

# **NEUROCOGNITIVE, BEHAVIORAL AND PSYCHOLOGICAL CHANGES ASSOCIATED WITH ALS**

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## TABLE OF CONTENTS

- I. Cognitive Change in ALS
- II. Behavioral Change in ALS
- III. Frontotemporal Dementia
- IV. Bulbar-Onset ALS
- V. Structural, Functional and Neuropathological Brain Alterations
- VI. Depression and Pseudobulbar Affect
- VII. Evaluation of Neuropsychological Deficits
- VIII. Implications of Cognitive and Behavioral Impairment
- IX. Literature Cited

### I. Cognitive Change in ALS

Cognitive impairment has not been identified in the ALS population until fairly recently. Studies suggest that approximately 35%<sup>1</sup> to 56%<sup>2</sup> of ALS patients experience cognitive deficits which may be identified early in the course of the disease.<sup>3</sup> In a study of patients at the time of diagnosis, 51% revealed cognitive abnormalities (below the 5<sup>th</sup> percentile) on at least 2 psychometric tests.<sup>4</sup> Impairment typically results from deterioration of the frontal regions adjacent to the motor cortex, and a small minority of patients fulfill diagnostic criteria for Frontotemporal Dementia (FTD).

ALS-associated cognitive impairments include deficiencies in visual attention<sup>5</sup>, working memory,<sup>3</sup> cognitive flexibility,<sup>3</sup> inhibition of response alternatives,<sup>5</sup> planning, problem solving,<sup>3</sup> and visual-perceptual skills.<sup>1,2,3,6,7</sup> Intrinsic response generation, i.e. verbal fluency independent of dysarthria, has also been identified.<sup>3,5,6,8,9</sup> Fluency deficits are not limited to verbal abilities but also non-verbal fluency (designs), supporting the notion of an underlying deficit of response generation.<sup>6,8</sup> These impairments encompass what is known as executive dysfunction.

Most ALS-associated cognitive deficits are attributed to abnormalities in frontal lobe function.<sup>1,2,7,10</sup> Impaired memory has been attributed to deficient retrieval processes associated with frontal lobe dysfunction rather than hippocampal atrophy.<sup>11</sup> Researchers hypothesize that fluency deficits stem from impaired supervisory attentional systems or a central executive component of working memory,<sup>12</sup> which are regulated by the frontal lobes. Fluency dysfunction is not attributable solely to speech weakness.

Strong and his colleagues<sup>3</sup> were the first to document changes over time (6 month time period) and discovered progressive neurocognitive abnormalities and changes on MR spectroscopy suggesting a loss of neurons in the cingulate gyrus for bulbar patients. However, other prospective studies have failed to detect notable change over the same time period aside from slower word retrieval.<sup>13</sup>

## II. Behavioral Change in ALS

An interview of 16 consecutive ALS patients revealed a range from behavioral stability consistent with premorbid functioning to profound frontally-mediated dysfunction.<sup>14</sup> Self-centeredness and irritability were reported in 69% and 61% of patients, respectively. Other changes included exaggerated display of emotions (50%), blunting of emotions (25%), disinhibition and lack of insight (13%).

According to spouses of ALS patients, neuropsychiatric symptoms increase over time even in patients who are not clinically depressed.<sup>3</sup> When testing fails to demonstrate cognitive impairment, patients may exhibit dysfunction in affective or social interactions, as well as decision-making problems.<sup>9</sup> Murphy et al<sup>15</sup> identified a subtype of ALS patients revealing behavioral dysfunction without cognitive change. In another study, more than 20% of cognitively normal ALS patients had profound behavioral abnormalities.<sup>9</sup>

## III. Frontotemporal Dementia (FTD)

A relationship between dementia and ALS was first made in the 1920's, and for most patients the impairment is consistent with Frontotemporal Lobar Dementia (FTLD).<sup>16</sup> A 2003 study revealed that 52% of ALS participants met research criteria for possible or probable FTLD.<sup>9</sup> However, at the first International Research Workshop on Frontotemporal Dementia in ALS, it was generally agreed that the percentage of patients meeting full Neary criteria for FTD was approximately 5%.

