# The Nondystrophic Myotonias

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**Summary:** The nondystrophic myotonias are a heterogeneous set of rare diseases that demonstrate clinical myotonia, electrical myotonia, or both. These disorders are distinguished from myotonic dystrophy type 1 (DM-1), the more recently described proximal myotonic myopathy/myotonic dystrophy type 2 (PROMM/DM-2), and proximal myotonic dystrophy (a variant of DM-2) by characteristic clinical features, lack of abnormal nucleotide repeat expansions in the DM-1 and DM-2 genes, lack of cataracts and endocrine disturbances, and absence of significant histopathology in the muscle biopsy. The present article reviews each of the nondystrophic myotonias by exploring the unique clinical features, electrodiagnostic findings, diagnostic criteria, gene mutations, and response to pharmacologic therapy. These diseases are divided into those with chloride channel dysfunction (the myotonia congenita disorders) and those with sodium channel dysfunction (paramyotonia congenita, potassium-aggravated myotonia, and hyperkalemic periodic paralysis with myotonia). The variants that occur in each of these conditions are commented on. The differentiating features of the nondystrophic myotonias are summarized, and their predominant clinical, electrodiagnostic, and genetic characteristics are tabulated. For a comprehensive review of pertinent research and studies with application to diagnosis and treatment of individuals with nondystrophic myotonic disorders, the present article is best read in the context of other articles in this issue, especially those on ion channel physiology (Cannon) and pharmacology (Conte-Camerino), and on hyperkalemic periodic paralysis (Lehmann-Horn). **Key Words:** Nondystrophic myotonia, Becker's disease, Thomsen's disease, myotonia levior, paramyotonia congenita, hyperkalemic periodic paralysis with myotonia.

## INTRODUCTION

Myotonia is an intrinsic disorder of muscle caused by defects in either ion channel or muscle membrane function. Clinically, myotonia in the individual muscle fibers summates to produce a prolonged time for relaxation after voluntary muscle contraction and external mechanical stimulation.[1] Patients with nondystrophic myotonia often describe their main symptom as a "painless stiffness" that occurs immediately after initiating a muscle contraction after a period of inactivity or rest. For example, suddenly climbing a flight of stairs after several minutes of sitting often serves as a clinical trigger.

Muscle action and percussion are effective methods of eliciting myotonia on physical examination. In action myotonia, a muscle continues to contract after use. Classically, the muscle action of myotonia produces an isotonic contraction. A patient is unable to release the grip after making a fist or after a strong handshake. Percussion myotonia, unlike action myotonia, is an abnormally prolonged muscle contraction after an abrupt external mechanical compression of a specific muscle. This is demonstrated by percussing a myotonic muscle with a reflex hammer. Any muscle can be tested this way; however, the thenar eminence and wrist extensor muscles are the ones most often evaluated.

Electrical hyperexcitability of individual muscle fibers is the fundamental alteration that underlies myotonia and causes the delay in muscle relaxation after contraction or percussion. Myotonic discharges appear in affected muscle fibers after stimulation or puncture with a needle electrode and leads to prolonged, spontaneous trains of muscle fiber action potentials that wax and wane in amplitude and frequency.[2] Frequencies may range from 20 to 150 Hz, with amplitudes of the potentials in the 10 to 1000 mV range. Myotonic discharges by definition last 500 ms or longer and should be identified in at least three areas of an individual muscle outside of an endplate region.[3] The sound produced by myotonic discharges during electrophysiological study is one of the most distinct in electromyography and has been likened to the sound of such things as a World War II dive bomber, a motorcycle motor, and a chain saw.[4] A myotonic potential

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appears on an EMG study as a positive wave or brief spike potential, typically occurring in trains of discharges.[2]

The majority of patients with myotonic disorders have both clinical and electrical myotonia. Some individuals have only electrical myotonia early in the course of their disease, with clinical myotonia occurring later in life. Historically, myotonias have been divided into two classes, based on the presence of progressive muscle wasting and weakness and on evidence of dystrophic changes from muscle histology. The dystrophic myotonic disorders consist of myotonic dystrophy type 1 (DM-1) or the classical Steinert's form of myotonic dystrophy, proximal myotonic myopathy/myotonic dystrophy type 2 (PROMM/DM-2), and proximal myotonic dystrophy (a variant of DM-2 with only electrical myotonia and more severe muscle wasting than typical DM-2). The remaining myotonic disorders without progressive weakness, wasting, and dystrophic histopathology fall into the diverse group of diseases known as the nondystrophic myotonias.[5]

The usual classification of nondystrophic myotonias includes myotonia congenita, paramyotonia congenita, potassium-aggravated myotonia, and hyperkalemic periodic paralysis with myotonia. All share a common etiology: ion channel dysfunction. These ion channel myotonic disorders have distinctive clinical findings that distinguish them not only from the dominantly inherited myotonic dystrophies but also from several other disorders that demonstrate myotonic discharges on EMG study.

There are other conditions that can produce electrical myotonia in the absence of prominent clinical myotonia and that often cause progressive weakness.[4] These include acid maltase deficiency, polymyositis, myotubular congenital myopathy, hypothyroidism, and malignant hyperpyrexia.[2,4] Occasionally, even severe denervation may produce non-sustained electrical myotonia.[2] Clinical and EMG myotonia may also be precipitated or unmasked by medication or toxin exposure. Such agents include clofibrate, propranolol, fenoterol, terbutaline, colchicine, penicillamine, diazocholesterol, monocarboxylic acids, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, cyclosporine, anthracene-9-carboxylic acid, and 2,4-dichlorophenoxyacetic acid.[2,4,6,7]

Other conditions, such as Schwartz–Jampel syndrome, stiff person syndrome, acquired generalized peripheral nerve hyperexcitability and hereditary familial episodic ataxia type 1 may mimic clinical myotonia; however, these are easily differentiated from the pure nondystrophic myotonias by their other clinical symptoms and the lack of characteristic electrodiagnostic features.[7,8]

Pure nondystrophic myotonias are divided into two groups: the chloride channelopathies and the sodium channelopathies. The forms of myotonia congenita originally described by Thomsen and by Becker, along with their variants, comprise the nondystrophic chloride channel myotonias. Paramyotonia congenita, hyperkalemic periodic paralysis, the three forms of potassium aggravated myotonia, and their variants comprise the nondystrophic sodium channel myotonias.[9]

