REVIEW ARTICLE

Muscle Channelopathies

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Trivedi discusses the use of acetazolamide, carbamazepine, eplerenone, flecainide, hydrochlorothiazide, lacosamide, lamotrigine, mexiletine, phenytoin, procainamide, quinine, ranolazine, rufinamide, spironolactone, tocainide, and triamterene as treatment options that are not US Food and Drug Administration (FDA) approved for the for the conditions discussed in this article.

ABSTRACT

PURPOSE OF REVIEW: This article describes the clinical features, diagnosis, pathophysiology, and management of nondystrophic myotonia and periodic paralysis.

RECENT FINDINGS: An increasing awareness exists about the genotype-phenotype overlap in skeletal muscle channelopathies, and thus genetic testing is needed to make a definitive diagnosis. Electrodiagnostic testing in channelopathies is highly specialized with significant overlap in various mutation subtypes. Randomized clinical trials have now been conducted in these disorders with expanded treatment options for patients with muscle channelopathies.

SUMMARY: Skeletal muscle channelopathies are rare heterogeneous conditions characterized by lifelong symptoms that require a comprehensive management plan that includes pharmacologic and nonpharmacologic interventions. The significant variability in biophysical features of various mutations, coupled with the difficulties of performing clinical trials in rare diseases, makes it challenging to design and implement treatment trials for muscle channelopathies.

INTRODUCTION

Muscle channelopathies are rare skeletal muscle ion disorders with marked phenotypic and genotypic heterogeneity and are caused by mutations in genes encoding sodium-channel (*SCN4A*), chloride-channel (*CLCN1*), calcium-channel (*CACNA1S*), or potassium-channel subunits (*KCNJ2* and *KCNJ18*).[1-3] Characteristic features include the episodic and fluctuating nature of symptoms, exacerbation by environmental factors, and frequently autosomal dominant inheritance. Symptoms start in the early years, are lifelong, and affect quality of life. The phenotypic and genetic heterogeneity of these channelopathies presents a challenge in diagnosis and management. For instance, *SCN4A* mutations can present as paramyotonia congenita, sodium-channel myotonia, hyperkalemic periodic paralysis, or hypokalemic periodic paralysis (FIGURE 11-1[4]). In contrast, nondystrophic myotonia can occur due to mutations in the *SCN4A* or *CLCN1* ion channel. The heterogeneous nature of these disorders has made it challenging to conduct therapeutic clinical trials. Treatment options are few and most are not US Food and Drug Administration (FDA) approved. Physicians often use off-label drugs to treat patients with muscle channelopathies. Lifestyle changes, dietary modifications, recognition and avoidance of triggers, and genetic counseling are important in treating these

