Muscle Channelopathies: the Nondystrophic Myotonias and Periodic Paralyses

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Relationship Disclosure: Dr Statland has served as a consultant for Cytokinetics, Inc, regarding outcome measures for facioscapulohumeral muscular dystrophy and receives salary support from the Muscular Dystrophy Association Clinical Research Training Grant. Dr Barohn has served on the speaker's bureaus of Genzyme and Grifols; on the advisory boards of MedImmune, LLC, and Novartis Corporation; and as a consultant for NuFACTOR. Dr Barohn has received research support from Biogen Idec; BioMarin Pharmaceutical Inc; Cytokinetics, Inc; Genzyme Corporation; Knopp Neurosciences, Inc; Neuraltus Pharmaceuticals, Inc; the National Institute of Neurological Disorders and Stroke; the NIH; PTC Therapeutics; Sangamo BioSciences, Inc; Teva Pharmaceutical Industries Ltd; and the US Food and Drug Administration Office of Orphan Products Development.

Unlabeled Use of Products/Investigational Use Disclosure: Drs Statland and Barohn discuss the unlabeled use of carbonic anhydrase inhibitors for the treatment of hypokalemic periodic paralysis and mexiletine for the treatment of nondystrophic myotonia.

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ABSTRACT

Purpose of Review: The muscle channelopathies are a group of rare inherited diseases caused by mutations in muscle ion channels. Mutations cause an increase or decrease in muscle membrane excitability, leading to a spectrum of related clinical disorders: the nondystrophic myotonias are characterized by delayed relaxation after muscle contraction, causing muscle stiffness and pain; the periodic paralyses are characterized by episodes of flaccid muscle paralysis. This review describes the clinical characteristics, molecular pathogenesis, and treatments of the nondystrophic myotonias and periodic paralyses.

Recent Findings: Advances have been made in both the treatment and our understanding of the molecular pathophysiology of muscle channelopathies: (1) a recent controlled trial showed that mexiletine was effective for reducing symptoms and signs of myotonia in nondystrophic myotonia; (2) the mechanisms by which hypokalemic periodic paralysis leads to a depolarized but unexcitable sarcolemma membrane have been traced to a novel gating pore current; and (3) an association was demonstrated between mutations in a potassium inward rectifier and patients with thyrotoxic periodic paralysis.

Summary: The muscle channelopathies are an expanding group of muscle diseases caused by mutations in sodium, chloride, potassium, and calcium ion channels that result in increased or decreased muscle membrane excitability. Recognizing patients with channelopathies and confirming the diagnosis is important, as treatment and management strategies differ based on mutation and clinical phenotype.

Continuum (Minneap Minn) 2013;19(6):1598–1614.

INTRODUCTION

The muscle channelopathies are a rare group of neuromuscular disorders caused by mutations in virtually any ion channel, including chloride, sodium, calcium, and potassium channels (**Table 4-1**). Interestingly, although most mutations depolarize the sarcolemma membrane (either at rest, during activity, or in particular metabolic states), this depolarization can lead to a sarcolemma that is either more or less excitable.[1] The net effect on membrane excitability determines the clinical syndrome. Classically, the channelopathies are divided into the nondystrophic myotonias and the periodic paralyses.[2,3] Most of the channelopathies are sporadic or inherited in an autosomal dominant fashion (with the exception of recessive chloride channel myotonia) and tend to be highly penetrant, but they can show considerable clinical variability for a

given mutation, both between families and within a family. Most have onset in the first two decades of life and do not affect survival, but they can cause significant lifetime morbidity from associated symptoms of muscle stiffness, pain, or weakness. Indeed, a study evaluating the disease-related impact on quality of life in muscle channelopathies found similar overall impact compared to myotonic dystrophy.[4] Nondystrophic myotonias are connected by increased membrane excitability causing myotonia (ie, delayed relaxation after muscle contraction).[5,6] In myotonia, there is an increase in muscle membrane excitability whereby a brief voluntary contraction elicits a burst of action potentials that persists for several seconds after motor neuron activity has stopped. This produces delayed relaxation of muscle force (myotonia), which is perceived by patients as muscle stiffness. Patients with mutations in chloride channels (*CLCN1*) have myotonia congenita, and have a characteristic reduction in myotonia with repeated muscle contractions, a phenomenon called ''warm-up.'' Patients with mutations in sodium channels (*SCN4A*) have more diverse clinical presentations with muscle pain or weakness, myotonia that warms up, or myotonia that gets worse with repeated activity (ie, paradoxical myotonia). In addition, a severe neonatal form has been described that can have respiratory involvement.[6,7] This includes diseases such as the potassium-aggravated myotonias and paramyotonia congenita. On the far end of the spectrum is hyperkalemic periodic paralysis, which straddles the border between nondystrophic myotonias and periodic paralyses. Patients with this condition have both myotonia and episodes of paralysis. Other periodic paralyses include patients with mutations in sodium (*SCN4A*) and calcium (*CACNA1S*) channels who have characteristic episodes of flaccid paralysis associated with low serum potassium.[8] Andersen-Tawil syndrome is due to mutations in a potassium inward rectifier (*KCNJ2*) and is characterized by the clinical triad of episodes of flaccid paralysis, dysmorphic features, and cardiac conduction abnormalities.[9] This review describes the clinical characteristics, molecular pathomechanisms, and treatment strategies for nondystrophic myotonias and periodic paralyses, as well as recent advances in our understanding of the pathophysiology of periodic paralyses, new treatments for nondystrophic myotonias, and newly discovered mutations associated with thyrotoxic periodic paralysis.

KEY POINTS

- Classically, the muscle channelopathies are divided into the nondystrophic myotonias and the periodic paralyses.
- Muscle channelopathies can be due to mutations that cause a gain or loss of function in muscle ion channels, including sodium, potassium, chloride, and calcium channels.