Clinically, the nondystrophic myotonias can usually be differentiated based on their inheritance pattern, response to stimuli (including cold, potassium ingestion, exercise, and drug therapy), electrodiagnostic features, muscle histology, genetic mutations, and myotonia characteristics.[1] Clinical response to cold exposure or exercise testing can help in classifying nondystrophic myotonias, and it is useful to inquire about these responses before undertaking electrodiagnostic testing. Cold frequently worsens clinical myotonia, a feature that has been verified electrodiagnostically in paramyotonia congenita and acetazolamide-responsive myotonia.[10] If a patient has a history of cold-induced symptoms, the arm may be wrapped in a plastic bag and submerged in cold water prior to EMG to either augment or eliminate myotonic features. Detailed descriptions of protocols used previously for cold-water immersion and testing are available in the pioneering studies by Ricker and colleagues.[11–13]

Long or short exercise testing as a part of the electrodiagnostic evaluation of a patient with myotonia may also prove useful in differentiating those with nondystrophic myotonia from other myotonic disorders.[2] The long exercise test is implemented by having a patient maximally contract an intrinsic hand muscle for 4 to 5 min, with periods of relaxation every 15 to 20 s.[3] This exercise is followed by a series of recordings at set time intervals, to analyze the amplitude and duration of the evoked compound muscle action potential (CMAP). Similarly, short exercise testing requires 5 to 10 s of maximal isometric contraction of an intrinsic hand muscle followed by a series of recordings of evoked CMAPs at set time intervals.[3]

Both cold immersion testing and exercise testing have limitations in establishing the diagnosis of a nondystrophic myotonia. Limited studies are available to establish the reliability and reproducibility of either type of testing in the same individuals over time, and there are no studies in kindreds with known genetic mutations that have established the usefulness of cold immersion and exercise testing in family members with mild or no symptoms. There are many opportunities for future studies to investigate the relationships among various diagnostic test procedures, phenotypic manifestations, and specific gene defects.

Many specific point mutations in the genes for the skeletal muscle chloride and sodium channels have been identified in patients with nondystrophic myotonias. The relationship between these different mutations and the specific phenotypic manifestations both within a given

kindred and between different kindreds having the identical mutation still require clarification. The presence of a particular mutation in the chloride or sodium channel can strongly suggest that the individual carrying the mutation is at risk of developing symptoms, if not already showing clear manifestations of the disorder. Nonetheless, we still need to understand why some individuals within a kindred affected by a nondystrophic myotonia can have a mutation but manifest only mild or minimal symptoms throughout their lives. Many vital questions remain to be answered regarding genotype–phenotype relationships for the nondystrophic myotonias.

## THE CHLORIDE CHANNELOPATHIES

The clinical and electrodiagnostic features of the chloride channel nondystrophic myotonias are summarized in Table 1.

### Thomsen's myotonia congenita

Thomsen's disease is a hereditary disorder of muscle function caused by dysfunction of the skeletal muscle chloride channel. This condition was first described in the 1870s by the Danish physician, Dr. Asmus Julius Thomas Thomsen. Dr. Thomsen observed frequent prolonged tonic muscle contractions, emotional stress-induced muscle stiffness in all four extremities, muscle hypertrophy, and muscle stiffness triggered by cold exposure in both himself and his family members in association with an autosomal dominant inheritance pattern.[14]

The predominant features of Thomsen's disease are a painless, transient, muscle stiffness with a predilection for both the upper extremity and the facial muscles.[15] True muscle weakness is uncommon, as are other systemic features such as respiratory, cardiac, endocrine, and cerebral dysfunction.[16] Painless myotonia begins early in infancy or childhood, with symptoms initiated by muscle activation after rest.[16] As with many nondystrophic myotonias, stiffness is reduced through repetitive muscle contractions, thus producing the so called warm-up phenomenon. This warm-up effect is transient and diminishes after a few minutes of inactivity.[17] Emotional surprises, or cold temperatures, may transiently worsen stiffness, but unlike the case with paramyotonia congenita, true weakness is conspicuously absent after cold exposure.[14] The incidence of Thomsen's disease is approximately 2 out of 50,000.[10] In contrast to most of the sodium channel myotonias, potassium ingestion does not worsen the clinical symptoms of myotonia congenita; pregnancy can both worsen and initiate symptoms.[16,17]

On physical examination, true muscle hypertrophy occurs in the upper extremities, lower extremities, and facial muscles (given the nearly perpetual state of muscle contraction at these regions) in 1/3 of male patients and 1/10 of female patients.[16,18] These frequent muscle contractions often cause myotonia congenita patients to be quite strong and athletic appearing, with above-average muscle mass. Thomsen's patients have been found to be more involved in sports than their age cohorts.[18] Occasionally, selected muscle groups, such as the sternocleidomastoids and distal forearm muscles, may show marked atrophy.

Clinical myotonia is present at many muscle groups, but is most easily elucidated through grip testing, eye closure, and lid lag.[8] Patients with Thomsen's disease need monitoring of their joint range of motion, especially in childhood. Because of imbalance in force across joints, flexion contractures can develop at the elbows and ankles, and in some cases require surgery to lengthen the Achilles tendon. Paraspinal and proximal myotonia may also be troublesome; these are best detected by having the patient lie supine for several minutes, followed by an attempt to quickly obtain a sitting position.[8] Reflexes, cerebellar function, sensation, and strength are typically normal.[8]

The diagnosis of Thomsen's disease is obtained through a careful history and physical examination. Electrodiagnostic studies typically show diffuse myotonia in association with normal motor unit potential morphology and recruitment. The duration of myotonic bursts may increase during cold exposure.[16] Muscle irritability in the form of fibrillation potentials and positive waves can occur.[14] Single-fiber EMG can show a mild increase in jitter and blocking with a normal fiber density.[7] Repetitive nerve stimulation at 3 Hz can produce a decrement of up to 65% in the amplitude of the CMAP amplitude. This decrement begins later and has less of a plateau than that seen in myasthenia gravis.[14] When a faster rate of stimulation is used, a greater decrement is produced.[4] The CMAP amplitudes may decrease after focal exercise, a response opposite to that seen in Lambert–Eaton myasthenic syndrome. The long exercise test rarely affects the amplitude of the evoked CMAP of Thomsen's disease patients.[16,17] On short exercise testing, patients will have a variable decline in CMAP amplitude with recovery after 2 min.[16] The time to recovery of baseline function may worsen with age in affected patients.[3] Muscle histology is not needed for diagnosis. Laboratory testing typically shows mildly elevated creatine phosphokinase (CPK) levels; potassium levels can be normal, low, or elevated.[2,8,16] Otherwise, laboratory findings are unremarkable.