FTLD is an overarching term describing a group of dementing disorders marked by frontal and temporal lobe degeneration.<sup>17</sup> Originally associated with Pick's disease, FTLD can be classified into several subtypes depending on clinical presentation. These include Frontotemporal Dementia (FTD), Semantic Dementia (SD) and Primary Progressive Aphasia (PPA). ALS patients tend to exhibit the frontal variant of FTLD (FvFTD or FTD). Neary criteria for FTD includes: insidious onset and gradual progression, early decline in social interpersonal conduct, early impairment in the regulation of personal conduct, early emotional blunting and early loss of insight.

FTD typically documented in ALS can be characterized in the initial stages by disinhibition, impulsivity, social inappropriateness, stereotypic behaviors and apathy. Other impairments can include a personality change, loss of initiative, impaired judgment and poor self-care. These changes are followed by executive dysfunction marked by deficits in planning and organization. Memory generally remains intact but can appear impaired secondary to deficient encoding.

More recent research has clarified what appears to be a continuum with distinct subgroups. While some ALS patients are cognitively and behaviorally normal, others reveal cognitive deficits without behavioral change (Executive Dysfunction Syndrome-EDS), some exhibit behavioral disturbance without cognitive deficits (possible FTD) and some present with probable FTLD.<sup>15</sup> The question of whether ALS-related cognitive impairment exists on a continuum with FTD as an endpoint has not been answered and needs further exploration.

#### IV. Bulbar-Onset ALS

There appears to be an association between the cognitive deficit and bulbar-onset of ALS, yet the absence of bulbar signs does not predict intact cognition.<sup>3</sup> Bulbar-onset patients tend to have more cognitive impairment than limb-onset patients,<sup>3,9</sup> with more varied deficits and progression over time.<sup>3</sup> Bulbar-onset ALS patients with cognitive loss and changes on brain imaging (MR spectroscopy) developed more neurocognitive dysfunction over time, in contrast to the limb-onset group which did not.<sup>3</sup> In one cohort, bulbar onset patients were more than twice as likely to receive an FTD diagnosis.<sup>9</sup>

Abrahams and colleagues<sup>12</sup> found that distractibility correlated with dysarthria, supporting the suggestion made by other researchers that the presence of the bulbar symptoms in ALS is associated with frontal lobe impairment. Neary<sup>7</sup> cited other studies which associate bulbar palsy with executive failure, thus suggesting a link between bulbar neuronal and anterior horn cell fallout and frontotemporal neocortical degeneration.

Ellis and colleagues<sup>18</sup> used H-MRS to identify a loss of gray matter in frontal regions and deficits in white matter volume in bulbar-onset patients. The study provided in vivo evidence of axonal degeneration in the subcortical white matter in the motor region, consistent with the 'dying back' process affecting cortical motor neurons in bulbar-onset ALS.

Forty eight percent of bulbar-onset patients evaluated in a 2001 study<sup>19</sup> revealed cognitive impairment with frontotemporal abnormalities including memory impairment, alteration of judgment and reasoning, behavioral disinhibition and alteration of daily living activities. Impairments correlated with event-related potentials (ERP) and SPECT studies, with all impaired patients having abnormal ERP's. A clear male predominance was noted in the cognitively impaired group.

Other researchers have not identified a difference between bulbar versus non-bulbar onset when comparing ALS patients with and without cognitive impairment.<sup>1,5</sup> Portet and colleagues<sup>2</sup> failed to identify a difference between bulbar and limb onset patients, although they did replicate findings of a dysexecutive syndrome and behavioral impairment. In a review of nearly 300 newly diagnosed patients, bulbar patients were not significantly different in level or pattern of cognitive impairment.<sup>4</sup>

#### V. Structural, Functional and Neuropathological Brain Alterations

Imaging studies reflect deficient frontal lobe functioning. Extra-motor neuronal involvement, indicated by glucose hypometabolism, has been documented in several ALS studies.<sup>7,8,12,20-22</sup> Deficiencies are not only identified in the frontal lobes but also subcortical regions<sup>8,23</sup> and overall cortex.<sup>8,24</sup> Regional cerebral blood flow can even be reduced in ALS patients who do not present with cognitive impairment.<sup>25</sup>

A study of non-demented ALS patients<sup>22</sup> revealed predominant cerebral dysfunction in the prefrontal regions. Significant decreases in flumazenil (marker) volume distribution were

identified in the prefrontal cortex, parietal cortex, visual association area, left motor/premotor cortex. Relative reductions were also found in the left ventrolateral and dorsolateral prefrontal cortex (DLPFC), Broca's area, right temporal area and right visual association cortex.

