Neuropsychiatric features of Amyotrophic Lateral Sclerosis

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1. Introduction

The traditional view of motor neuron disease (MND) has been that it is a neurodegenerative disorder isolated to the motor system, affecting motor activity under voluntary control and sparing all other systems. When explaining the diagnosis to patients, neurologists were able to focus on this silver lining and emphasize that “... while your body may fail, your mind will remain clear.” Patients and families seemed to take great comfort in this knowledge. However, over the last 10 years evidence has accumulated that a proportion of patients with amyotrophic lateral sclerosis (ALS) have measurable cognitive and behavioral deficits that are sometimes severe enough to be clinically relevant [1, 3,4,22,23,32,34–36,38,42,45]. This paper will review the growing body of data on neuropsychiatric features of ALS, including disorders of language, behavior and mood.

2. Cognitive dysfunction in motor neuron disease

Large studies have shown that screening tests detect cognitive deficits in 30–50% of ALS patients [22, 23,34–36]. The most common cognitive abnormality found in ALS patients is impaired verbal fluency secondary to executive dysfunction [4,6]. A subset of patients with ALS has clinically apparent dementia, which may be the presenting feature of disease. When dementia co-occurs with ALS, it presents in a pattern most similar to that seen in frontotemporal lobar dementia (FTLD), which is characterized by progressive impairments in language as well as social and executive function, with relative sparing of memory and visuospatial skills. There are three defined phenotypes of FTLD: 1) progressive non-fluent aphasia, characterized by effortful speech with phonemic paraphasic errors or agrammatism; 2) semantic dementia, characterized by fluent but empty speech with impaired word meaning; and 3) frontotemporal dementia, characterized by personality changes and lack of compliance with social norms [7,27]. It remains to be seen whether the cognitive deficits in ALS will fall neatly into these three categories, though early observation suggests the existence of each of these phenotypes amongst ALS patients with dementia [22]. Additionally, there is a pathological link between ALS and FTLD. The most common pathology in both disorders is tau-negative [11,21]. TDP-43 has recently been identified as the common disease protein [28].

3. Assessment of cognitive impairment in motor neuron disease

Detection of cognitive impairment can be accomplished with formal neuropsychiatric testing, but this is
costly, time consuming and complicated by motor and speech impairments. Efforts are under way to develop a brief and effective screening tool that will rely minimally on motor function [10,22]. The most widely used screening tool to date is a timed word generation task that requires patients to generate words that either begin with a certain letter or fit into a defined category, such as animals. Words may be written or spoken depending upon the motor limitations of the patient. Nevertheless, this is a timed task that places demands on motor performance even in the better modality of expression, and additional work is needed to identify a brief, sensitive, clinical test with minimal confounds of this sort. The neurobehavioral symptoms most commonly seen in FTLD include irritability, hyperoral behavior, disinhibition, anhedonia, lack of empathy, withdrawal and alexithymia [31]; many of these symptoms can be detected using the Frontal Behavioral Inventory, which is administered to caregivers [19].

4. Risk factors for cognitive impairment in motor neuron disease

It is difficult to predict on clinical grounds which patients are at risk for having cognitive impairment. Some series have reported a higher prevalence of cognitive impairment in patients with bulbar onset disease [29,38,42]; others have not [35,36]. Other identified risk factors for cognitive impairment have included dysarthria, low education, greater severity of motor impairment [23] presence of pseudobulbar palsy [2], and older age, lower forced vital capacity, and family history of dementia [22].

5. Clinical implications of cognitive impairment in patients with motor neuron disease

Somewhat surprisingly, it is unclear whether cognitive difficulties are progressive in patients without frank dementia. There is little available longitudinal cognitive data in ALS patients, but it is suggested that cognitive abnormalities tend to be present early in the course of ALS, with only slow progression over time that is not in concert with motor decline [3,38]. A recent 6-month longitudinal study did demonstrate cognitive decline as measured by changes in neuropsychological performance in approximately one-third of patients tested [37]. Further dedicated studies are needed to clarify this issue.

The clinical implications of cognitive impairment in patient care are myriad. Certain features of FTLD have special relevance for patients with ALS. Early behavioral changes in FTLD include disinhibition and impulsive behavior, often manifested as changes in eating habits [26]. This presents a special problem for patients with significant dysphagia who may need to alter their food consistency choices and eat slowly to maintain safety. Impulsive motor behavior and propensity for increased risk taking [25] may also be especially dangerous for patients with motor limitations who should use adaptive equipment or refrain from walking to maintain safety. Lack of insight can be an early clinical feature of FTLD [24] that impairs the ability to participate meaningfully in several decision-making processes. For example, as ALS progresses and motor function is lost, there is reduced insight into problems associated with prolonged maintenance in a particular position, so caregivers must take greater responsibility for re-positioning at an earlier point in the condition in order to minimize the development of decubitus ulcers. Likewise, decisions regarding the placement of a feeding tube and the use of invasive and non-invasive ventilation can be more difficult because of limitations in the patient’s ability to fully participate in these considerations. Decreased speech output and other language abnormalities manifested by patients with FTLD adversely impacts the ability to carry out a complex conversation [25]. This highlights the need to address these issues early in the course of disease, perhaps well before clinically indicated. The presence of signs of cognitive decline should prompt initiation of an advance directive discussion and designation of a surrogate decision maker who is aware of the patient’s wishes when they are in a non-demented state.