Prognosis is quite good in Thomsen's myotonia congenita, with no reduction in life expectancy.[14] Patients can expect no significant progression of symptoms during their lifetime, although blepharospasm can be disabling in some patients.[10,14] Social and cognitive regression do not occur, nor does significant occupational limitation.[14,18] The worsening of symptoms during preg-

**TABLE 1.** *Clinical and Electrodiagnostic Features of the Chloride Channel Nondystrophic Myotonias*

| | | Thomsen's Disease Variants | | |
|---|---|---|---|---|
| | Thomsen's Disease | Fluctuating Myotonia Congenita | Myotonia Levoir | Becker's Disease |
| **Clinical Myotonia** | Moderate: Generalized (upper extremity and face > lower extremity) | Fluctuating (mild to moderate): Generalized (lower extremity, ocular, and masticatory muscles commonly affected) | Mild to moderate: Generalized (predominantly grip) | Moderate to severe: Generalized (lower extremity> upper extremity) |
| **Age of Onset** | Early first decade | Late first decade | First decade to early second decade | Late first decade |
| **Inheritance** | Dominant | Dominant | Dominant | Recessive |
| **Chromosome** | Chromosome 7q | Chromosome 7q | Chromosome 7q | Chromosome 7q |
| **Potassium Sensitivity** | None | *None | *None | None |
| **Effect of Exercise** | Myotonia relieved | Myotonia relieved | *Myotonia relieved | Myotonia relieved |
| **Effect of Cold** | Can worsen myotonia | Worsening myotonia | None to minimal | Can worsen myotonia in hands and legs |
| **Paradoxical Myotonia** | No | No | No | No |
| **Warm Up Effect** | Yes | *Yes | *Yes | Yes |
| **Treatment** | Mexiletine, quinine, procainamide, acetazolamide | Mexiletine, quinine, procainamide, acetazolamide | Mexiletine, quinine, procainamide, acetazolamide | Mexiletine |
| **Other Provocative Stimuli** | Movement after prolonged rest, pregnancy, emotional surprise | Movement after rest, cold, pregnancy, fasting state, emotional stress | Movement after rest or maintenance of posture | Movement after rest or maintenance of posture |
| **Alleviating Factors** | Repeated exercise | * | * | Repeated exercise |
| **Episodic Weakness** | No | No | No | Variable: typically transient (lasting seconds) and proximal |
| **Progressive Weakness** | No | No | *No | Rare |
| **Muscle Hypertrophy** | Yes | No | No | Yes (mostly at the lower extremities) distal atrophy may also occur |
| **Pain** | *No | Yes | *No | Rare |
| **Nerve Conduction Studies** | Normal, repetitive stimulation: may see moderate decremental response | Normal, repetitive stimulation normal | *Normal | Decremental response to repetitive stimulation |
| **Electrical Myotonia** | Proximal and distal | Proximal and distal | Present | Proximal and distal |
| **Motor Unit Action Potentials** | Normal | * | * | Normal, occasionally myopathic |
| **Fibrillation Potentials** | * | * | * | * |
| **Electrodiagnostic Effect of Cold Exposure** | Increased myotonia duration | * | * | *Increased myotonia, some say no effect |

**TABLE 1.** *Continued*

| | Thomsen's Disease Variants | | | |
|---|---|---|---|---|
| | Thomsen's Disease | Fluctuating Myotonia Congenita | Myotonia Levoir | Becker's Disease |
| **Short Exercise Test** | Variable drop of CMAP amplitude with recovery over minutes | May show a CMAP decrement after short exercise | * | Reproducible large drop in CMAP with recovery over 2 minutes |
| **Long Exercise Test** | Minimal effects | * | * | Small drop in amplitude after exercise with recovery over 3 minutes |

*Sources:* Hudson et al.,[1] 1995; Preston and Shapiro,[2] 1998; Moxley,[5] 2004; Shapiro and Ruff,[16] 2002; Brown,[45] 1993; Ptacek et al.,[46] 1994; Fournier et al.,[47] 2004.
*Further evaluation needed to definitively determine result.

nancy typically abates after delivery.[19] Clinical myotonia may be reduced through activity modification and pharmacologic therapies.

### Becker's myotonia congenita

Becker's disease, or recessive generalized myotonia, is an autosomal recessive form of mytonia congenita also caused by dysfunction of the chloride channel. Becker's disease was named in honor of the researcher who first described it, in the 1970s.[14,17] Classically, it produces localized muscle hypertrophy, electrical myotonia, and clinical myotonia, with occasional associated persistent weakness. Compared with Thomsen's myotonia congenita, Becker's disease is more common, more insidious, and has initial symptoms that occur later in childhood. Becker's myotonia congenita may also be differentiated from Thomsen's disease by the presence of a slowly progressive weakness in some patients, by a pronounced hypertrophy of the muscles of the lower extremity, by occasional atrophy of selected distal muscle groups, and by the transient episodes of proximal muscle weakness that are common for most patients.[8,16]

As a rule, the periods of transient weakness in Becker's disease last only seconds to minutes and can be triggered by asking the patient to arise quickly after several minutes of supine rest. Exacerbating triggers of myotonia include cold exposure, prolonged muscular strain, menses, pregnancy, and emotional tension; accompanying pain is reported by 15% of patients.[18] In Becker's disease, 56% of patients (compared with 12% for Thomsen's disease) experience symptoms first in the lower extremity, before any upper extremity involvement.[18] For this reason, Becker's myotonia has been called the ascending myotonia congenita.

On physical examination, generalized myotonia is prominent, with some patients displaying weakness in the lower extremities. Patients may have marked difficulty upon attempting to ambulate from rest, mainly because of a combination of myotonic stiffness and transient weakness. Often a patient's gait improves after several steps, an effect attributed to the warm-up phenomenon.[18] In severe cases, lower extremity weakness persists despite warm-up activities.[18] Common myotonic physical findings include grip myotonia (96%), neck myotonia (83%), masticatory myotonia (76%), myotonia of the tongue (51%), and lid lag (52%).[18] Muscle hypertrophy occurs at the thighs, gluteal muscles, shoulder girdle, and calves, with occasional involvement of the trapezius muscles and proximal arms. Overall, severe muscle hypertrophy tends to be most prominent in male Becker's patients and, ironically, may correlate with a reduction in muscle strength. Other muscle groups, such as those of the forearms, hands, and anterior neck (sternocleidomastoids specifically) may be of normal girth or even atrophic on examination. If direct muscle palpation

is performed, 54% of patients will have multiple firm or tight muscle groups.[18] Reflexes may also be depressed, a feature most commonly seen in the lower extremities.[18] Coordination, tone, and cognitive function do not appear to be affected in Becker's myotonia congenita.