ELECTRODIAGNOSTIC TESTING IN CHANNELOPATHIES

When a patient presents with concerns of episodic symptoms consistent with myotonia or paralysis, the initial workup traditionally has consisted of electrodiagnostic testing to help better characterize the sarcolemma membrane defect and guide confirmation by genetic testing. EMG can be normal, or it may show nonspecific small, polyphasic motor units seen in chronic myopathic processes or a characteristic pattern of spontaneous increased insertional activity in myotonia. In addition to EMG, two other provocative tests have been used to help guide genetic testing: a short and long exercise test.

In both short and long exercise testing, the forearm is stabilized and compound muscle action potentials (CMAPs) are recorded over the abductor digiti minimi after supramaximal stimulation of the ulnar nerve at the wrist.[10–13] Patients are then asked to exercise the abductor digiti minimi in isometric conditions (eg, distal fingers secured with tape). In short exercise

TABLE 4-1 Muscle Channelopathies Discussed in This Review

	Myotonia Congenita	Paramyotonia Congenita	Other Sodium Channel Myotonia	Hyperkalemic Periodic Paralysis
Gene	*CLCN1*	*SCN4A*	*SCN4A*	*SCN4A*
Chromosome	7q35	17q23	17q23	17q23
Clinical features	Myotonia	Myotonia, episodic weakness	Myotonia	Episodic weakness, myotonia
Triggers	Cold (some patients)	Cold	Potassium (some patients)	Potassium, rest after exercise
Acute treatment	n/a	n/a	n/a	Carbohydrate/ glucose
Chronic treatment	Mexiletine, phenytoin, procainamide	Mexiletine, phenytoin, procainamide	Mexiletine, phenytoin, procainamide, acetazolamide	Acetazolamide, dichlorphenamide
Exercise testing	Short exercise test (SET): Postexercise decrement, rapid return to baseline	SET: Postexercise decrement, facilitated by repetition or cold	SET: Often nondiagnostic	Long exercise test (LET): Postexercise decrement
Laboratory features	n/a	n/a	n/a	Ictal high potassium[c]
Commercially available genetic testing	Yes	Yes	Yes	Yes

[a] Calcium channel gene chromosome 1, sodium channel gene chromosome 17.
[b] Exact location not determined.
[c] Case reports of families with mutations associated with hyperkalemic periodic paralysis and normal potassium.

testing (**Figure 4-1**), the patient performs 10 to 12 seconds of muscle contraction, then CMAPs are recorded immediately after exercise and every 10 seconds for 1 minute. In long exercise testing (**Figure 4-2**), the patient performs repeated isometric contractions over 5 minutes, with 15 seconds of exercise alternating with 3 to 4 seconds of rest, and CMAPs are recorded every minute for up to 50 minutes after exercise. Characteristic patterns of postexercise changes in CMAP amplitude after short or long exercise testing are associated with different channelopathies. The short exercise protocol can be repeated or performed after cooling to facilitate responses and is most useful for nondystrophic myotonias. The long exercise protocol is most useful for periodic paralyses. As the cost of genetic testing decreases, the need for exercise testing to guide genetic testing may diminish.

NONDYSTROPHIC MYOTONIAS

Nondystrophic myotonias are clinically distinct from the dystrophic myotonias. The dystrophic myotonias (myotonic dystrophy types 1 and 2)

Hypokalemic Periodic Paralysis	Andersen-Tawil Syndrome	Thyrotoxic Periodic Paralysis	Central Core/ Malignant Hyperthermia
CACNA1S, *SCN4A*	*KCNJ2*	*KCNJ18*	*RYR1*
1q32, 17q23[a]	17q24	17[b]	19q13
Episodic weakness	Episodic weakness, premature ventricular contractions, ventricular tachyarrhythmia	Episodic weakness	Weakness, malignant hyperthermia, and rarely myotonia
Carbohydrates, rest after exercise	Rest after exercise, carbohydrates (some patients), potassium (some patients)	Thyrotoxicosis	Anesthesia
Potassium oral, rarely IV	Potassium (if attacks associated with hypokalemia)	Potassium, adrenergic blocking agents	IV fluids, support
Potassium, acetazolamide, dichlorphenamide, potassium-sparing diuretic	Potassium, (if attacks associated with hypokalemia), acetazolamide, dichlorphenamide, potassium-sparing diuretic	Treatment of thyrotoxicosis	n/a
LET: Postexercise decrement	LET: Postexercise decrement	LET: postexercise decrement (when symptomatic)	n/a
Ictal low potassium	Ictal high/low potassium	Ictal low potassium, elevated thyroid hormone	Elevated creatine kinase during malignant hyperthermia
Yes	Yes	No	Yes

are associated with significant progressive muscular weakness and other systemic organ involvement. On the other hand, nondystrophic myotonia usually presents with muscle stiffness as the primary symptom, in the absence of severe fixed weakness and muscle wasting. Nondystrophic myotonias are caused by mutations in chloride and sodium channels[14–18]; as a group, they are rare diseases and have an estimated worldwide prevalence of 1:100,000.[19] Nondystrophic myotonia is not life limiting, but patients often report muscle stiffness, pain, fatigue, and muscle weakness. In a recently completed natural history study of nondystrophic myotonias, all patients with sodium and chloride nondystrophic myotonia reported stiffness, and 53% to 82% reported painful stiffness, with an average intensity of 5 on a 9-point scale.[20] Diagnosis is based on clinical suspicion, electrodiagnostic testing, and genetic testing. Common to all is myotonia—delayed muscle relaxation following contraction—which can be both clinical and electrical. Electrical myotonia is characterized by spontaneous motor

KEY POINTS

- Electrical myotonia is characterized by a stereotypical waxing and waning action potential frequency and amplitude that, when amplified, produces a ''dive-bomber'' sound.
- Myotonia congenita can be inherited in an autosomal dominant or recessive fashion and is caused by mutations in the chloride channel gene (*CLCN1*).