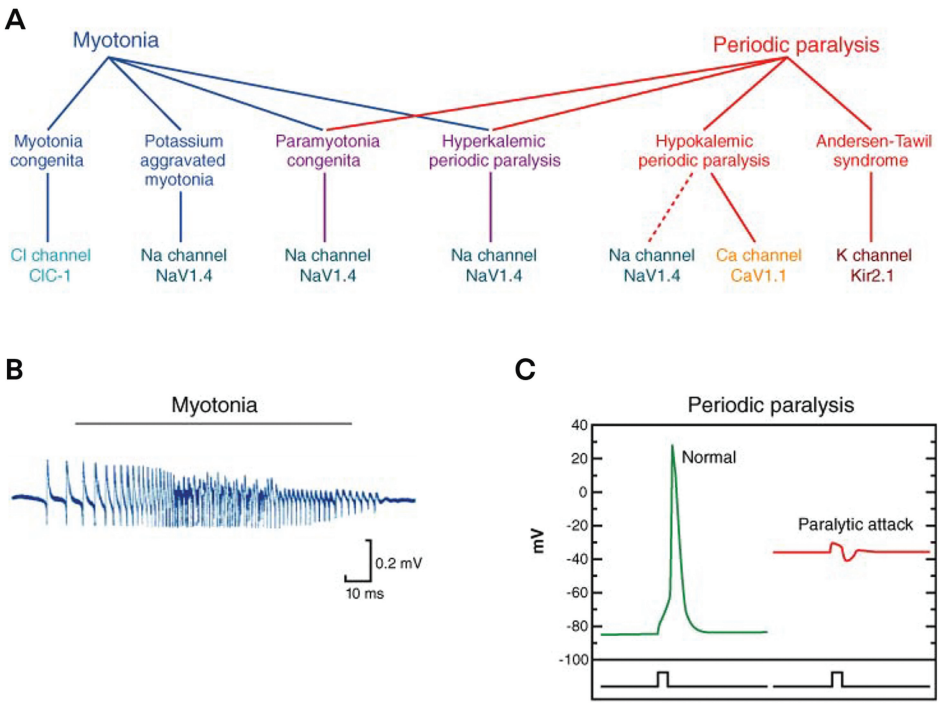

FIGURE 11-1

Clinical spectrum of the nondystrophic myotonias and periodic paralyses. Myotonia predominates in disorders further to the left in this spectrum, whereas periodic paralysis is the major symptom for those further to the right (*A*). The underlying molecular genetic defects in each of these disorders are mutations in voltage-gated ion channels (*A*, *bottom row*). An electromyographic recording of a myotonic burst (*B*), computer simulations of an action potential in normal muscle, and depolarization-induced loss of excitability during an attack of periodic paralysis (*C*) are also shown.

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KEY POINTS

- **Nondystrophic myotonias are classified based on genotype as either skeletal muscle chloride or sodium channelopathies. Phenotypically, nondystrophic myotonias are classified as myotonia congenita, paramyotonia congenita, and sodium-channel myotonias.**
- **Common symptoms in nondystrophic myotonia include muscle stiffness, weakness, fatigue, and pain.**

patients. This article reviews the clinical features, diagnostic studies, pathophysiology, and treatment options in nondystrophic myotonia and periodic paralyses.

NONDYSTROPHIC MYOTONIA

Nondystrophic myotonias are caused by gain-of-function mutations in the skeletal muscle sodium ion channel (*SCN4A*) and loss-of-function mutations in the chloride ion channel (*CLCN1*). They are classified based on genotype as either skeletal muscle chloride or sodium channelopathies.[5] Phenotypically, nondystrophic myotonias are classified as myotonia congenita, paramyotonia congenita, and sodium-channel myotonias. Myotonia congenita is related to *CLCN1* mutations and can be autosomal dominant or autosomal recessive, whereas paramyotonia congenita and sodium-channel myotonias, related to *SCN4A* mutations, are autosomal dominant.[4,6-12] These are rare disorders with a prevalence of less than 1 in 100,000.[6,10] Typically, symptom onset occurs in the first two decades of life, although sodium-channel myotonias may present earlier than chloride-channel myotonias.[13] Common symptoms of nondystrophic myotonia include muscle stiffness, weakness, fatigue, and pain. Muscle stiffness occurs in the

absence of severe fixed weakness or atrophy. This is in contrast to myotonic dystrophy types 1 and 2, which present with progressive muscle weakness and multisystem involvement.[2] Of note, the myotonic dystrophies can rarely present with a pure myotonic phenotype that may be clinically indistinguishable from myotonia congenita.[7] Genetic testing for myotonic dystrophy types 1 and 2 in an individual presenting with myotonia should therefore be considered.

Clinical features of nondystrophic myotonia vary from mild muscle stiffness to severe myotonia with respiratory involvement in neonates.[14] Voluntary contraction of muscles leads to sustained bursts of action potentials originating from muscle fibers, and this manifests as delayed relaxation of muscle contraction, which corresponds to clinical myotonia. Patients describe this delayed relaxation as "stiffness."[4] A key history question for patients is to ask if they have difficulty opening their hands after holding objects or if their eyes get stuck after sneezing. It is also important to ask patients about triggers; some will report that cold exposure makes their symptoms worse. Other reported triggers include pregnancy, hunger, emotional stress, fatigue, and dietary potassium; some of these have traditionally been thought to help distinguish some of the nondystrophic myotonia subtypes. Symptoms of myotonia can be treated with sodium-channel blockers including antiseizure medications, anesthetics, and antiarrhythmics. The concurrence of *CLCN1* or *SNC4A* nondystrophic myotonia with myotonic dystrophy type 2 has been reported, with patients presenting with early-onset and severe clinical and electrical myotonia.[15-17]

CASE 11-1

A 46-year-old man presented with a long-standing history of muscle stiffness in his legs. His symptoms would worsen with initial movements after a state of inactivity. The stiffness would get better when he moved around.