The diagnosis of Becker's disease is a clinical one, obtained through a careful history and physical examination; ancillary tests may help verify the diagnosis. Repetitive stimulation is often abnormal, with decrements in amplitude of the CMAP at frequencies as low as 2 Hz.[7] In contrast to Thomsen's disease, the long exercise test in Becker's myotonia may demonstrate a small decrement after exercise with complete recovery after 3 min.[16,17] On short exercise testing, Becker's patients typically experience a large decline in CMAP amplitude, a quick 2-min recovery, and a persistent decline in amplitude on subsequent trials.[16] Laboratory tests show a trend towards a more pronounced elevation in CPK than in Thomsen's disease; potassium levels can be normal, low, or elevated.[2,8,16]

Overall, the prognosis is good in Becker's myotonia congenita, with no reduction in life expectancy. Social problems and cognitive regression do not occur. Muscle weakness may vary from patient to patient.[14] Of those patients with persistent weakness, many notice it only upon extreme effort or sudden movement. Still others may develop a crippling disability from their lack of strength.[14,16,18] The most typical course in Becker's disease is a slow progression of symptoms until a patient reaches the third or fourth decade. Many patients then experience a stabilization of symptoms, although the occasional patient experiences either improvement or continued worsening of their symptomatology.[18]

### Myotonia levior and fluctuating myotonia congenita

Two additional forms of myotonia congenita have been described: myotonia levior and fluctuating myotonia congenita. Like Becker's and Thomsen's disease, both of these conditions are associated with a defect in the chloride channel. Whether these two entities are truly distinct disorders is under debate, and some propose that they are variants of Thomsen's disease.[1]

Myotonia levior is an autosomal dominant disease. Its clinical symptoms consist of stiffness, predominantly of the grip, that is provoked by prolonged rest. In contrast to Thomsen's disease, myotonia levior has milder symptoms, a later onset, and does not produce muscle hypertrophy. Pharmacologic therapies are identical for both diseases.[5,20]

Similarly, fluctuating myotonia congenita is an autosomal dominant disease that causes stiffness provoked by movement after rest, cold exposure, pregnancy, fasting, and emotional stress. In contrast to Thomsen's disease, this disorder is associated with lower extremity pain. The myotonia also fluctuates, and there are periods lasting weeks to days in which all clinical stiffness abates. This disorder affects the legs much more than the arms, and has a varying severity of stiffness occurring in the ocular and masticatory muscles.[5,21] On physical examination, there is no muscle hypertrophy, but percussion and action myotonia are common.[21] Electrodiagnostically, chloride channel fluctuating myotonia produces an abundance of myotonic discharges and a CMAP amplitude that decreases after brief exercise; there is a normal response to repetitive stimulation.[21]

### Pathogenesis and treatment of the myotonia congenita

The pathogenesis of the myotonia congenita disorders is not fully understood. All forms of myotonia congenita have dysfunction of chloride conductance and have mutations affecting the skeletal muscle voltage-gated chloride channel gene (*CLCN1*) at its chromosome 7q locus.[16] The responsible mutations of *CLCN1* alter the skeletal muscle chloride channel protein, ClC-1.[22] A reduction in chloride conductance occurs and leads to membrane hyperexcitability. Myotonia results, due to reduced chloride conductance across the transverse tubular system.[8,16]

In normal muscle, a high chloride conductance allows for fast repolarization of the t-tubules, largely eliminating recurrent depolarization.[5] In myotonia congenita, depolarization results in repetitive firing of the muscle fiber and subsequent myotonia.[5] There are a growing number of newly identified mutations in the *CLCN1* gene that can lead to Becker's myotonia and a lesser number of new mutations that cause Thomsen's disease. Eighty mutations have been detailed in a recent article on phenotypic variability in myotonia congenita.[17] One hypothesis for the fact that mutations at the same gene locus can cause both the autosomal recessive and the dominant disorders proposes that, in Becker's myotonia congenita, the chloride channel homodimer loses functionality through a mutation of both monomers, whereas in the dominant forms of the disease the mutant gene product interacts with the normal monomer to produce dysfunction.[15] Another theory suggests that dominant mutations affect the common outflow chloride channel (slow flow channel), whereas recessive mutations involve two faster flow entry gates.[8,23] Furthermore, some mutations are present in both recessive and dominant pedigrees, thus complicating the proposition that genetic mutations can be used as the sole classifier of disease.[17]

Symptomatic therapies for muscle stiffness are the mainstay of treatment of myotonia congenita patients. Many patients lack disability and do not request treatment. Antimyotonia drugs include mexiletine, quinine, procainamide, acetazolamide, lithium carbonate, tocainide, carbamazepine, and phenytoin.[24] These agents are thought to reduce membrane hyperexcitability by affect-

ing extracellular–intracellular ionic ratios.[14] Of these agents, mexiletine may be the best choice, based on its efficacy and relatively benign side-effect profile.[16,25] The starting dose of mexiletine in adult myotonia congenita patients is 150 mg twice daily, with a titration up to 300 mg three times as day as needed and tolerated.[16] Occasionally, longstanding stiffness may cause contractures at the heel cords and elbows of myotonia congenita patients.[8] In such cases, aggressive physical therapy with heel-cord stretching and with antimyotonic agents should be implemented to limit disability. Occasionally, tendon-lengthening surgery is necessary.

Medication use must be monitored closely in myotonia congenita patients. Malignant hyperthermia or worsening muscle stiffening have been reported with anesthetic or muscle relaxant use, and aggravation may occur with beta-antagonists such as propranolol.[14,17]

## THE SODIUM CHANNELOPATHIES

The clinical and electrodiagnostic features of the sodium channel nondystrophic myotonias are summarized in Table 2.