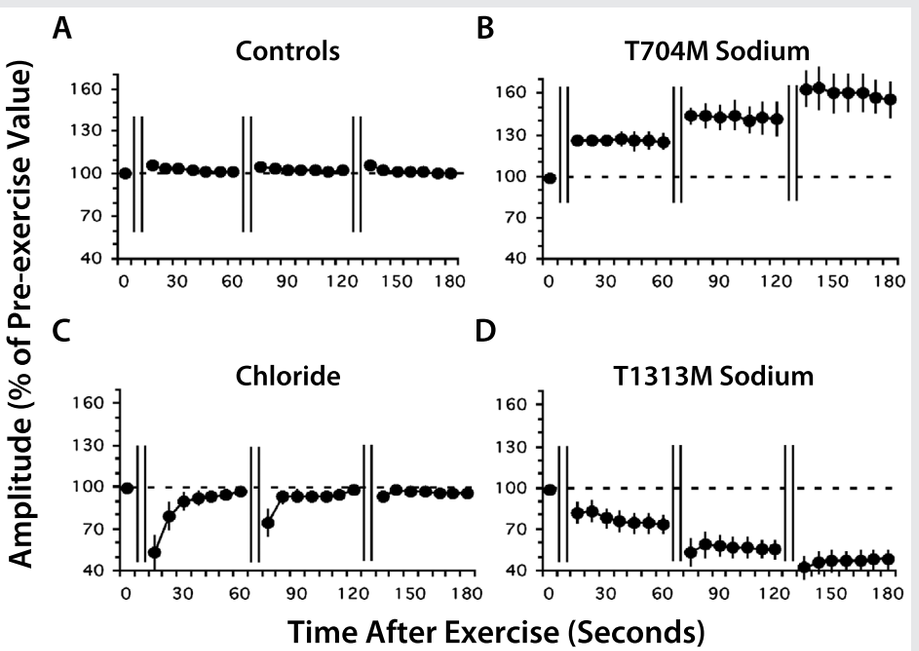

FIGURE 4-1 Short exercise test in nondystrophic myotonias. The pattern of changes in compound muscle action potential (CMAP) amplitude postexercise can suggest the underlying genetic mutation. Normal individuals have a fairly stable CMAP amplitude after short periods of exercise (*A*). Patients with hyperkalemic periodic paralysis may show a pattern of increasing CMAP amplitude (*B*), while patients with myotonia congenita show a characteristic rapid drop in CMAP amplitude which quickly returns to baseline (*C*), and paramyotonia congenita a pattern of dropping CMAP amplitudes facilitated by repetition or cold (*D*).

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unit firing, fibrillation potentials, or positive sharp waves, with a distinctive waxing and waning frequency and amplitude of motor unit firing producing a sound like a dive-bomber when amplified on a speaker or like a motorcycle accelerating or decelerating (**Supplemental Digital Content 4-1**, *links.lww.com/CONT/A110*). Clinical myotonia can be provoked by asking patients to close their fist or eyes tightly, then to open them as fast as possible. In addition, myotonia can be seen with percussion of the extensor digitorum communis or thenar eminence (**Supplemental Digital Content 4-2**, *links.lww.com/CONT/A111*). Treatment for all nondystrophic myotonias has been aimed at reducing sarcolemma excitability, although some sodium channel myotonias also respond to the diuretic acetazolamide.

Chloride Channel Myotonias

Myotonia congenita is due to mutations in the chloride gene (*CLCN1*) on chromosome 7q35, and prevalence varies by region between 0.2 and 7.3 per 100,000.[19,21] Both autosomal dominant (Thomsen disease) and recessive (Becker disease) types have been described. Myotonia usually begins in the first or second decade of life, with men more severely affected than women. Patients classically have a hypertrophic, muscular build and experience a characteristic improvement in myotonia with exercise (**Supplemental Digital Content 4-3**, *links.lww.com/CONT/A112*). Patients

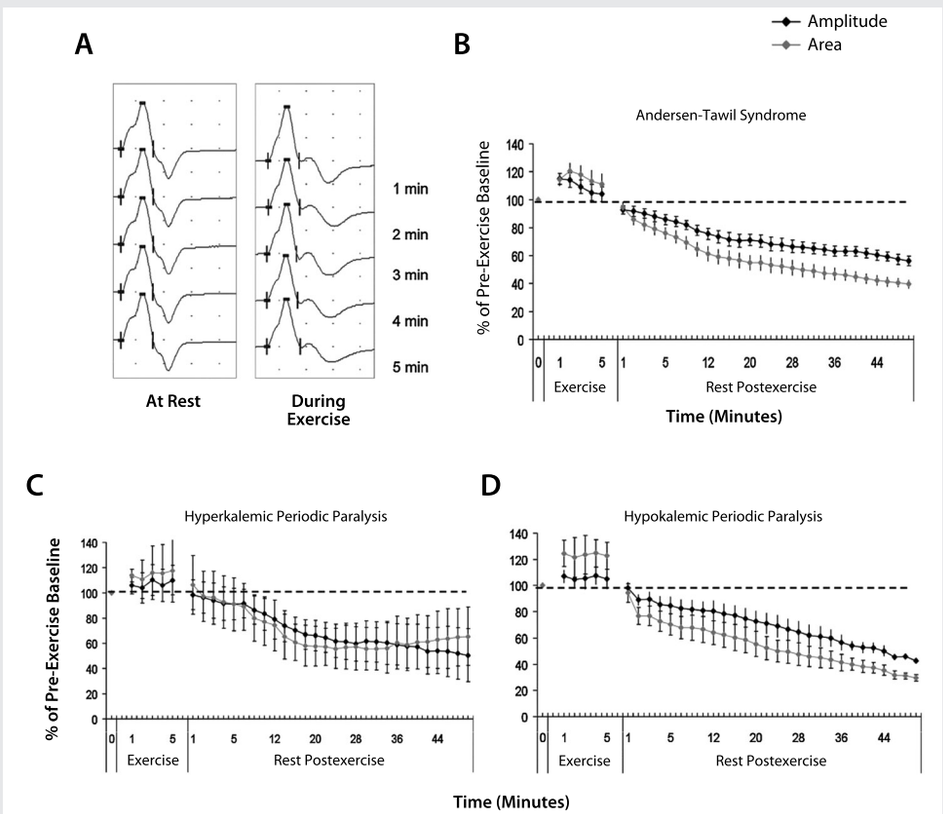

FIGURE 4-2 Long exercise test. Patients with periodic paralysis can show increases in compound muscle action potential (CMAP) amplitude during exercise with an often dramatic postexercise drop in CMAP amplitude, typically greater than 40% from baseline, which reaches its nadir between 25 and 30 minutes after exercise. *A*, Small afterpotentials during exercise in a patient with Andersen-Tawil syndrome. *B*, Andersen-Tawil syndrome, *C*, hyperkalemic periodic paralysis, and *D*, hypokalemic periodic paralysis.