On examination, he had muscle hypertrophy in his hands, forearms, arms, thighs, and calves. He also had grip myotonia with warm-up phenomenon and percussion myotonia over the forearm (ie, extensor digitorum communis muscle). Muscle strength was normal.

Thyroid-stimulating hormone (TSH) was normal and creatine kinase was elevated at 508 U/L. Needle EMG revealed diffuse myotonic discharges in distal and proximal limb muscles. Motor units were of normal morphology. He was treated with mexiletine 250 mg 3 times daily and his symptoms improved remarkably. Genetic testing was performed and revealed a *CLCN1* mutation.

COMMENT

This is a typical presentation of a chloride channelopathy with a myotonia congenita phenotype in which muscle stiffness improves with activity and strength remains intact. However, it should be noted that a warm-up phenomenon can also be seen in select sodium-channel myotonias. This case illustrates the importance of genetic testing to confirm the diagnosis. Besides treatment with mexiletine, the patient would benefit from recognition and avoidance of triggers. Genetic counseling would also be helpful for the patient.

Clinical Features

While considerable overlap in symptoms occurs, careful delineation of the pattern of symptoms and examination findings can help distinguish the various nondystrophic myotonia subtypes.

SKELETAL MUSCLE CHLORIDE CHANNELOPATHIES. These channelopathies present as myotonia congenita and are caused by a mutation in the *CLCN1* gene encoding the main skeletal muscle chloride channel CIC-1. Prevalence varies by region between 0.2 and 7.3 per 100,000.[6,18] Myotonia congenita can be autosomal dominant (Thomsen disease) or recessive (Becker disease), with the latter having a more severe and earlier-onset phenotype.[1,7,19] Symptom onset is in the first two decades of life. Clinical heterogeneity within a family is common. Patients have a muscular build due to muscle hypertrophy.[20] They have "action myotonia," where stiffness occurs during rapid voluntary movement following a period of rest. The most common site of stiffness is the legs, while the face is less commonly affected.[13] The stiffness in myotonia congenita improves with exercise, referred to as the "warm-up phenomenon." Percussion myotonia can be elicited over the thenar eminence or forearm extensors, as demonstrated in **CASE 11-1**. Patients can experience a unique feature of transient weakness with initiation of movement that subsequently improves with exercise.[21] This is more common in Becker disease.[7]

SKELETAL MUSCLE SODIUM CHANNELOPATHIES. These channelopathies are dominantly inherited and can present with two major phenotypes: paramyotonia congenita and sodium-channel myotonia.

PARAMYOTONIA CONGENITA. Paramyotonia congenita is caused by missense mutations of the muscle sodium channel *SCN4A* gene on chromosome 17. Prevalence is 0.17 in 100,000.[22] Paramyotonia congenita is allelic with other *SNC4A* disorders which include sodium-channel myotonias, hyperkalemic periodic paralysis, and hypokalemic periodic paralysis; common features include worsening of symptoms with rest after exercise, fasting, and cold exposure.[23,24] In contrast to myotonia congenita, muscle stiffness worsens with sustained exercise in paramyotonia congenita in a phenomenon referred to as "paradoxical myotonia" (hence the name "paramyotonia"). Muscle stiffness commonly affects the face. Paradoxical eye closure myotonia, where the eye closure and opening get worse with repetition, is unique to paramyotonia congenita and is a useful distinguishing feature from other forms of nondystrophic myotonia.[13] **CASE 11-2** describes a typical example of paramyotonia congenita. Patients with paramyotonia congenita may experience prolonged muscle weakness following sustained exercise lasting from several hours to 2 days.[25] Besides episodic weakness, patients with paramyotonia congenita may develop permanent weakness.[26,27]

SODIUM-CHANNEL MYOTONIAS. Sodium-channel myotonias typically present in the first decade of life. They may also be referred to as the potassium-aggravated myotonias, but not all patients are sensitive to potassium. Subtypes include acetazolamide-responsive myotonia, myotonia fluctuans, and myotonia permanens. Common to these subtypes is lack of cold sensitivity or weakness; however, pure myotonic syndromes that do have cold sensitivity have been linked to the *SCN4A* gene.[28-32] The presence of warm-up phenomenon can make these patients difficult to distinguish clinically from myotonia congenita.

