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Commentary: Amyotrophic Lateral Sclerosis and Myasthenia Gravis Overlap Syndrome: A Review of Two Cases and the Associated Literature

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A commentary on

Amyotrophic Lateral Sclerosis and Myasthenia Gravis Overlap Syndrome: A Review of Two Cases and the Associated Literature
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The recent paper by Tai et al. (1) is a timely reminder that age-related neurodegenerative diseases rarely exist in isolation, and that we should make every effort to use points of commonality to better understand the pathophysiology of these largely untreatable conditions. In their paper (1), the authors present two cases of amyotrophic lateral sclerosis (ALS) coexisting with myasthenia gravis (MG) and review the literature on this. They report that motoneuronal death in this rare syndrome can be preceded or followed by MG and conclude that the weight of evidence points toward a common neuromuscular defect operating in both diseases. This is important because the interdependence of motoneurones and their peripheral targets is well known. This was shown in the early studies of Hamburger (2, 3) and confirmed in more recent studies of the myotrophic and neuroprotective effect of muscle-derived molecules in experimental motoneuronal death and models of human motoneuronal diseases (4–6). Since MG is characterized by autoantibodies to the acetylcholine receptor at the neuromuscular junction (NMJ), Tai et al. (1) unsurprisingly implicate autoimmune damage at the NMJ in the pathogenesis of ALS. Further studies may show this may be the case, but we can broaden this concept to include failure of neuromuscular reciprocal interaction. This could include failure of motor axon and muscle to respond to trophic molecules due to reduced or aberrant receptor synthesis, impaired downstream signaling or axonal transport. Axon degeneration, from distal synaptic compartments, has been described as an early event in both human disease and animal models (7, 8). These observations support the "dying back" hypothesis by which the degeneration of the NMJ and associated muscle function precede the death of motor neurons and contributes to the disease process (7–9). Moreover, the notion of non-cell autonomous degeneration in ALS involves defects not just confined to the glial cells but retained by the muscle as well. ALS has been associated with alterations of energy homeostasis induced by mitochondrial muscle breakdown (10), and by trophic factors such as insulin-like growth factor-1 (IGF-1) and glial cell-derived neurotrophic factor that are secreted by skeletal muscle, and are known to stabilize the NMJ and thereby promote motoneuron survival (11, 12). A recent study of motor axonopathy induced in mice by overexpression of an inhibitory binding protein for IGF-1, led to the suggestion that a defect in well-known neurotrophic and myotrophic effects of IGF-1 might be common to both diabetic neuropathy and ALS (13). There is no doubt that disruption of the NMJ, seen as

fasciculation and motor unit enlargement is an early feature of ALS (14, 15), and associations between excessive motor activity or enlarged motor units and the development of ALS have been recognized (16). Thus muscles, similarly to glial cells, can promote a vicious cycle of energy impairment and lack of trophic factor release that interacting with other systems, when set in motion, amplify their own processes and may accelerate the development of ALS.

Whether disease primarily affects muscle or motoneurones is critical to disease management, but this progression may be an endpoint that reveals little about its origins. In this regard, the paper by Tai et al. (1) prompts us to reevaluate the role of the peripheral target in neurodegenerative diseases where attention has traditionally been focused centrally.

AUTHOR CONTRIBUTIONS

IJ wrote the initial draft. PL revised the initial draft and contributed further writing. Both the authors collected data from literature and revised the final manuscript.

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