiatric Inventory or other behavioral interviews provide a structure for asking caregivers to rate specific frontal lobe–based behavior changes. The Table illustrates specific criteria used to distinguish ALSci, ALSbi, and ALS-FTD.

**FIRST INTERNATIONAL MEETING ON THE OVERLAP BETWEEN FTLD AND ALS**

A consensus conference on the overlap between ALS and FTLD was held in March 2005 in London, Ontario. Leaders in the fields of FTLD and ALS came together to discuss the considerable progress made in characterizing these overlapping syndromes. Areas of agreement included the identification of important clinical variables to control for when identifying ALS patients with cognitive and behavioral impairment. Depression, pseudobulbar affect, hypoxia, forced vital capacity status, edu-
cational level/baseline intellectual functioning, presence of bulbar palsy, and level of disease progression are important clinical variables to control for when studying ALS patients. Neuropsychologists in the field also agreed that an acceptable neuropsychologic battery should be weighted toward tests of executive function, including at least 1 measure of verbal fluency. Also included in the battery should be at least 1 caregiver interview that measures frontal lobe behavior. Finally, the gold standard of identifying full-blown frontotemporal lobar dementia should use the criteria of Neary et al.1

Perhaps most hotly debated is the question of the true prevalence of ALS patients with comorbid FTLD. This question is most likely fueled by referral bias, with some investigators studying all ALS patients in a given clinic and other laboratories studying selected patients referred from other clinics. Complicating this issue is that the rapid progression of the motor neuron disease outpaces the FTLD, frequently resulting in patient death before the frontotemporal neuron loss becomes severe. As a result, estimates of dementia rates in ALS patients have been documented to be as low as 3% of sporadic cases and 15% of familial cases. In contrast, a study13 of unselected patients at an ALS clinic found a rate of 22%.

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Table. Specific Characteristics Used to Distinguish ALSci, ALSbi, and ALS-FTD*

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Clinical Characteristics</th>
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<tr>
<td>ALS</td>
<td>A pure motor system disorder as defined by the El Escorial criteria; no clinical evidence of frontotemporal dysfunction</td>
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<tr>
<td>ALSci</td>
<td>Deficits (1.5 SDs below the age-matched mean) on ≥2 neuropsychologic tests of executive functioning but insufficient to meet the criteria of Neary et al.1 for FTD</td>
</tr>
<tr>
<td>ALSbi</td>
<td>Frontal lobe–type behavioral impairment in ≥2 areas as measured by means of a standardized caregiver interview</td>
</tr>
<tr>
<td>ALS-FTD</td>
<td>ALS patient meeting the criteria of Neary et al.1 for FTD</td>
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*Partially adapted from Lomen-Hoerth and Strong.5

The utility of subtyping patients into distinct categories of cognitive and behavioral impairment (lumpers vs splitters) has become a second, closely related debate. Patients with mild or moderate cognitive and behavioral deficits can either be subdivided into distinct categories or...
lumped into the category of “nondemented.” We maintain that by carefully measuring behavioral impairment and cognitive functioning on a continuum, using sensitive measures that identify mild to moderate cognitive and behavioral changes, distinctions can be made between patients who have only 1 area of pathologic abnormality and others who share both. Our investigations suggest that ALS-Sci patients do not display behavioral abnormalities consistent with FTLD. Yet other patients categorized as having ALSbi did not meet the criteria for significant cognitive impairment and did not meet the criteria of Neary et al1 for a full-blown dementia syndrome. By distinguishing these 2 groups from patients traditionally characterized as having ALS-FTD, investigators may uncover unique pathologic mechanisms and different trajectories of clinical course.

CONCLUSIONS

The concept that cognitive and behavioral dysfunction in ALS is rare can no longer be substantiated. Critical questions now include the prevalence of the dysfunction and the possible etiologic differences between ALS patients who are cognitively and behaviorally normal and those with abnormalities. Amyotrophic lateral sclerosis may exist as a degenerative process of the motor system, in which degeneration of the frontotemporal lobar type can occur. When prominent, these changes may manifest as FTLD (ALS-FTLD). In its more subtle manifestations, a frontal dysexecutive syndrome, a frontal behavioral syndrome, or both may occur. However, frontal, temporal, and parietal cortical atrophy, observed on neuroimaging and disproportionate to that observed in age-matched controls, is seen across all ALS patients. These data suggest that the “pure” phenotype of ALS in which the disease process is restricted to the motor neurons is in fact rare and that the more common variant is a more complicated phenotype in which the neurodegeneration extends well outside the boundaries of the motor system.

Consensus terminology is required to bring some order to what is becoming an increasingly complex picture. Approaching the same entity from a dementia perspective may ignore the complexity of ALS and vice versa, so groups of investigators from both specialties are needed to discuss the terminology and reach consensus. Do patients with ALSbi and ALS-Sci progress to full FTLD? Prospective studies are beginning to emerge14 to answer this and other pressing questions.

Accepted for Publication: December 7, 2006.

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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 and Lomen-Hoerth. Acquisition of data: Murphy, Henry, and Lomen-Hoerth. Analysis and interpretation of data: Murphy, Henry, and Lomen-Hoerth. Drafting of the manuscript: Murphy, Henry, and Lomen-Hoerth. Critical revision of the manuscript for important intellectual content: Murphy, Henry, and Lomen-Hoerth. Statistical analysis: Murphy. Obtained funding: Lomen-Hoerth. Administrative, technical, and material support: Murphy and Henry. Study supervision: Lomen-Hoerth.

Financial Disclosure: None reported.

Funding/Support: This study was supported by the Amyotrophic Lateral Sclerosis Association.

REFERENCES