### Paramyotonia congenita

Paramyotonia congenita, also known as Eulenburg's disease, is an autosomal dominant inherited disease caused by dysfunction of the skeletal muscle sodium channel. This disorder was first described by Eulenburg in 1886 after noting an inherited cold-induced muscle stiffness in a family living in the Baltic Sea region.[26,27] Genetically, paramyotonia congenita has a high penetrance, with symptoms beginning in the first decade.[1]

The predominant feature of paramyotonia congenita is episodic cold- or exercise-induced muscle myotonia in the facial, lingual, neck, and hand muscles lasting minutes to hours.[8] Patients often complain of "tongue slowness" after eating ice cream, or a "frozen smile" after being exposed to cold temperatures. Facial stiffness may cause narrowing of the palpebral fissures, dimpling of the chin, and an alteration of facial expression.[24] Infants may have prolonged eye closures after episodes of crying or face washing with cool water.[16] In between episodes of stiffness, patients can have residual myotonia of the face, eyelids, and pharyngeal muscles.[28]

Unlike the majority of myotonic conditions, the stiffness associated with paramyotonia congenita worsens rather than improves with repeated muscle contractions.[5] This effect is most prominent in the ocular and grip muscles and is opposite to the so-called warm-up phenomenon. In the late teens and in adult life, the worsening muscle stiffness with exercise after exposure to cold can be followed by flaccid paralysis of the exposed and exercised muscles.[16,26] Other conditions that may trigger weakness in paramyotonia congenita include rest followed by exercise, potassium ingestion, and prolonged fasting.[26] Weakness may not develop for many minutes after a bout of exercise, and a 20-min lag may separate a period of weakness from its inducing exercise.[28]

On physical examination, paramyotonia congenita patients often have above-average muscle mass and strength. The classic physical feature of paramyotonia congenita is the inability to immediately open the eyes after repeated sustained eye closures. A patient's eyelids may also remain open after a prolonged upward gaze.[24] Percussion myotonia, hand-grip myotonia, and lid lag are commonly observed, although not as frequently as eyelid paramyotonia. Tendon reflexes, cerebellar function, and sensation are normal.[3] Paramyotonic stiffness and subsequent paralysis may be provoked by immersion of the hand in cold water for 15 min, followed by exercise.[8] A wash cloth soaked in cold water and placed over a patient's eyes may also produce symptoms.[24] Variation in the severity of disease manifestations occurs, even among family members with the same mutation.

The diagnosis of paramyotonia congenita is based on its clinical features. Other features may also help establish the diagnosis. Motor and sensory nerve conduction studies are normal. Five-hertz repetitive stimulation may produce a reduction in CMAPs.[7] Electrical myotonia is diffuse, and is most prominent in the distal muscles. Electrodiagnostic findings are markedly temperature dependent. As a limb is cooled, muscle irritability in the form of P-waves and fibrillations occurs and myotonia may worsen.[24] When temperatures drop below 28°C, fibrillation potentials dissipate. At temperatures below 20°C, myotonic discharges disappear and an electrically silent contracture occurs.[16] In some cases, an electrodiagnostic evaluation at room temperature may be entirely normal.[10]

During a short exercise electrodiagnostic test after cold exposure to the hand, there is a decline in amplitude of the CMAP. An hour or more may be required for the CMAP amplitude to return to baseline height.[16] During the long exercise electrodiagnostic test, a moderate amplitude decrement is apparent immediately and reaches a maximum at 3 min. Recovery often takes more than 1 h.[16] In some instances, a potassium challenge during exercise can cause dramatic focal weakness and EMG changes.[3] Single-fiber testing can demonstrate increased fiber densities, increased jitter, and occasionally blocking.[7] A muscle biopsy is not required for diagnosis.

Life expectancy is not limited in paramyotonia congenita, and episodes of stiffness typically do not worsen throughout a patient's lifetime.[16,29] Nevertheless, stiffness and episodic weakness in paramyotonia congenita patients can cause significant disability and functional limitations.

Paramyotonia congenita is caused by a mutation in the $\alpha$-subunit of the human skeletal muscle voltage-gated

**TABLE 2.** *Clinical and Electrodiagnostic Features of the Sodium Channel Nondystrophic Myotonias*

| | Paramyotonia Congenita | Hyperkalemic Periodic Paralysis with Paramyotonia | Myotonia Fluctuans | Myotonia Permanens | Acetazolamide-Responsive Myotonia | Hyperkalemic Periodic Paralysis with Myotonia |
|---|---|---|---|---|---|---|
| **Clinical Myotonia** | Mild to moderate: Face, hands, thighs | Moderate: Upper extremity > lower extremities | Fluctuating: Proximal > distal | Very severe: Proximal > distal | Painful and severe: Proximal > distal | Absent to moderate: Generalized |
| **Age of Onset** | First decade | First decade | First or second decade | First decade | First decade | First decade |
| **Inheritance** | Dominant | Dominant | Dominant | Dominant | Dominant | Dominant |
| **Chromosome** | Chromosome 17 | Chromosome 17 | Chromosome 17 | Chromosome 17 | Chromosome 17 | Chromosome 17 |
| **Potassium Sensitivity** | Mild | None to mild | Severe (myotonia, not weakness) | Probable | Severe | Severe |
| **Effect of Exercise** | Myotonia worsened | Myotonia worsened | Myotonia enhanced after 20 to 40 minute delay. Weakness does not occur. | Myotonia worsened | *Variable: occasionally mytonia is worsened | Weakness after delay, myotonia is relieved |
| **Effect of Cold** | Induced Myotonia, weakness may occur with prolonged exposure | Weakness (less triggering then in paramyotonia congenita) | No major effect | Variable, minor increase in myotonia | Minor increase in myotonia | May induce weakness |
| **Paradoxical Myotonia** | Yes | Yes | May occur in eyelids | No | Yes (eyelids) | Occasionally (eyelids) |
| **Warm Up Effect** | Variable | * | Variable | * | * | Yes |
| **Other Provocative Stimuli** | Rest followed by exercise (weakness), fasting state | Rest after exercise | Exercise-rest-exercise, suxamethonium | Exercise-rest-exercise, | Fasting, infection | Rest after exercise, fasting state |
| **Alleviating Factors** | Warming of muscles | * | * | * | Carbohydrates | Carbohydrates, exercise |
| **Periodic Paralysis** | Rare | Yes | No | No | No | Yes |
| **Paralysis trigger** | Cold, fasting, rest after exercise | Cold, rest after exercise | NA | NA | NA | Cold, fasting, rest after exercise |
| **Paralysis Ameliorator** | Warming, exercise | * | NA | NA | NA | Exercise, potassium |
| **Attack Length** | Minutes to days | 3-7 days | NA | NA | NA | Minutes to days |
| **Progressive Weakness** | Variable | * | No | *No | No | Variable |
| **Pain** | * | * | * | * | Yes | * |
| **Muscle Hypertrophy** | Minimal | *Minimal | Common | No | Occasionally | No |
| **Treatment** | Mexiletine, acetazolamide (in certain cases), HCTZ, mild exercise | Mexiletine, thiazide | Mexiletine, acetazolamide | Mexiletine, acetazolamide | Acetazolamide, mexiletine, glucose | Thiazide, mexiletine, acetazolamide, salbutamol, dichlorphenamide |