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describe difficulty releasing a doorknob when opening a door, difficulty performing sports that require quick starts, or locking up of muscles with activity (**Case 4-1**). Patients do not describe frank weakness; however, patients with recessive myotonia congenita have more severe disease, with an earlier age of onset, and can experience a transient paresis at the onset of activity, which can be fairly dramatic and warms up with activity.[22] Virtually all patients with myotonia congenita report stiffness, with muscle pain and fatigue affecting quality of life.[4] Diagnosis is suggested in patients with a positive family history, myotonia on clinical examination and EMG, and absence of systemic features suggestive of myotonic dystrophy. Electrodiagnostic testing can show a characteristic drop in CMAP amplitude in the abductor digiti minimi after short periods of exercise, which rapidly returns to baseline (**Figure 4-1C**). This can be seen in one-half to two-thirds of patients with myotonia congenita but may be normal in patients with dominant disease.[13] The diagnosis is confirmed by genetic testing, which

KEY POINT

- Electrodiagnostic short exercise testing in myotonia congenita can show a characteristic postexercise decrement in compound muscle action potential amplitude that rapidly returns to baseline.

Case 4-1

A 27-year-old man presented for evaluation of painful stiffness. He had always been considered muscular; for as long as he could remember, people had asked him whether he worked out. Beginning in grade school, he noticed he had trouble with sports that require quick reflexes. When running races in track, he would freeze when the starting gun would go off. Even after warming up, if he overexerted himself he would remain sore for the rest of the day. He never thought of this as a problem. His father was also always muscular despite never working out. The patient noticed more pain with the stiffness as he grew older, and in high school these symptoms required him to alter his choice of sports or activities. He eventually sought treatment because he was no longer able to play basketball with his friends. At presentation, he denied any weakness or other systemic problems such as early cataracts, diabetes mellitus, or palpitations. On examination, he had normal strength but had both handgrip and percussion myotonia. His needle EMG showed characteristic myotonic discharges in all muscles tested. A short exercise test showed a characteristic drop in compound muscle action potential amplitude after short periods of exercise. Genetic testing for myotonic dystrophy type 2 was negative. Subsequent genetic testing revealed a point mutation in the muscle chloride channel gene (amino acid substitution from glycine to glutamine at codon 230). He was started on mexiletine 150 mg orally 3 times daily for his symptoms, with a significant reduction in his myotonia.

Comment. This patient has a fairly characteristic story, including the muscular phenotype in the absence of resistance weight training, and a positive family history. He also fairly characteristically did not seek help for this condition until the stiffness interfered with an activity (in this case, playing basketball), at which time a physician noticed the stiffness on his physical examination. The authors usually obtain a baseline ECG before initiating mexiletine therapy and start at 150 mg orally 3 times daily. If tolerated, the dose can be increased to 200 mg 3 times daily for symptomatic relief. The patients most responsive to mexiletine tend to be those with the most noticeable myotonia at rest.

is readily available commercially (*www.ncbi.nlm.nih.gov/gtr/*).

Myotonia congenita is caused by missense or nonsense mutations, insertions, or deletions scattered throughout the *CLCN1* gene on chromosome 7q35, with a possible "hot spot" (ie, area with a cluster of identified mutations) around exon 8.[23] Over 100 mutations have been reported. *CLCN1* is expressed as a dimer with two gating pores and is a major contributor to the resting membrane potential in skeletal muscle. Recessive mutations result in a loss of chloride conductance, whereas dominant mutations typically work through a dominant-negative effect on channel function. Regardless of the mutation, the pathogenesis of myotonia congenita is due to a reduction in chloride conductance. During repetitive muscle fiber firing, potassium accumulates in the T-tubule system. In myotonia congenita, the loss of chloride conductance is thought to make the sarcolemma unable to correct for the depolarizing influence of this buildup of potassium on the sarcolemma membrane, leading to depolarization and increased excitability.[1]

In general, treatments for myotonia congenita have been aimed at reducing the excitability of the muscle membrane in a nonspecific fashion. Not all patients require treatment; however, for patients with symptomatic myotonia, medications such as phenytoin, carbamazepine, or procainamide are useful but limited because of their side-effect profiles. Mexiletine, a type 1B cardiac antiarrhythmic medication with a high affinity for muscle sodium channels, was recently shown to significantly reduce muscle stiffness, weakness, pain, and fatigue in nondystrophic myotonias, and was well tolerated over the 4-week study period.[24]

Sodium Channel Myotonias

Mutations in the voltage-dependent muscle sodium channel (*SCN4A*) gene on chromosome 17q23 cause a diverse group of muscle conditions that run the spectrum from (1) muscle pain with minimal myotonia, to (2) myotonia and muscle stiffness difficult to distinguish from myotonia congenita, to (3) paradoxical myotonia with weakness, to (4) frank paralysis. The clinical phenotype appears to at least partially relate to the degree of anomalous current in the mutated channel, although considerable variability in clinical expression even within a given family can be seen.[1] All of the sodium channel myotonias are inherited in an autosomal dominant fashion, with onset typically in the first decade of life, generally considered earlier than chloride channel myotonias. In a recent nondystrophic myotonia natural history study, the authors found considerable overlap in symptoms between patients with chloride mutations and sodium mutations; that said, eye-closure myotonia was more common in sodium mutations (75% versus 25% for chloride), and paradoxical eye-closure myotonia was only seen in participants with sodium mutations (around 50%).[20] A clinical distinction is often made between patients with paramyotonia congenita and other sodium channel myotonias, including the potassium-aggravated myotonias (acetazolamide-sensitive myotonia, myotonia fluctuans, and myotonia permanens). Paramyotonia congenita has a prevalence of approximately 1:250,000 and is characterized by myotonia that worsens with activity or in cold weather (**Supplemental Digital Content 4-4**, *links.lww.com/CONT/A113*).[18] Patients may describe their body freezing up when jumping into a cold pool or being unable to open their eyes after sneezing (**Case 4-2**) (**Supplemental Digital Content 4-5**, *links.lww.com/CONT/A114*). Patients can describe episodes of weakness associated with worsening myotonia that last variable periods of time, and up to one-third of patients can show nonspecific myopathic changes on muscle biopsy.[8] The potassium-aggravated myotonias, as the name suggests, tend to be sensitive to potassium-loading or potassium-rich foods but typically do not have cold sensitivity or weakness. As the names imply, acetazolamide-responsive myotonia has symptoms that respond to acetazolamide[25]; myotonia fluctuans can have dramatic fluctuations in the severity of myotonia, with a delayed increase in muscle stiffness approximately 20 minutes after exercise[26]; and myotonia permanens can cause severe, persistent myotonia.[27]

