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Review article

The neuropathological signature of bulbar-onset ALS: A systematic review

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ABSTRACT

ALS is a multisystem disorder affecting motor and cognitive functions. Bulbar-onset ALS (bALS) may be preferentially associated with cognitive and language impairments, compared with spinal-onset ALS (sALS), stemming from a potentially unique neuropathology. The objective of this systematic review was to compare neuropathology findings reported for bALS and sALS subtypes in studies of cadaveric brains. Using Cochrane guidelines, we reviewed articles in MEDLINE, Embase, and PsycINFO databases using standardized search terms for ALS and neuropathology, from inception until July 16th 2016. 17 studies were accepted for analysis. The analysis revealed that both subtypes presented with involvement in motor and frontotemporal cortices, deep cortical structures, and cerebellum and were characterized by neuronal loss, spongiosis, myelin pallor, and ubiquitin+ and TDP43+ inclusion bodies. Changes in Broca and Wernicke areas – regions associated with speech and language processing – were noted exclusively in bALS. Further, some bALS cases presented with atypical pathology such as neurofibrillary tangles and basophilic inclusions, which were not found in sALS cases. Given the limited number of studies, all with methodological biases, further work is required to better understand neuropathology of ALS subtypes.

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1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that affects upper and lower motor neurons in the brain, brainstem, and spinal cord, but has also been associated with extra-motor (i.e., cognitive and language) impairments, similar to those found in frontotemporal dementia (FTD) (Phukan et al., 2012; Schreiber et al., 2005). ALS has two typical presentations at disease onset – approximately 70% of patients present initially with the spinal form of the disease, characterized by muscle weakness and atrophy in the limbs and trunk, when the remaining patients present with bulbar changes, affecting speech and swallowing musculature (Bonduelle, 1975). Nearly 85% of patients with spinal-onset ALS, however, exhibit bulbar changes with disease progression (Armon and Moses, 1998; Haverkamp et al., 1995). Approximately 50% of all patients diagnosed with ALS show cognitive and language impairments, while 10% of the patients present with clear signs of FTD (Massman et al., 1996; Ringholz et al., 2005). ALS is a complex disorder with considerable heterogeneity across affected individuals (Green et al., 2013; Robert et al., 1999). This heterogeneity is not well understood, however. Addressing the heterogeneity by developing accurate means of patient subtyping (Brooks et al., 1991) is essential for providing more targeted approaches to treatment development, recruitment into clinical trials, and disease management in a clinic (e.g., early identification of bulbar disease in order to plan supportive interventions and predict disease progression).

Bulbar ALS is arguably the most devastating variant of the disease as it is characterized by the fastest decline, the shortest survival (<2 years post diagnosis), and a significantly reduced quality of life (Goldstein et al., 2002; Mitsumoto and Del Bene, 2000). In addition to the rapid motor decline, some neuroimaging and behavioural studies have observed that bulbar ALS may present with an increased burden of cognitive/language impairments (Lomen-Hoerth et al., 2003; Massman et al., 1996; Ogawa et al., 2009; Ota et al., 2005; Schreiber et al., 2005; Sterling et al., 2010; Strong et al., 1999). This latter finding remains disputed, however (Gordon et al., 2010a; Taylor et al., 2013). Two hypotheses have been proposed regarding the association between motor and extramotor abnormalities in ALS, in relation to the disease subtype: 1) it has been suggested that the site of symptom onset may be related to the burden of extra motor impairments, with bulbar-onset ALS showing a unique neurodegenerative profile associated with specific and concomitant extramotor impairments (Ichikawa et al., 2008a; Kato et al., 1994; Lomen-Hoerth et al., 2003; Massman et al., 1996; Ogawa et al., 2009; Portet et al., 2001; Schreiber et al., 2005; Strong et al., 1999); and 2) the presence of bulbar motor dysfunction, regardless of site of onset, may be associated with extramotor impairments (Massman et al., 1996; Ota et al., 2005; Ringholz et al., 2005; Sterling et al., 2010). Neither of the two hypotheses has been investigated neuropathologically in cadaveric brain tissue.

Studies that examined the underlying neuropathology in cases with cognitive and language impairments showed that ALS cases typically present with frontotemporal lobar degeneration (FTLD) (Geser et al., 2010; Liscic et al., 2008). The pathology in the frontotemporal regions consisted of neuronal loss, marked gliosis, and intraneuronal inclusion bodies that were positive for ubiquitin and TAR DNA-binding protein 43 (TDP-43) (Arai et al., 2006; Liscic et al., 2008; Neumann et al., 2006). The severity and distribution of TDP-43 in the brain has been shown to be well-correlated with antemortem cognitive profiles, often giving insight into the phenotypic presentations of the disease and representing a clinicopathologic spectrum (Mackenzie and Feldman, 2003; Mackenzie, 2007; Prudlo et al., 2016; Yoshida, 2004) that ranges from pure motor neuron disease to frontotemporal dementia. The underlying neuropathology, however, has not been well-characterized in the context of bulbar- versus spinal-onset subtypes in the existing literature. An examination of the neuropathological findings from the subtype perspective might shed light into the underlying similarities and/or differences in clinical disease presentations.

This study aimed to contribute to our understanding of ALS subtypes through neuropathological studies of cadaveric brains, and elucidate whether these subtypes are neuropathologically distinct or lie within a spectrum of the same disease. To do this, we conducted a systematic review investigating similarities and differences between neuropathological profiles of bulbar-onset ALS (bALS) and spinal-onset ALS (sALS) by regional distribution and types of pathology.

2. Methods

2.1. Operational definitions

Our search was guided by the following operational definitions, determined a priori: *Amyotrophic Lateral Sclerosis*, defined as a progressive neurological disease with upper and lower motor neuron involvement determined by clinical, electrophysiological