**TABLE 2.** *Continued*

| | Paramyotonia Congenita | Hyperkalemic Periodic Paralysis with Paramyotonia | Myotonia Fluctuans | Myotonia Permanens | Acetazolamide-Responsive Myotonia | Hyperkalemic Periodic Paralysis with Myotonia |
|---|---|---|---|---|---|---|
| **Nerve Conduction Studies** | Normal, repetitive stimulation may have a decremental response | * | Normal | Normal | Normal | Low CMAPs during attacks |
| **Electrical Myotonia** | Distal > proximal | *Generalized | Proximal and distal | Proximal and distal | Proximal and distal | Diffuse, exacerbated during attacks |
| **Motor Unit Action Potentials** | Normal | * | Normal | Normal | * | May be myopathic, normal, or show decreased recruitment |
| **Fibrillation Potentials** | Yes | * | Common | * | * | Yes |
| **Electrodiagnostic Effect of Cold Exposure** | Fibrillations and myotonic discharges disappear below 28 and 20 degrees Celsius respectively | *May worsen electrical myotonia | *No effect | *No effect | No effect | No effect |
| **Short Exercise Test** | CMAP drop with cold exposure with prolonged recovery over 1 hour | * | * | * | * | CMAP may increase after exercise or during an attack |
| **Long Exercise Test** | Moderate decrement after exercise, maximal at 3 minutes, recovery over an hour | * | * | * | * | May have CMAP increase (35%) followed by 50% drop over 20-40 minutes with slow recovery over an hour |

*Sources:* Hudson et al.,[1] 1995; Preston and Shapiro,[2] 1998; Moxley,[5] 2004; Shapiro and Ruff,[16] 2002; Brown,[45] 1993; Ptacek et al.,[46] 1994; Fournier et al.,[47] 2004.
*Further evaluation needed to definitively determine result. NA = Not available.

channel gene (*SCN4A*) on chromosome band 17q23.[16] The sodium channel has four regions of internal homology, each having at least six hydrophobic segments within.[30] Both the S3–S4 segments in domain 4 near the extracellular surface and the cytoplasmic loop between domains 3 and 4 may be affected, the latter being associated with the variant hyperkalemic periodic paralysis with paramyotonia.[1,8] The mutation of *SCN4A* in paramyotonia congenita is thought to cause an increased inward sodium current with muscle cooling and depolarization with alteration in fast inactivation.[16] Some hypothesize that the temperature dependence of slow inactivation in sodium channel function results in increased membrane excitability; however, the exact mechanism of how cold temperatures trigger paramyotonic symptoms has yet to be elucidated.[16]

Treatment of paramyotonia congenita is symptomatic. Patients are coached to avoid simultaneous exposure to both cold and exercise. Mexiletine can be used at dosages of 150 mg twice a day, with increases in dosage as needed. If nonprovoked spontaneous episodes of weakness are a prominent feature, hydrochlorothiazide can be added to mexiletine for additional benefit. Tocainide is an effective treatment, with less frequent but more serious side effects than mexiletine.[26] These side effects have led to removal of tocainide from the market. In cases of the variant hyperkalemic periodic paralysis with paramyotonia congenita, thiazide diuretics or acetazolamide are beneficial.[8] Interestingly, acetazolamide is effective in paramyotonia congenita, but only in cases in which cold exposure does not produce weakness.[16]

As with the chloride channel forms of myotonia congenita, several variants of paramyotonia congenita have been described. In one variant, hyperkalemic periodic paralysis with paramyotonia (also known as periodica paramyotonica), weakness is triggered less by cold exposure and more by isolated exercise or potassium ingestion, singly or in combination.[5,16] As with hyperkalemic periodic paralysis, episodes of weakness are common in the morning, and elevated potassium levels may occur. Clinically, hyperkalemic periodic paralysis with paramyotonia may be challenging to differentiate from the other hyperkalemic paralysis disorders.

Another variant of paramyotonia congenita, aptly named paramyotonia congenita without cold paralysis, has no associated cold paralysis. A feature of this condition is its tendency to severely affect women who are pregnant and men with increased muscle bulk.[26] The original description was by De Jong in 1955. The existence of this condition as a separate entity to paramyotonia congenita has since been debated.[31]

### The potassium-aggravated myotonias

Potassium-aggravated myotonia (PAM) is a term used to describe three somewhat similar phenotypes of nondystrophic myotonia caused by mutations in the skeletal muscle sodium channel. The diseases are myotonia fluctuans, myotonia permanens, and acetazolamide-sensitive myotonia.[9,15] The myotonia in these diseases is exacerbated by potassium ingestion. In contrast to paramyotonia congenita, PAMs do not worsen significantly after exposure to cold. In contrast to hyperkalemic periodic paralysis, PAMs do not have prominent weakness.[9]

#### Myotonia fluctuans

Myotonia fluctuans is an autosomal dominant disorder caused by at least three different point mutations in the skeletal muscle sodium channel. This disease was first described in 1990 in five family members over three generations.[32] Clinical features begin in the first or second decade and involve extraocular, bulbar, and limb stiffness exacerbated by potassium ingestion or by exercise.[24,29,33] Unlike the case with most other myotonias, the exercise-induced stiffness is dramatically worse only after a narrow window of time in which the patient rests. After 20 to 40 min of rest, a second bout of exercise produces severe myotonia and patients can occasionally become immobilized by their muscle stiffness. This phenomenon, called exercise-induced delayed-onset myotonia, is distinctly different from the paradoxical myotonia typical of paramyotonia.[33]

The five classic features of myotonia fluctuans are fluctuating myotonia of varying severity, the presence of the warm-up phenomenon, the absence of episodic weakness, the presence of increased myotonia after exercise or potassium ingestion, and the absence of cold-induced myotonia.[33]