Considerable phenotypic overlap exists between hyperkalemic periodic paralysis (discussed separately) and paramyotonia congenita. Although many sodium channel mutations show no changes on electrodiagnostic short exercise testing, patients with paramyotonia congenita show a characteristic pattern of decreasing motor unit

KEY POINTS

- Mexiletine was shown to improve symptoms and signs of myotonia in nondystrophic myotonias.
- Mutations in the sodium channel gene (*SCN4A*) cause a spectrum of clinical diseases from myotonia to paralysis and include diseases such as paramyotonia congenita, potassium-aggravated myotonia, and hyperkalemic periodic paralysis.

KEY POINTS

- Electrodiagnostic short exercise testing in paramyotonia congenita shows a characteristic postexercise decrement in compound muscle action potential amplitude that is facilitated by repetition or cold.
- The periodic paralyses are associated with mutations in the sodium channel gene *SCN4A*, the calcium channel gene *CACNA1S*, and potassium inward rectifier gene *KCNJ2*.

Case 4-2

A 21-year-old woman presented for evaluation of stiffness. She first noticed that her body would freeze up at 8 years old, when she swam in cold water. In addition, she noticed that in cold weather she would often become stiff and achy. Sometimes after sneezing, especially if she sneezed more than once, she was unable to open her eyes. Once in high school, after a particularly bad episode of pain and stiffness, she felt weak for a whole week. Her mother, aunt, and first cousin all had stiffness and achiness when swimming in cold pools. Her aunt also had many episodes of weakness, which seemed to be brought on by cold weather or when she ate potassium-rich foods. On examination, she had mild symmetric proximal weakness (she had to bend forward when getting up from chairs) and prominent myotonia, which worsened with repetition. Genetic testing revealed a mutation in the *SCN4A* gene (T1313M) consistent with a diagnosis of paramyotonia congenita. She tried mexiletine, which helped when she was having severe bouts of stiffness, but only used it on an as-needed basis.

Comment. This patient's family history demonstrates the overlap in symptomology between paramyotonia congenita and hyperkalemic periodic paralysis, with some family members describing attacks of paralysis sensitive to potassium. She also described the classic worsening of her symptoms with cold weather.

amplitude after short courses of exercise in the abductor digiti minimi, which is exacerbated by repetition or cold (**Figure 4-1D**). This electrodiagnostic pattern after cooling occurs in up to two-thirds of all patients with paramyotonia congenita.[10,13] Similar to chloride channel myotonias, the diagnosis is confirmed by genetic testing.

Over 50 missense mutations in the sodium channel gene (*SCN4A*), with a possible clustering around exons 22 and 24, are associated with the sodium channel myotonias. Most mutations are considered gain-of-function mutations causing either a delay in inactivation or enhanced activation of sodium channels. In each instance, this produces anomalous inward sodium current, which during muscle fiber firing tends to further depolarize the sarcolemma.

Treatment for sodium channel myotonias is similar to treatment for chloride channel myotonias, with few exceptions. Some sodium channel myotonias can have a good response to acetazolamide. In a recent randomized control trial of mexiletine, 35% of the participants had sodium mutations. Post hoc subgroup analysis revealed no differences between participants based on underlying mutation, suggesting mexiletine was effective for symptoms of muscle stiffness in both groups; however, the study was not powered to detect differences based on mutation.[24]

PERIODIC PARALYSES

The periodic paralyses have been associated with mutations in the sodium channel gene *SCN4A*, the calcium channel gene *CACNA1S*, or the potassium channel gene *KCNJ2*, and need to be distinguished from other secondary causes of episodic paralysis (**Table 4-2**[28]). Common to all the periodic paralysis diseases are episodic attacks of flaccid muscle weakness, typically associated with changes in extracellular potassium during attacks (high or low), with normal potassium between attacks.[5,8] Symptoms typically start before 20 years of age and

TABLE 4-2 Secondary Causes of Periodic Paralysis

▶ **Hypokalemic**
Thyrotoxic
Primary hyperaldosteronism (eg, Conn syndrome)
Renal tubular acidosis (eg, Fanconi syndrome)
Juxtaglomerular apparatus hyperplasia (eg, Bartter syndrome)
Gastrointestinal potassium wastage
Villous adenoma
Laxative abuse
Pancreatic non–insulin-secreting tumors with diarrhea
Nontropical sprue
Barium intoxication
Potassium-depleting diuretics
Amphotericin B
Licorice
Corticosteroids
Toluene toxicity
p-Aminosalicylic acid
▶ **Hyperkalemic**
Addison disease
Hypoaldosteronism
Excessive potassium supplementation
Potassium-sparing diuretics
Chronic renal failure

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can be triggered by certain foods (carbohydrates or potassium-rich foods) or rest after exercise. Although the common clinical feature is flaccid paralysis, electrophysiologically depolarization of the sarcolemma membrane occurs, causing sodium channels to switch into an inactive configuration. Muscle biopsies can show chronic myopathic changes, vacuoles, or tubular aggregates (**Figure 4-3**,[29] **Figure 4-4E**).[8] Electrodiagnostic exercise testing shows a characteristic drop in CMAP amplitude after sustained periods of exercise in the abductor digiti minimi, which typically reaches its nadir around 25 to 30 minutes after exercise; the sensitivity of this test is generally considered high, with around 80% showing a decrement greater than 40% after exercise (**Figure 4-2**).[11,13] In all disorders, treatment with carbonic anhydrase inhibitors (dichlorphenamide or acetazolamide) can help decrease the frequency and severity of paralytic episodes.[30]