KEY POINTS

- In nondystrophic myotonia, muscle stiffness occurs in the absence of severe fixed weakness or atrophy. This is in contrast to myotonic dystrophy types 1 and 2, which present with progressive muscle weakness and multisystem involvement.
- The most common site of stiffness in myotonia congenita is the legs, while the face is less commonly affected. The stiffness in myotonia congenita improves with exercise, referred to as the "warm-up phenomenon."
- In contrast to myotonia congenita, muscle stiffness worsens with sustained exercise in paramyotonia congenita in a phenomenon referred to as "paradoxical myotonia" (hence the name "paramyotonia").
- Paradoxical eye closure myotonia is unique to paramyotonia congenita and is a useful distinguishing feature from other forms of nondystrophic myotonia.

Pediatric Manifestations of Nondystrophic Myotonia

Pediatric patients with nondystrophic myotonia may have additional symptoms; awareness and recognition of these can reduce diagnostic delays and subsequently limit the physical and psychological impact on children. In patients with *SCN4A* mutations, these symptoms include abnormal gait, leg cramps, eyelid or extraocular myotonia, strabismus, stridor, and choking episodes. Neonates may have episodic life-threatening laryngospasm, which responds well to carbamazepine.[33] Hypotonia may also be seen in some *SCN4A* mutations. Pediatric patients with *CLCN1* mutations are slow runners compared to their peers and can have an atypical gait, ankle contractures, and scoliosis. Obstetricians and pregnant mothers should be made aware of the hypotonia and potential for respiratory and bulbar compromise in *SCN4A* patients so they can take appropriate precautions.[34]

Diagnosis

Diagnosis of nondystrophic myotonia is based on symptoms, examination findings of muscle hypertrophy and clinical myotonia or paramyotonia, family history, electrodiagnostic testing, and genetic testing. EMG is recommended as an initial step. If evidence of electrical myotonia is seen, the next step would be genetic testing.

CASE 11-2

A 35-year-old woman presented with a long-standing history of muscle stiffness in her legs. She also reported fatigue of her jaw while chewing, painful tongue stiffness when eating cold foods along with slurring of her speech, and mobility issues in cold weather. Her friends thought she worked out regularly in a gym as she had bulky muscles. Her sister, maternal aunt, and maternal cousin had similar symptoms.

On examination, she had muscle hypertrophy in her upper and lower extremities and eye closure paramyotonia. Muscle strength was normal in all extremities.

Thyroid-stimulating hormone (TSH) was normal and creatine kinase was elevated to 484 U/L. EMG revealed diffuse myotonic discharges in distal and proximal limb muscles. Motor units were of normal morphology. Genetic testing revealed a T1313M mutation of the sodium-channel gene. She was treated with mexiletine 250 mg 3 times a day with significant improvement in her presenting symptoms.

COMMENT

This is a typical presentation of autosomal dominant sodium channelopathy with a paramyotonia congenita phenotype. It is important to remember that all nondystrophic myotonias can present with muscle stiffness. However, eye closure paramyotonia is a unique finding in paramyotonia congenita and can guide genetic testing. Similar to *CLCN1* nondystrophic myotonia, patients with paramyotonia congenita can respond to mexiletine. Another recommendation would be to have her family members evaluated for nondystrophic myotonia so they could also be offered symptomatic treatment and genetic counseling.

GENETIC TESTING. Genetic testing is the gold standard in making a definitive diagnosis of nondystrophic myotonia. Over 100 *CLCN1* mutations and 30 *SCN4A* mutations have been identified.[28,35] Commercial testing for a wide variety of genetic neuromuscular disorders is available, including testing for *CLCN1* and *SCN4A* mutations. Some of these panels are available at no cost to the patient through sponsored programs, allowing genetic testing to now be the first diagnostic step in suspected nondystrophic myotonia. If genetic testing for nondystrophic myotonia is negative, the next diagnostic step should include laboratory and electrodiagnostic studies. As clinically appropriate, further genetic testing should also be considered to exclude other causes of myotonia, including but not limited to myotonic dystrophy types 1 and 2 and Pompe disease.