Episodes of clinical myotonia vary spontaneously in severity, last from 30 to 120 min, and may be separated by prolonged periods of normality—thus prompting the name, myotonia fluctuans.[1,29] Handgrip myotonia is rare, but paramyotonia of the eyelids may occur.[7,10] Myotonia fluctuans is differentiated from paramyotonia congenita and from periodic paralysis, respectively, in that patients do not experience substantial stiffness with cold exposure and do not experience true weakness.[7,29] Potassium ingestion and exercise are the most common triggers and may cause immobilizing clinical myotonia. Some patients with myotonia fluctuans benefit from warm-up activities, whereas others experience an exacerbation of symptoms.[24] On physical examination, tendon reflexes, sensory systems, muscle function, and muscle bulk are all normal.[33]

Electrodiagnostic studies show fibrillation potentials, generalized myotonia, and normal nerve conduction.[1,7] Other diagnostic features may include CPK levels two to three times greater than normal, increased central nuclei, increased fiber size variability, and the presence of subsarcolemmal vacuoles during electromagnetic testing.[7]

Like many of the other nondystrophic myotonias, different point mutation in the *SCN4A* gene can cause myotonia fluctuans. Defects include substitutions of alanine for glycine 1306 on *SCN4A*, as well as abnormalities in exons 22 and 14 of the sodium channel gene.[24,29] Exon 22 encodes for the sodium channel protein containing the cytoplasmic loop, whereas exon 14 is thought to encode for the inner portion of the transmembrane and a part of the sodium channel cytoplasmic loop.[33]

Symptoms are improved with either mexiletine or acetazolamide.[24] Mexiletine has been found to improve subjective myotonia and normalize relaxation time. Some patients decline antimyotonia therapy, because their symptoms are infrequent and do not disturb their usual daily activities.[33] Rigidity and rhabdomyolysis may occur during surgery, although malignant hyperthermia does not appear to be a main feature of this condition.[33] Patients may also reduce their symptoms by avoidance of potassium-rich foods.

### Myotonia permanens

Myotonia permanens is a dominantly inherited, very rare, severe form of nondystrophic myotonia. It is thought to be caused by a G1306E mutation of the *SCN4A* gene on chromosome region 17q23~25 that causes an abnormality in the function of the voltage gate.[7,34] Clinical symptoms can be severe, often begin before age 10, and consist of a persistent clinical and electrical myotonia predominantly in the face, limbs, and respiratory muscles.[5] Myotonia may worsen with exercise or potassium exposure, but may or may not be affected by cold exposure.[7,34]

On physical examination, patients often have muscle hypertrophy, especially of the neck and shoulder muscles.[22] Pulmonary compromise may occur secondary to severe stiffness in the intercostal muscles provoking hypoxia and acidosis. One patient was described as having dwarfism, retarded motor dysfunction, a high-pitched voice, a short neck, a receded chin, an upturned nose, and a long philtrum; however, the absence of these findings in other patients with this condition suggests that these are not required features of this disease.[34] In addition, the features of this patient could easily be confused with a patient having Schwarz–Jampel syndrome. EMG studies in myotonia permanens show diffuse continuous myotonic discharges accentuated by needle displacement.[34] CPK levels may be elevated but nerve conduction studies and motor unit action potentials remain normal.[7]

Mild symptomatic relief is obtained with either mexiletine or tocainide.[1] Acetazolamide has also been found to reduce exercise-induced muscle cramps.[34]

### Acetazolamide-responsive myotonia

Acetazolamide-responsive myotonia (ARM), previously known as acetazolamide-responsive myotonia congenita, is a disorder of the sodium channel originally described in 1987. Patients have generalized myotonia triggered by potassium ingestion, cold, or fasting.[35] Clinical myotonia in ARM is often painful, only mildly affected by exercise, and usually relieved by the use of acetazolamide. The severity of symptoms progresses during childhood and involves the extraocular muscles, muscles of mastication, and the proximal limbs.[7] Periods of weakness or paralysis do not occur. Physical findings include percussion myotonia of the tongue, thenar eminence, and proximal upper extremity muscles, with paramyotonia present in the eyelids.[7] CPK levels may be normal or mildly elevated, with muscle histology occasionally showing generalized muscle fiber hypertrophy.[7,36]

Genetically, acetazolamide-responsive myotonia stems from a mutation of the $\alpha$-subunit of the voltage-gated sodium channel.[7] Electrodiagnostic studies demonstrate normal nerve conduction velocities and motor unit action potentials with prominent electrical myotonia.[7] In contrast to paramyotonia congenita, no electrically silent episodes of muscle rigidity occur.[35] Symptoms begin before age 10 and can be treated with dramatic improvement with acetazolamide (125 mg per day, titrated up to 250 mg three times a day as needed).[1] Mexiletine is also quite effective, if acetazolamide does not control the myotonia or if side effects, such as kidney stone formation, warrant a change in antimyotonia treatment. Close monitoring must be used during surgery to evaluate for rigidity and rhabdomyolysis.[5]

### Hyperkalemic periodic paralysis with myotonia

Hyperkalemic periodic paralysis, also known as adynamia episodica hereditaria, is a disease caused by a mutation in the sodium channel predisposing the individual to episodic attacks of weakness. Originally described in 1955, hyperkalemic periodic paralysis is an autosomal dominant disorder with nearly complete penetrance. Genetically, it is caused by a mutation in the $\alpha$-subunit of the human skeletal muscle voltage-gated sodium channel gene (*SCN4A*) on chromosome band 17q23.[16] When clinical and electrical myotonia are a feature of this disease, the condition is referred to as hyperkalemic periodic paralysis with myotonia.

Clinical symptoms begin in early childhood with attacks of weakness lasting minutes to hours that are triggered by cold temperatures, a fasting state, rest after exercise, emotional stress, or potassium supplementation.[16] Both clinical and electric myotonia are present in hyperkalemic periodic paralysis with myotonia. Electrical myotonia in hyperkalemic periodic paralysis is easily obtained during attacks of weakness, and clinical myotonia can be reduced with repeated exercise.[10,16] Episodes of true weakness may be generalized or focal in one limb. Attacks typically spare the facial and respiratory muscles.

Diagnosis is based on clinical features, although electrodiagnostic testing and DNA analysis may serve as confirmatory tests. Unfortunately, DNA testing is both expensive and limited in its availability to screen for all the mutations known to cause the disorder. This limitation exists likewise for other DNA testing for mutations in the sodium or chloride channel genes that cause nondystrophic myotonia. Baseline CPK levels in hyperkalemic periodic paralysis are usually elevated, as are serum potassium levels during attacks.

