Frontotemporal Dysfunction and Dementia in Amyotrophic Lateral Sclerosis

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KEYWORDS

• Frontotemporal dementia • Frontotemporal lobar degeneration
• Cognitive impairment • Neural network • Theory of mind • TDP-43 • Tau

KEY POINTS

- Syndromes of frontotemporal dysfunction in amyotrophic lateral sclerosis (ALS) affect up to 50% to 60% of patients irrespective of the presence or absence of an underlying genetic basis for the disease.
- The syndromes of ALS include frontotemporal dementia (FTD), behavioral impairment, and/or cognitive impairment, which are best diagnosed through formal neuropsychological testing.
- The presence of frontotemporal dysfunction reduces the disease course in ALS by approximately 1 year, specifically in patients with FTD or executive dysfunction.
- Language impairment is a sensitive indicator of frontotemporal dysfunction in ALS.

INTRODUCTION

The classic description of amyotrophic lateral sclerosis (ALS) has little to do with the presence of neuropsychological dysfunction, and instead focuses largely on the motor manifestations of the disorder. However, the contemporary view of ALS is that a significant proportion of patients have evidence of frontotemporal dysfunction that can include a frontotemporal dementia (FTD), syndromes of ALS with behavioral impairment (ALSbi) or ALS with cognitive impairment (ALSci), deficits in social cognition, or language impairment.[1–3] Although clinically manifest dementia was historically thought to be rare in ALS, when carefully examined, 45% to 55% of patients with ALS show extramotor deficits. Although in most cases frontotemporal dysfunction

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precedes the development of ALS, the converse is also true.[4] International consensus criteria have been developed to aid in differentiating among these individual syndromes, and, when applied prospectively, suggest that approximately a third will develop ALSci, 4% ALSbi, 9% ALS-FTD, and 4% probable Alzheimer disease.[2,5] Less than half would be considered neuropsychologically intact. These figures have remained remarkably consistent across several contemporary studies, although, as reviewed here, with refinements in neuropsychological tools, further clarity is arising regarding the exact nature of these syndromes.[6–8]

The presence of frontotemporal dysfunction is of more than academic interest. When present, frontotemporal dysfunction is associated with a significant reduction in ALS survival.[6,9,10] Although the basis of this is not clear, there is increasing evidence that the nature of the frontotemporal syndrome is key. For instance, the presence of executive dysfunction is a greater risk factor for poor prognosis than FTD.[6] This greater risk is independent of age at onset, delay to diagnosis, baseline disease severity, education, and respiratory status. Patients with nonexecutive cognitive impairment do not have significantly worse prognosis. In a study of prognosis,[6] patients with ALS-FTD survived 23 months from the time of symptom onset compared with 34 months for patients with ALS without dementia. Those with executive dysfunction survived an average of 24 months, compared with 38 months for nonexecutive cognitively impaired or cognitively normal ALS. The presence of abnormal behavior is similarly a negative prognostic variable.[10]

Longitudinal studies regarding the evolution of cognitive impairment are difficult to conduct while maintaining adequate statistical power, contributing in part to the lack of consensus as to whether cognitive deficits progress over time. Although impairments in verbal fluency are key markers of altered cognition in ALS, there is no evidence that such deficits progress over time.[11] In contrast, a recent longitudinal study observed clear evidence of progression.[12]

Region of onset does not improve prognostication related to cognition or behavior. Similar to neuroimaging studies, neuropsychological testing is more feasible with patients with limb onset over time and therefore longitudinal studies tend to capture more data for limb onset. Studies are mixed about whether bulbar onset increases risk for cognitive impairment,[13,14] but studies with larger cohorts do not support increased prevalence of cognitive impairment in patients with bulbar onset.[15–18]

This article reviews the characteristics of frontotemporal dysfunction in ALS from both a clinical and molecular vantage.

ILLUSTRATIVE CASE

A 53-year-old male accountant first presented with reduced organizational skills, increasing inattention, word-finding difficulties, and an inability to perform his daily banking. Within a month, he developed a marked increase in his appetite, increasingly obsessive behavior, and stubbornness. Two months later, he develop choking, slurring of his speech, and a reduced speech volume. Neuropsychological studies revealed intact auditory and verbal comprehension, naming, and repetition, whereas impairments were noted in verbal fluency and spelling, and visuospatial task performance. His clinical examination and electrophysiologic studies were consistent with a diagnosis of ALS. MRI showed prominent atrophy of the mesial frontal lobes and the anterior superior temporal gyrus (**Fig. 1**A). He died 1 year following symptom onset from respiratory failure.

At autopsy, prominent atrophy of the mesial frontal lobe was observed (see **Fig. 1**B). Spinal motor neurons showed TAR DNA binding protein of 43 kDa (TDP-43),