LABORATORY AND ELECTRODIAGNOSTIC STUDIES. Creatine kinase can range from normal to mildly elevated in the nondystrophic myotonias. Thyroid function should be checked since hypothyroidism can cause clinical and electrical myotonia.[36] EMG testing reveals electrical myotonia in proximal and distal limb muscles in nondystrophic myotonias.[13] Motor unit potentials are typically normal. Differential diagnosis of electrical myotonia is extensive, including but not limited to myotonic dystrophy types 1 and 2, some distal myopathies, inflammatory myopathy, toxic myopathy, and Pompe disease.[37,38] Notably, in these conditions patients will also have muscle weakness, atrophy, markedly elevated creatine kinase, and myopathic motor units on EMG.

The short-exercise and long-exercise tests have been used to further characterize nondystrophic myotonia. For the short-exercise test, the patient performs maximum voluntary contraction of the abductor digiti minimi for 5 to 10 seconds. Compound muscle action potential (CMAP) is recorded by stimulating the ulnar nerve at the wrist; this is done prior to the exercise and subsequently every 10 seconds up to 1 minute postexercise. The protocol is repeated three times at 60-second intervals. To evaluate for changes after cold exposure, the short-exercise test may be repeated after cooling the hand down to 20°C (68°F). A CMAP amplitude reduction of greater than 10% is considered abnormal.[39,40]

The short-exercise test may reveal the following patterns.

- **Paramyotonia congenita: greater than 10% CMAP reduction, facilitated by cold or repetition**
- **Recessive myotonia congenita: transient CMAP drop greater than 10% with rapid return to baseline CMAP**
- **Dominant myotonia congenita or sodium-channel myotonia: no change**

For the long-exercise test, patients perform maximum voluntary contraction of the abductor digiti muscle for up to 5 minutes, alternating contraction for 15 seconds with 3 to 4 seconds of rest. CMAP is recorded prior to exercise and then every 1 to 2 minutes postexercise for up to 50 minutes. A CMAP amplitude reduction of greater than 40% from the maximum CMAP during or postexercise is considered abnormal. The sensitivity of this test in diagnosing periodic paralysis is 70%.[39,41,42]

KEY POINTS

- **Genetic testing is the gold standard in making a definitive diagnosis of nondystrophic myotonia.**
- **In the long-exercise test, a compound muscle action potential (CMAP) amplitude reduction of greater than 40% from the maximum CMAP during or postexercise is considered abnormal.**

The long-exercise test may reveal the following patterns.

- **Myotonia congenita: mild decrease in CMAP**
- **Paramyotonia congenita: persistent CMAP decrement greater than 40% that starts immediately postexercise**

Limitations of electrodiagnostic testing include the following: (1) certain *SCN4A* mutations can manifest as either sodium-channel myotonia or paramyotonia congenita phenotypes with variable abnormalities on exercise testing; (2) significant overlap among different forms of non-dystrophic myotonia may be seen on the short-exercise test, suggesting that these patterns may not be sensitive or specific enough to make a definitive diagnosis.

MUSCLE MRI. In a cohort of 21 genetically confirmed nondystrophic myotonia patients (11 *CLCN1* mutations and 10 *SCN4A* mutations), close to one-half of the patients had T1-weighted changes on muscle MRI, indicative of fatty infiltration. The fatty infiltration is suggestive of permanent muscle damage in nondystrophic myotonia patients. Short tau inversion recovery (STIR) hyperintensity was observed in 18 of 21 patients and a unique "central stripe" was present in ten *CLCN1* and three *SCN4A* patients.[43] These abnormal findings suggest that MRI could potentially be used as a biomarker in treatment trials.

Pathophysiology

The pathophysiology of nondystrophic myotonia is complex and varies in both *CLCN1*-related and *SCN4A*-related nondystrophic myotonia.

***CLCN1*-RELATED NONDYSTROPHIC MYOTONIA.** In a healthy state, chloride ions account for most of the muscle membrane conduction. Chloride conductance also contributes to repolarization. Reduced sarcolemmal chloride conductance in myotonic goats was demonstrated by Bryant and colleagues; this is the basis for the increased muscle excitability in myotonia congenita.[44] Repolarization is impaired in the absence of chloride conductance, leading to summation of electrical potentials.[44] Hence, an increase in the potassium concentration in the T-tubules during electrical activity causes a depolarizing shift in the resting membrane potential of the sarcolemma, leading to hyperexcitability and myotonia.[45]

The dominant form of myotonia congenita occurs when a mutated subunit dimerizes with the wildtype subunit, which leads to a shift in the gating potential preventing the opening of chloride channels during repolarization.[46] In the recessive form, homozygous or compound heterozygous loss-of-function mutations lead to the accumulation of potassium and after depolarization bursts which manifest as myotonia.[45]