6. Prognosis in motor neuron disease with cognitive impairment

It is not yet clear whether the presence of mild cognitive abnormalities or dementia portends a worse prognosis in patients with ALS. One study showed that ALS patients who fulfill strict criteria for FTLD have a worse prognosis than non-demented patients with ALS [29]. Worsened prognosis in this study sample may have been related to the higher proportion of cognitively impaired bulbar onset patients versus limb onset patients, as bulbar-onset predicts a shorter disease course. An alternative explanation was the lower rates of compliance with recommendations regarding the use
of non-invasive positive pressure ventilation (NIPPV) and feeding tube placement in demented patients. Another series did not find a relationship between survival and the presence of cognitive impairment [36].

7. Treatment of cognitive impairment in motor neuron disease

To date, no effective treatment has been identified for the cognitive abnormalities in FTLD. Treatment efforts have been directed at the behavioral aspects of the disease. This is related to the neurochemical underpinnings of FTLD, which is characterized by decreased binding of serotonin in the frontal lobes [12,40,41], rather than abnormalities of the cholinergic system as seen in Alzheimer’s disease. Disinhibition, impaired impulse control, intermittent aggression toward others, compulsions, and carbohydrate craving may be responsive to serotonergic drugs, making selective serotonin reuptake inhibitors (SSRI) a good first choice for therapy [31,44]. Aggressive behavior should be treated with low doses of atypical antipsychotics [9] or atypical antidepressants such as trazodone [16], rather than benzodiazepines or typical neuroleptics [31]. Other options include anti-epileptic drugs that function as mood stabilizers, including valproic acid and carbamazepine [9, 15]. Patients with FTLD may develop features of the Klüver-Bucy syndrome, which occurs in the setting of bilateral amygdala damage and includes compulsive eating and hyperorality, passivity and hypersexuality. Passivity and hyperorality are commonly seen in patients with FTLD [26], though hyposexuality is more common than hypersexuality [8,26]. SSRI [39] and propranolol [30] have been effective in the Klüver-Bucy syndrome, and leuprolide may be added if hypersexuality is present [30]. Important non-pharmacologic interventions focus on education of the family and caregivers regarding the lack of insight and judgment that the patient is likely to show. Safety considerations include preventing patients with FTLD from driving and removing them from direct child care situations [31].

8. Depression in motor neuron disease

The prevalence of depression in ALS is not well known; reported rates have ranged between 9% and 22% [13,18,33]. Overall physical disability is not a good predictor of depression but bulbar disease and respiratory insufficiency may be more highly correlat-
ed with depression [14,17]. A negative correlation has been found between the likelihood of depression and disease duration, suggesting that depression may be more prevalent proximate to the diagnosis as part of an adjustment disorder [17]. The prevalence of depression does not increase uniformly with advancing disease, even as death approaches [33]. In fact, the wish to die in late-stage disease may be a separable phenomenon from clinical depression and may be more appropriately conceived as part of a syndrome of end-of-life despair, for which religiousness is not protective [5]. Social support and marital intimacy during early disease are predictive of anxiety and depression as disease progresses [14], but spiritual belief is not [33].

There is overlap between some features of FTLD and depression, though there are important differences. The typical mood disturbance of patients with FTLD includes euphoria, irritability, anhedonia, social withdrawal, apathy, disinhibition and increased appetite with weight gain but lacks guilt and suicidality [43]. Apathy is a particularly prominent feature of FTLD that can also be seen in depression, but the degree of apathy in typical FTLD is out of proportion to measurable depression [20]. It is not yet clear whether ALS patients with FTLD are more likely than cognitively normal ALS patients to have depression.

9. Conclusion

It is no longer appropriate to assure the ALS patient and family that they need not expect cognitive and behavioral changes. To date, there is not a standardized screening tool in use for cognitive assessment of ALS patients. Early suggestions have included tests of verbal fluency (F-word generation task), the Frontal Behavioral Inventory and the Beck Depression Inventory as a coarse screen for disorders of language, comportment and mood. These measures require only a few minutes to complete and can be administered easily as part of the routine office visit. Detailed neuropsychiatric testing can be obtained based on results of these tests or if there is clinical suspicion of dementia. The recognition of neuropsychiatric abnormalities should prompt education of the patient and family about this aspect of the disease, which adds significant burden to the caregiver. Assessment for cognitive and behavioral dysfunction and depression should be part of ALS patient care and can lead to appropriate pharmacologic therapy as well as education for families and early planning for end of life care.
References


