Muscle Channelopathies

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KEYWORDS

• Channelopathies • Ion channel • Nondystrophic myotonia • Periodic paralysis
• Congenital myasthenic syndrome

KEY POINTS

- Skeletal muscle channelopathies are rare heterogeneous disorders and include nondystrophic myotonia, congenital myasthenic syndrome, and periodic paralyses.
- Clinical diagnosis is confounded by marked phenotypic heterogeneity.
- Electrodiagnostic testing can aid in diagnosis, but genetic testing is confirmatory.
- Treatment options are few and not approved by the US Food and Drug Administration.

INTRODUCTION

Skeletal muscle ion channelopathies are rare disorders characterized by episodic and fluctuating symptoms, exacerbation by environmental factors, and frequently autosomal dominant inheritance patterns. However, there is major genotypic and phenotypic heterogeneity of ion channelopathies. For instance, a sodium channel mutation of the skeletal muscle can cause paramyotonia congenita (PMC), sodium channel myotonia, hyperkalemic periodic paralysis, or hypokalemic periodic paralysis. Myotonic disorders can similarly be caused by sodium channel or chloride channel defects. Skeletal muscle channelopathies, in particular nondystrophic myotonias (NDMs), represent some of the first known examples and best studied ion channelopathies.[1] This article reviews clinical features, diagnostic testing, pathophysiology, and treatment options in NDM, congenital myasthenic syndrome, and periodic paralyses.

NDM

NDM has a prevalence of less than 1 per 100,000.[2,3] NDM is caused by mutations in the skeletal muscle sodium (SCN4A) and chloride (CLCN1) channels and includes

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myotonia congenita (MC), PMC, hyperkalemic periodic paralysis with myotonia, and a diverse group of sodium channel myotonias.[2–9]

Clinical Features

The most characteristic symptom in NDM is muscle stiffness generated by voluntary movement. A brief voluntary contraction elicits a sustained burst of action potentials originating from the muscle fiber, which persists for several seconds after motor neuron activity has ceased. This sustained activity results in myotonia, or an involuntary delay in the relaxation of muscle contraction; patients describe this as stiffness.[4] Other commonly reported symptoms include transient or prolonged weakness, pain associated with myotonia, and fatigue. Environmental factors that may increase myotonia include pregnancy, dietary potassium, cold temperature, hunger, fatigue, and emotional stress; some of these have traditionally been thought to help distinguish some of the NDM subtypes.[10–13] Clinical manifestations may range in severity from severe neonatal myotonia with respiratory compromise[14] to milder late-onset myotonic muscle stiffness. Myotonic dystrophy type 2 can present with a pure myotonic phenotype that may be clinically indistinguishable from MC.[5]

MC

MC is the most common skeletal muscle channelopathy and is caused by a mutation in the CLCN1 gene encoding for the main skeletal muscle chloride channel ClC-1. MC may be inherited as an autosomal dominant (Thomsen disease) or recessive (Becker disease) trait, with a more severe phenotype in the latter.[5,15,16] Clinical heterogeneity within a family is common. These patients typically have hypertrophic muscles, action myotonia, and percussion myotonia.[17] Patients experience muscle stiffness that is most evident during rapid voluntary movements following a period of rest; stiffness improves with several repetitions of the same movement, a finding referred to as a warm-up phenomenon.[18] The most common site of stiffness is the legs, whereas the face is less commonly affected.[19] Patients with Becker disease classically have transient weakness that improves with exercise. This transient weakness is unique to MC and is not seen with PMC.[20]

PMC

PMC is autosomal dominant and is caused by mutations of the sodium channel SCN4A gene on chromosome 17. Cold-induced, prolonged, painful myotonia and episodic weakness are the hallmarks of PMC.[4,21–23] Paradoxic myotonia, or myotonia appearing during muscle activity and increasing with continued exercise, is associated with PMC. Facial stiffness and eye closure myotonia are more common, and paradoxic eye closure myotonia is typically exclusive to PMC.[19] Although myotonia typically lasts seconds or minutes, muscle weakness following prolonged exercise can last from several hours to 2 days in PMC[24]; this is in contrast with the transient weakness that can be seen in the recessive form of MC. Interattack weakness is common and some patients go on to require assistive devices such as a wheelchair or wheeled walker.[23] Paramyotonia is triggered by rest after exercise, fasting, and cold; these characteristics are also seen in hyperkalemic periodic paralysis, which is allelic with PMC.[25,26]

Sodium channel myotonias

The sodium channel myotonias (SCMs) include acetazolamide-responsive myotonia, myotonia fluctuans, and myotonia permanens. Common features include autosomal dominant inheritance pattern, absence of episodic weakness or cold sensitivity, and potassium aggravation; they are also known as potassium-aggravated myotonias.