Hyperkalemic Periodic Paralysis

Hyperkalemic periodic paralysis is on one end of a spectrum of disorders associated with mutations in the *SCN4A* gene on chromosome 17q23.[15,31] The prevalence of hyperkalemic periodic paralysis is less than 1:100,000, and patients typically become symptomatic in the first decade of life. Attacks of weakness are usually considered shorter than hypokalemic periodic paralysis, lasting minutes to hours, at a frequency of around 16 per month. Attacks are precipitated by fasting, rest after exercise, or ingestion of potassium-rich foods or compounds. During attacks, patients are areflexic with normal sensation, and cardiac and respiratory muscles are not typically involved. Traditionally, serum potassium levels greater than 5 mmol/L during attacks, or increases of 1.5 mmol/L during attacks, define hyperkalemic periodic paralysis; however, the serum potassium level may or may not be increased during the attack, and therefore a more appropriate term may be potassium-sensitive periodic paralysis. Strength is generally normal between attacks, but some patients can have mild fixed limb-girdle weakness. Some families with potassium-sensitive periodic paralysis also have either myotonia or paramyotonia. Episodes of

KEY POINT

- Carbonic anhydrase inhibitors can decrease the frequency or severity of paralytic episodes in all of the periodic paralyses.

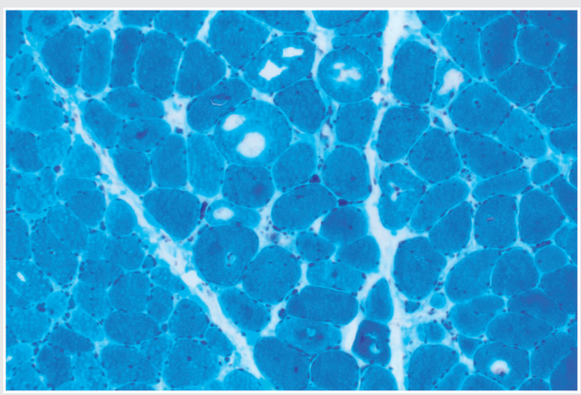

FIGURE 4-3 Muscle biopsy of a patient with hypokalemic periodic paralysis showing central vacuoles in various stages of development. Also note chronic myopathic changes, including variability in fiber size, rounded fibers, and central nuclei.

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weakness are rarely serious enough to require acute therapy; oral carbohydrates or glucose may improve weakness. Treatment options to prevent attacks include acetazolamide, dichlorphenamide, thiazide diuretics, and preventive measures such as a low-potassium, high-carbohydrate diet and avoidance of fasting, strenuous activity, and cold.[32]

Hypokalemic Periodic Paralysis

Approximately two-thirds of patients meeting clinical criteria for hypokalemic periodic paralysis turn out to have mutations in one of two genes: the calcium channel gene *CACNA1S* on chromosome 1q32 and the sodium channel gene *SCN4A* on chromosome 17q23.[2,32] Hypokalemic periodic paralysis affects approximately 1:100,000

KEY POINTS

- Testing for hyperkalemic periodic paralysis should be considered in patients who describe episodes of paralysis and have myotonia on EMG.
- Approximately two-thirds of patients who meet clinical criteria for hypokalemic periodic paralysis will have mutations in the calcium channel gene *CACNA1S*, or less frequently the sodium channel gene *SCN4A*.

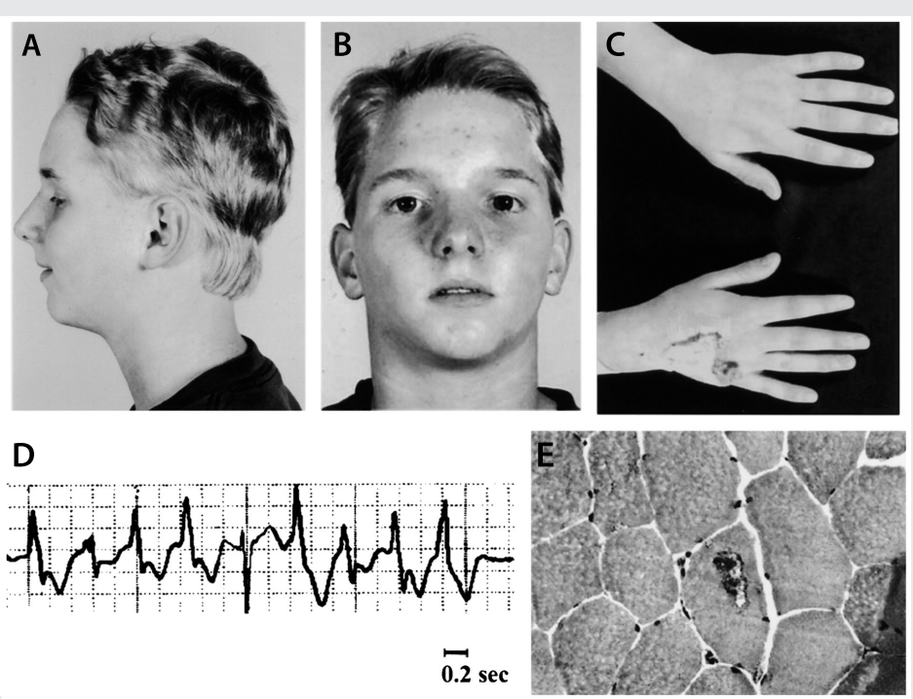

FIGURE 4-4 Andersen-Tawil syndrome. Patients show characteristic dysmorphic features including low-set ears (*A*), micrognathia (*A, B*), hypertelorism (*B*), and clinodactyly of the fifth digit (*C*). ECG can show a characteristic polymorphic ventricular tachyarrhythmia (*D*). Muscle biopsy can show tubular aggregates (*E*).

