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Update in Neuromuscular Disorders

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Neuromuscular diseases have been revealed as complex disorders with biological diversity. The classification of molecular subtypes of motor neuron disease, neuropathy, and neuromuscular junction disorders is necessary for the translation of current developments in basic science into emerging therapies. This review summarizes the recent advances in pathogenesis and new targeted therapies in amyotrophic lateral sclerosis and frontotemporal dementia (ALS-FTD), inflammatory neuropathies, and autoimmune myasthenia gravis (MG).

Since the discovery of the C9orf72 mutation in ALS-FTD, there have been numerous investigations to understand the pathogenic mechanism in these diseases. Two potential pathomechanisms, gain or loss of function, have been postulated. The current weight of the evidence suggests that gain-of-function from C9orf72 repeat expansions results in neurodegeneration and plays a primary role in the disease mechanism. This has important clinical implications for the development of targeted therapies such as antisense oligonucleotides.

The inflammatory neuropathies have diverse pathological mechanisms. Recently, nodal and paranodal elements are recognized as immunological targets in the inflammatory neuropathies. Breakdown of electrical integrity at these spots induce conduction block without other demyelinating features. These findings suggest that the traditional electrodiagnostic classification into axonal and demyelinating neuropathy may not always accurately reflect the underlying pathologic process. Although diagnoses of clinical syndrome are mainly made on phenotypes, serological tests are required to clarify immunopathological subtypes. A wide range of paraclinical tests for antibodies, growth factors, and cytokines have been recently developed for the diagnosis and management of inflammatory neuropathies.

Seropositive MG is heterogeneous, determined by autoantibodies to AChR, MuSK, Lrp4, or low-affinity AChR. Nowadays, a broad availability of antibody testing leads to an early diagnosis. In B-cell studies, long-lived plasma cells in bone marrow and spleen appear as the major contributors of anti-AChR antibodies and the new therapeutic targets. Indeed, treatments to remove these plasma cells, such as proteasome inhibitors, have proved feasibility in experimental autoimmune MG. MicroRNAs have been suggested as a biomarker in MG, because of their immune regulatory roles. MuSK-MG is biologically and clinically distinct to AChR-MG. MuSK forms the core of a protein complex in the postsynaptic membrane and maintains long-term homeostasis of neuromuscular junctions. Active immunization and passive transfer of MuSK-antibodies in animal models demonstrated decreased postsynaptic acetylcholine receptors, disrupted synaptic alignment, and reduced synaptic potentials. In MuSK MG, bulbar and respiratory muscles are particularly involved, which increases a rate of myasthenic crises. Plasma exchange and immunosuppressive agents, such as corticosteroids and rituximab, are most effective treatment in MuSK MG, whereas the cholinesterase inhibitors are less suitable option.

Key Words: Amyotrophic lateral sclerosis; C9orf72; Inflammatory neuropathies; Autoimmune myasthenia gravis

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