Neuropathology of Amyotrophic Lateral Sclerosis and Its Variants

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KEYWORDS

• Amyotrophic lateral sclerosis • Neuropathology • TDP-43
• Motor neuron degeneration • C9orf72

KEY POINTS

- ALS has a distinctive and complex neuropathology, from which its name is derived.
- Many developments in ALS research have been driven by key neuropathologic insights, such as the identification of ubiquitinated cytoplasmic inclusions, which led to the identification of TDP-43 in ALS.
- New microscopic, molecular, and computerization techniques are allowing researchers unprecedented visualization of the inner workings of the disease at the tissue, cellular and molecular levels.

INTRODUCTION

The first case reports of amyotrophic lateral sclerosis (ALS) date back to Charles Bell in 1824.[1] Although a variety of other clinical descriptions followed throughout the 1850s,[2–4] the correlations between key clinical features of progressive muscle atrophy and muscle spasticity and key neuropathologic features of loss of anterior horn cells and sclerosis in the lateral columns of the spinal cord were first made by Charcot in the 1860s,[5] and thus, he named the clinical disease by its distinctive neuropathology.[6] Significant subsequent contributions included the observation of loss of the giant cells of Betz, best summarized by Brodmann in 1909,[7] of eosinophilic inclusions now called Bunina bodies in 1962,[8] the discovery of ubiquitinated cytoplasmic inclusions in 1988,[9,10] and the discovery that the ubiquitinated inclusions comprised primarily TDP-43 in 2006.[11,12] The association between ALS, the clinical disease frontotemporal dementia (FTD), and FTD neuropathology referred to as frontotemporal lobar dementia (FTLD) has taken 3 decades to establish.[13,14] With advances in genetics beginning in

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1993, distinctive neuropathology is being identified in the genetic forms, the main ones being SOD1,[15] TDP-43,[16] FUS,[17,18] and C9orf72 repeat expansions.[19,20]

CLASSIC AMYOTROPHIC LATERAL SCLEROSIS NEUROPATHOLOGY

Gross

In most brains with ALS, no gross abnormalities are observed. The spinal cord often shows atrophy of the anterior nerve roots.[21] Some cases show atrophy of the precentral gyrus.[21] In patients with dementia, atrophy of the frontal or temporal cortex may be seen,[21–24] the atrophy being greatest in brains from patients with overlap ALS–frontotemporal dementia. In addition to these gray matter abnormalities, white matter reduction is also observed, particularly, but not exclusively, in the corticospinal tract.[14,25,26]

Microscopic

Microscopic changes include neuronal and axon loss. There is loss of myelinated axons in the lateral and anterior columns of the spinal cord and decreases in size of anterior horn of the spinal cord, best shown by myelin stains such as Luxol fast blue (**Fig. 1**A, B).[21] There is degeneration and loss of the large motor neurons in the anterior horn of the spinal cord, lower cranial motor nuclei of the brainstem, and Betz cells in the motor cortex, best seen with routine stains such as hematoxylin-eosin (H&E) (see **Fig. 1**C, D; **Fig. 2**A–F).[21,27–29] Morphometric studies of the spinal anterior horn have shown a global reduction of all neurons in the anterior horn, not just the large α motor neurons.[30] There is evidence of reduction in neuron size as well as loss and atrophy of nerve fibers. Other pathologic features of ALS include vacuolization, large empty

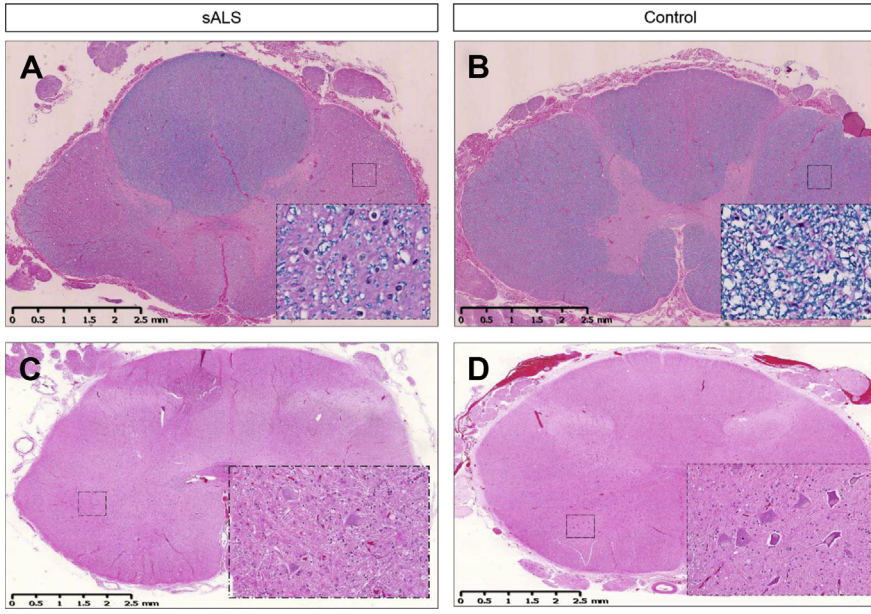

Fig. 1. ALS. Lateral sclerosis is shown in the thoracic spinal cord in SALS (*A*) and compared with control (*B*). Inserts show loss of myelin in the white matter tracts under higher power (20X). Loss of motor neurons is shown in the lumbar spinal cord in SALS (*C*) and compared with control (*D*). Inserts (40X) show motor neurons in anterior horns under higher power (40X) (Luxol fast blue with H&E [*A*, *B*]; H&E [*C*, *D*]). Low power views are 1X.