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people, with onset before 20 years of age, with the highest frequency of attacks between 15 and 35 years of age and attack frequency decreasing thereafter. Patients experience attacks of variable severity, from mild weakness to outright paralysis, occurring at a frequency of around seven to nine episodes per month, each lasting from hours to days.[8] Carbohydrate-rich foods, stress, alcohol, and rest after exercise can trigger attacks, and potassium levels during attacks can drop to less than 3.0 mmol/L. Transient elevations in serum creatine kinase during attacks are often seen, and patients may develop fixed limb-girdle pattern weakness later in life. A vague prodrome of stiffness or heaviness in the legs can occur, and if the patient performs mild exercise, a full-blown attack may be aborted. Rarely, ocular, bulbar, and respiratory muscles can be involved in severe attacks.

Interestingly, electrophysiologic studies failed to demonstrate increased conductance through either mutated calcium or sodium channels in hypokalemic periodic paralysis. Researchers were recently able to demonstrate an anomalous gating pore current in both calcium and sodium mutations, and mouse models for both have been created. During rest, these currents are small and have little effect on the cell. When in the setting of low extracellular potassium, the gating pore current increases out of proportion to the potassium inward rectifier channel's ability to correct, creating sustained depolarization and transition of sodium channels to an inactive configuration.[33–35]

Treatment for acute attacks of hypokalemic periodic paralysis consists of potassium, typically given orally (10 mEq to 20 mEq can be given every 15 to 30 minutes over 1 to 3 hours, not to exceed 200 mEq in a 24-hour period); if the patient is unable to take potassium orally, IV potassium should be mixed with 5% mannitol instead of glucose or sodium chloride, as these can precipitate attacks (35 mEq potassium in 1 L 5% mannitol, run at 250 mL/hour, and not to exceed 200 mEq in 24 hours). Patients are instructed to maintain low-carbohydrate and low-sodium diets and take potassium salt supplementation (typically 10 mEq to 20 mEq potassium per dose up to 3 times daily, with goal of maintaining serum potassium concentration of approximately 4 mEq/L). Attack frequency and severity can be reduced by the use of carbonic anhydrase inhibitors (acetazolamide or dichlorphenamide) or potassium-sparing diuretics. Recently, researchers were able to both abort and prevent attacks of muscle weakness in low-potassium baths in a mouse model of sodium channel hypokalemic periodic paralysis, using the high-potency loop diuretic bumetanide, through its antagonism of a sodium-potassium-chloride cotransporter; however, clinical trials will be required to determine whether this is safe for use in people.[36]

Andersen-Tawil Syndrome

Andersen-Tawil syndrome is characterized by the clinical triad of (1) episodic flaccid muscle weakness in the setting of high, low, or normal potassium; (2) ventricular arrhythmias and prolonged QT interval; and (3) dysmorphic features (**Case 4-3**). Patients are short statured with any combination of low-set ears, ocular hypertelorism, broad nasal root, small mandible, fifth-digit clinodactyly (abnormally bent or curved finger), and syndactyly (digits joined at the base) of the second and third toes. Cardiac arrhythmias consist of bidirectional, polymorphic, and multifocal ventricular tachyarrhythmia and premature ventricular contractions; however, sudden cardiac death is rare.[9] Muscle biopsy can show

KEY POINTS

- The pathomechanism of hypokalemic periodic paralysis has been traced to an anomalous gating pore current in both calcium and sodium mutations.
- Andersen-Tawil syndrome is related to a mutation in a potassium inward rectifier (*KCNJ2*) and is characterized by episodes of flaccid paralysis, cardiac conduction abnormalities, and dysmorphic features.

chronic myopathic changes and tubular aggregates (see **Figure 4-4**).

Andersen-Tawil syndrome was traced to a mutation in a potassium inward rectifier (*KCNJ2*, Kir 2.1) on chromosome 17q23, found in approximately 60% of patients.[2,9] The potassium inward rectifier helps set the sarcolemma resting potential, and mutations cause a loss of function and decreased potassium conductance, causing membranes to become depolarized and the sodium channel to switch to an inactive state.

Treatment for Andersen-Tawil syndrome consists of a multidisciplinary team approach. A yearly ECG and Holter monitor are recommended, as well as consideration for an implantable defibrillator for unexplained syncopal episodes associated with cardiac arrhythmias. If patients are hypokalemic during episodes of paralysis, potassium supplementation can be used. Drugs that prolong the QT interval should be avoided. Similar to the other periodic paralyses, carbonic anhydrase inhibitors can decrease the frequency or severity of paralytic attacks.

OTHER CHANNELOPATHIES

Thyrotoxic Periodic Paralysis

Thyrotoxic periodic paralysis is a unique disease that requires both environmental (thyrotoxicosis and hypokalemia) and genetic susceptibility for paralytic attacks to occur.[37] Thyrotoxic periodic paralysis is the most common form of periodic paralysis, affecting approximately 0.1%

Case 4-3

A 10-year-old boy presented for evaluation after an episode in which he seemed to pass out. He had always been short for his age, and when he was 6 years old, he developed his first attack of paralysis, which occurred when he first woke up in the morning. His weakness did not completely resolve for 3 days, and his mother did not feel that he was back to normal for a week. His mother stated that he had been evaluated at that time, and the only abnormality was a potassium level of 2.8 mmol/L. She noticed that he had attacks of weakness after eating certain foods (for example, a large plate of spaghetti), so she cut these foods out of his diet. His doctor found a long QT interval on ECG, with a U wave. Although he was not weak, his doctor noticed his short stature, low-set ears, pointed chin, and broad base to his nose; in addition, his second and third toes appeared to come off a common origin. The patient was referred to a neuromuscular specialist who found a mutation in the potassium channel gene (*KCNJ2*) consistent with a diagnosis of Andersen-Tawil syndrome. He was also referred to a cardiologist for evaluation with a Holter monitor. On review of his family members, his father also was short in stature, with a long QT interval on ECG.