Treatment of hyperkalemic periodic paralysis with myotonia is the same as for hyperkalemic periodic paralysis. Frequent low-potassium meals, the avoidance of extensive exercise followed by rest, and the use of beta-adrenergic agonists for impending attacks may all provide benefit to the patient.[37] Daily use of carbonic anhydrase inhibitor therapies or thiazide diuretics may limit the severity and frequency of attacks. Both acetazolamide (beginning at 125 mg twice daily) and dichlorphenamide (beginning at 25 mg twice daily) have been found to be effective carbonic anhydrase therapies.[16,38] During occasions in which severe hyperkalemia occurs, potentially life-threatening elevations in potassium levels may be quelled with intravenous insulin and glucose under careful electrolyte and EKG monitoring. (For more information regarding hyperkalemic periodic paralysis please refer to the article by Lehmann-Horn in this issue.)

## ADDITIONAL CONSIDERATIONS

### Anesthesia in the nondystrophic myotonias

Care must be taken to prevent anesthesia-related complications in patients with nondystrophic myotonias. Propofol may induce myotonia, or cause a prolonged recovery time after its use in myotonia patients.[10] Depolarizing neuromuscular blocking agents should also be used with care. Suxamethonium has been reported to cause exacerbation of myotonic symptoms with subsequent difficulty in both intubation and ventilation.[10] Anticholinesterase drugs, clofibrate, and propranolol may precipitate myotonia, with the latter two having less marked clinical effects.[10]

### Specific pharmacologic treatments of the nondystrophic myotonias

Very few well-designed randomized clinical trials to determine the most efficacious pharmacologic therapies for the nondystrophic myotonias have been conducted. Treatment strategies are based on selective case reports, results from the myotonic dystrophy trials, clinical experience, and theoretical benefit. Perhaps the most promising antimyotonic medication is mexiletine. Mexiletine is a lidocaine derivative, sodium channel blocking, and class IB antiarrhythmic medication that is safe and effective in treating myotonic symptoms. Compared with other antimyotonic medications, it has an optimal ratio of efficacy to side effects.[25] It has been used in myotonia congenita, paramyotonia congenita, myotonia fluctuans, myotonia permanens, and myotonia fluctuans with reported benefit. Common side effects include rash, diarrhea, dyspepsia, lightheadedness, and tremor.[16]

Like mexiletine, tocainide is a lidocaine derivative, antiarrhythmic agent, and sodium current blocker that provides potent symptomatic benefit in patients with myotonia. In one study of paramyotonia congenita patients, tocainide was found to improve electrodiagnostic results and muscle stiffness with a maximal benefit felt after only 10 days of use.[39] Some patients during this study experienced light-headedness, headaches, and irritability from this medication. Tocainide has been used at dosages of 400 to 1200 mg a day in patients refractory to mexiletine. Unfortunately, tocainide is no longer available in many countries, including the United States. The side-effect profile of tocainide prevents both its widespread use and availability, given its potential for agranulocytosis, anemia, interstitial lung disease, and death.[7,16,26] If tocainide is used, frequent testing of liver function, and white blood cell counts (with platelets and differential analysis) should be implemented.

Acetazolamide, a carbonic anhydrase inhibitor, is an effective agent in myotonia congenita, hyperkalemic periodic paralysis, myotonia fluctuans, acetazolamide-responsive myotonia, and paramyotonia congenita patients with cold-independent weakness. Dosages generally begin at 125 mg twice a day, with titrations to 250 mg three times a day as needed. Side effects may include nephrolithiasis, nausea, anorexia, depression, mood instability, drowsiness, confusion, altered taste of carbonated beverages, vision impairment, rash, hepatic dysfunction, and paresthesias.[16,40] Liver function and complete blood count should be monitored with use of acetazolamide.

Hydrochlorothiazide is used in hyperkalemic periodic paralysis, hyperkalemic periodic paralysis with paramyotonia, and paramyotonia congenita patients with episodes of weakness not provoked by cold or exercise.[16] The exact mechanism of action is not clear, but may be secondary to the reduction of potassium levels.[16]

Many third-line antimyotonic agents exist. These include quinine, carbamazepine, phenytoin, diphenylhydantoin, procainamide, lithium, flecainide, and dantrolene. Quinine is thought to act on sodium membrane conductance.[41] The use of quinine in myotonia congenita dates back to 1937, although the extent of its effectiveness has never been established.[42] Carbamazepine is a sodium channel blocker best known for its use as an antiepileptic medication. In a case report of a 5-year-old Becker's myotonia congenita patient, carbamazepine was noted to reduce the time to climb a flight of stairs

from 15 s to 7 s.[43] Phenytoin, a sodium gradient altering antiepileptic medication, has also been historically used as a myotonia relieving agent in nondystrophic myotonic patients. Procainamide may reduce myotonia by acting on membrane sodium transport and permeability.[43] Unfortunately, lupus-like reactions, agranulocytosis, and cardiac arrhythmias may occur with this use of procainamide.[14] Lithium has been reported to improve physical function in a case report of a myotonia congenita patient.[44] The effects were only seen at levels greater than 2.3 mEq/L, and ultimately the medication had to be discontinued secondary to the risk of impairing renal function.[44] Flecainide is a class IC antiarrhythmic medication that has been reported to decrease myotonia in a family with a painful sodium channel congenital myotonia who failed therapies of both mexiletine and tocainide.[48] Lastly, dantrolene may reduce myotonia through its blocking of calcium release from the sarcoplasmic reticulum.[7] Seizures, confusion, and a life-threatening hepatotoxicity may occur with use of dantrolene, thus limiting its choice as a first line antimyotonic agent.

Despite the variety of antimyotonia agents available, it is likely that further research will develop and discover additional effective and safe agents. For now, more research is required to scientifically determine the optimal medication selection and dosage for each of the specific nondystrophic myotonias.

## CONCLUSIONS

The nondystrophic myotonias are an understudied group of treatable disorders that cause both clinical and electrical myotonia in the absence of dystrophic histological features. The nondystrophic myotonias share a common etiologic profile with the channelopathies, in that both sodium and chloride channel dysfunction provide a responsible pathomechanism. Despite a growing knowledge of the genetic underpinnings of these disorders, clinical and electrodiagnostic features remain paramount in diagnosing and differentiating these diseases. As a group, the nondystrophic myotonias remain an intriguing and underrecognized classification of disease.

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