Several researchers have identified glucose hypometabolism in the entire cortex and the basal ganglia in a majority of ALS patients<sup>24</sup> which correlated with the duration of the disease.<sup>20,21,24</sup> Ludolph and colleagues<sup>8</sup> failed to find a correlation with disease duration. However, the later study did not scan patients longitudinally but rather made comparisons between patients based on a measure of disease duration.

Researchers have identified cerebral activation correlates to neurocognitive impairments.<sup>8,12,25</sup> PET studies have suggested a correlation between verbal fluency deficits and dysfunction of the dorsolateral prefrontal cortex (DLPFC).<sup>12</sup> Word fluency correlated with metabolism on the entire cortex and right thalamus, as well as a weaker but significant correlation with caudate nucleus.<sup>8</sup>

Neuropathologically, cognitive impairment in ALS is associated with superficial linear spongiosis, microglial proliferation and astrocytic degeneration.<sup>26</sup>

#### VI. Depression and Pseudobulbar Affect

Self-reported depression occurs in approximately 40% of ALS patients over the course of the disease.<sup>27</sup> Depression onset has been correlated with the time of diagnosis<sup>28</sup> although patients are susceptible throughout the disease course. There is no clear evidence that depression rates increase with impending death.<sup>29</sup> When measured using clinical rating scales and interview-based assessments, rates of depression among ALS patients ranged from 10%<sup>29</sup> to 43%.<sup>30</sup> Depression has been associated with more severe emotional withdrawal and lower subjective spirituality.<sup>31</sup> Results have varied regarding whether depression is correlated with ALSFRS scores or physical disability.

Pseudobulbar affect (a.k.a. emotional lability, emotional incontinence, affective lability or pathological laughing/crying) is seen in ALS and characterized by sudden outbursts of uncontrollable laughing or crying. These episodes are not necessarily provoked by humorous or sad conditions, often occur spontaneously and can be incongruent to the patient's mood state. These episodes are difficult to control and are not symptoms of depression or other psychiatric condition.

Pseudobulbar affect is more typically seen in bulbar-onset ALS patients at the rate of approximately 25-50%. Uncontrollable laughter or crying decreases the capacity to regulate breathing and increases risk for shortness of breath. Additionally, affective outbursts can exacerbate sialorrhea and lead to choking. Pseudobulbar affect has not been directly linked to FTD.

#### VII. Evaluation of Neuropsychological Deficits

Cognitive functioning is difficult to characterize in ALS patients due to disease-specific motor and speech deficits. After patients lose their ability to communicate effectively, the reliable

evaluation of cognition is limited, leaving open the question of the capacity to make sound treatment decisions or apply appropriate judgment.

Evaluating cognitive changes in ALS patients is most accurately completed through neuropsychological assessment. This involves the systematic administration of cognitive tests which characterize different areas of thinking including attention, language, memory, visual-spatial processing and executive functioning. Currently, there is no standardized battery for the assessment of cognition in ALS.

A detailed clinical interview with family or friends may help identify changes consistent with frontal dysfunction. Often this is a more reliable means of information gathering since the patient may have limited insight into their deficits. Assessments must also include the evaluation of depression, anxiety, sleep disorders, O<sub>2</sub> levels, and medication side effects.

Neuropsychological testing is often sensitive to dorsolateral prefrontal cortex (DLPFC) changes when early lesions in FTD-related disorders tend to involve the orbitofrontal regions. More sensitive measures are called for to identify these earliest changes.

#### VIII. Implications of Cognitive and Behavioral Impairment

ALS patients with executive and behavioral dysfunction have a worsened prognosis for survival and poor compliance with non-invasive ventilation and PEG.<sup>32</sup> Decreased impulse control may increase the risk for choking or falls, and use of AAC devices and wheelchairs may be reconsidered secondary to executive dysfunction. Increases in apathy may affect motivation for adequate self-care. Neuropsychological impairments may also impede in a patient's capacity to make appropriate health care decisions. Caregiver burden associated with cognitive and behavioral impairments is considerable and can lead to more stress than that associated with physical disability alone. It is important to counsel patients early in the disease process to make decisions about finances and health care to avoid problems if neurocognitive symptoms emerge.

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