Comment. This patient demonstrates all of the classic features of Andersen-Tawil syndrome. His episodes of paralysis occurred in the setting of low potassium, but Andersen-Tawil syndrome patients can have episodes of paralysis with low, high, or normal potassium. In addition, patients often have family members who only have one or two of the classic clinical triad, but genetic testing is warranted in suspected family members because of the potential cardiac complications of Andersen-Tawil syndrome. This patient responded well to potassium supplementation and acetazolamide.

of thyrotoxic patients in the white population, but up to 10% of the thyrotoxic Asian or Hispanic populations. Adrenergic blocking agents reduce the frequency and severity of attacks, but the ultimate treatment is directed toward treatment of the thyrotoxicosis. Although the exact mechanism is still being worked out, approximately one-third of patients will have mutations in a potassium inward rectifier (KCNJ18, Kir 2.6) located on chromosome 17 that is regulated by thyroid hormone.

Malignant Hyperthermia and Central Core Disease

Patients with mutations in the ryanodine receptor (*RYR1*, chromosome 19q13), located in a calcium channel in the sarcoplasmic reticulum involved in excitation-contraction coupling, can have two clinical syndromes: malignant hyperthermia and central core myopathy.[2,38] Although electrical myotonia has been reported with *RYR1* mutations, central core myopathy is different than other channelopathies discussed here, as it is a progressive chronic myopathy not typically characterized by episodic attacks. Patients with malignant hyperthermia are susceptible to severe muscle rigidity and fevers when exposed to depolarizing anesthetic agents.

CHANNELOPATHIES AND ANESTHETIC AGENTS

In general, depolarizing anesthetic agents should be avoided in patients with any of the channelopathies. Life-threatening muscle spasms and secondary ventilation difficulties have been described following preoperative use of suxamethonium chloride in a patient with myotonia congenita.[39] Indeed, both nondystrophic myotonias and periodic paralyses are associated with exacerbation of attacks with anesthesia, and it is important that the anesthesiologist be made aware of the underlying genetic condition when any surgery is planned.[2,39]

CONCLUSIONS

The muscle channelopathies are a diverse group of rare neuromuscular disorders with the common feature of mutations disrupting the function of muscle ion channels. Almost any muscle ion channel can be involved, including sodium, calcium, potassium, chloride, and ryanodine receptors. Mutations can cause either a gain in or loss of function, but common to all is depolarization of the sarcolemma membrane. When the depolarization remains within the physiologic functioning range of the muscle sodium channel, the result is a hyperexcitable clinical syndrome and myotonia. When the depolarization is outside the physiologic operating range, sodium channels get switched to an inactive state, and patients have attacks of paralysis. Although not typically life limiting, the channelopathies should not be considered benign. Patients experience considerable lifetime morbidity due to symptoms. Patients with periodic paralysis can develop fixed limb-girdle weakness over time, and those with Andersen-Tawil syndrome can develop life-threatening arrhythmias. Treatment consists of nonspecifically decreasing sarcolemma excitability in nondystrophic myotonias, and decreasing the frequency and severity of attacks in periodic paralyses. As our understanding of the specific molecular pathophysiologic mechanisms of these disorders advances, more disease-directed therapies may become possible. Large international collaborations make the possibility of testing interventions in formalized placebo-controlled trials feasible, even for these rare disorders.

KEY POINTS

- Approximately one-third of patients with thyrotoxic periodic paralysis will have a mutation in the potassium inward rectifier (Kir 2.6).
- General anesthesia should be used with caution in all patients with muscle channelopathies because of reports of malignant hyperthermia or severe episodes of paralysis associated with their use.
- Although not typically life limiting, muscle channelopathies should not be considered benign. Treatments should be offered for symptomatic patients.

USEFUL WEBSITES

Human Genome Variation Society: Locus Specific Mutation Databases
www.hgvs.org/dblist/glsdb.html

NIH/*GeneReviews*
www.ncbi.nlm.nih.gov/sites/GeneTests/review

Clinical Trials
www.clinicaltrials.gov/

Periodic Paralysis Association
www.periodicparalysis.org/english/view.asp?x=1

Muscular Dystrophy Association
mdausa.org/

Washington University Neuromuscular Disease Center
neuromuscular.wustl.edu/

VIDEO LEGENDS

Supplemental Digital Content 4-1

Electrical myotonia. This video demonstrates the characteristic waxing and waning motor unit amplitude and frequency seen with myotonia on EMG. This produces the distinctive dive-bomber or motorcycle revving sound when amplified.

links.lww.com/CONT/A110

Supplemental Digital Content 4-2

Percussion myotonia. This video demonstrates the clinical evaluation of percussion myotonia over the extensor digitorum communis. A fast strike with the reflex hammer over the extensor digitorum communis produces the characteristic extension of the fingers and wrist, with subsequent myotonic catch and delay of muscle relaxation.

links.lww.com/CONT/A111

Supplemental Digital Content 4-3

Warm-up of myotonia in myotonia congenita. This video demonstrates the characteristic reduction in myotonia, or warm-up, with repetitive hand grips seen in patients with myotonia congenita. The patient is instructed to squeeze his hand closed as tightly as he can and then open his hand quickly. This maneuver is repeated to evaluate for warm-up of myotonia or paradoxical worsening.

links.lww.com/CONT/A112

Supplemental Digital Content 4-4

Paradoxical myotonia in paramyotonia congenita. This video demonstrates the characteristic paradoxical increase in myotonia with repetitive hand grips, or paramyotonia, seen in patients with paramyotonia congenita. The patient is instructed to squeeze her hand closed as tightly as she can and then open her hand quickly. This maneuver is repeated to evaluate for warm-up of myotonia or paradoxical worsening.

links.lww.com/CONT/A113

Supplemental Digital Content 4-5

Eye-closure myotonia. This video demonstrates the difficulty in opening the eyes after forced eye closure that can be seen in patients with myotonic disorders. Eye-closure myotonia is seen most frequently in patients with sodium channel mutations. The patient is instructed to squeeze his eyes shut tightly and then open them as quickly as possible. The maneuver can be repeated to check for evidence of warm-up or paradoxical worsening.

links.lww.com/CONT/A114

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