***SCN4A*-RELATED NONDYSTROPHIC MYOTONIA.** The *SCN4A* gene encodes the $Na_v1.4$ sodium channel consisting of four domains, each of which has six segments (FIGURE 11-2[4]). Chloride conductance was found to be normal in paramyotonia congenita and hyperkalemic periodic paralysis.[47,48] Instead, these patients had a voltage-gated sodium-channel defect which was identified when a persistent inward current was blocked by tetrodotoxin. Missense mutations in the *SCN4A* gene lead to paramyotonia congenita, sodium-channel myotonia, and hyperkalemic periodic paralysis through a variety of gating defects in the sodium channel.[49,50] These defects result in a gain of function with an increase in sodium

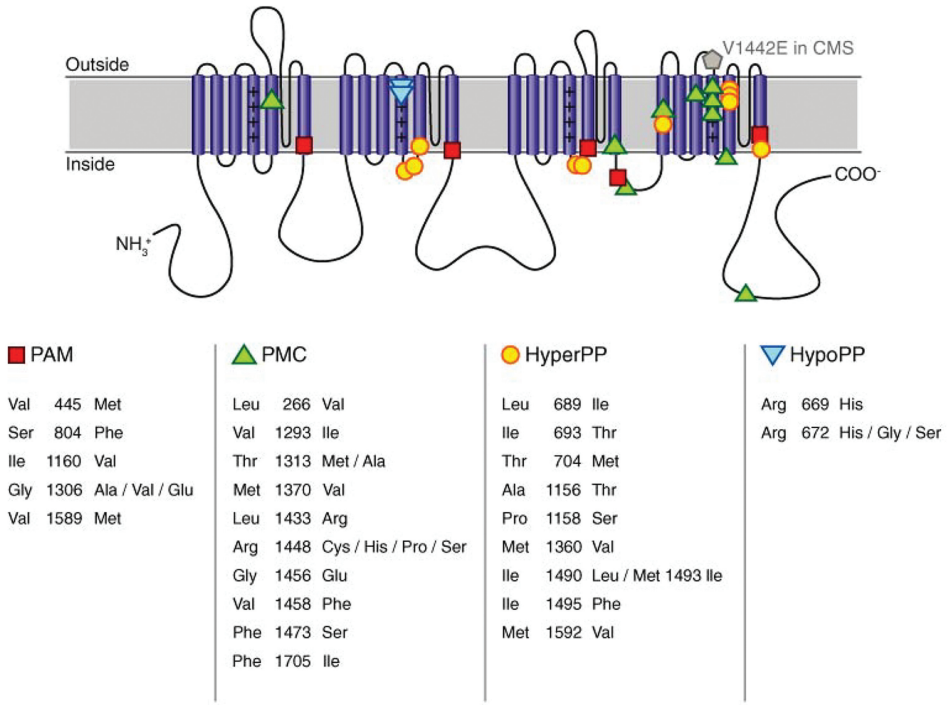

FIGURE 11-2

Missense mutations in NaV1.4 associated with disorders of muscle excitability. The schematic diagram for the membrane-folding structure of NaV1.4 shows the relative locations of missense mutations associated with potassium-aggravated myotonia (PAM), paramyotonia congenita (PMC), hyperkalemic periodic paralysis (HyperPP), hypokalemic periodic paralysis (HypoPP), and a congenital myasthenic syndrome (CMS).

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ion influx through disruption of fast inactivation of the mutated sodium channel or, in some cases, by enhancing activation.[51]

Therapeutic Options in Nondystrophic Myotonia

The quality of life of nondystrophic myotonia patients is comparable to that of some muscular dystrophies, where about one-quarter of patients are disabled or unemployed. About 40% are not on any antimyotonic treatment for their symptoms, which could also contribute to the impaired quality of life.[13,52,53] At this time, no FDA-approved treatments exist for nondystrophic myotonia. Sodium-channel blockers are used off label and include antiseizure medications, anesthetics, and antiarrhythmic drugs (**TABLE 11-1**[54]). These drugs reduce sarcolemmal excitability and thus reduce myotonia, regardless of the underlying channel defect, be it *CLCN1* or *SCN4A*.[64] This suggests that the effects may be due to the modulation of normal sodium channels rather than a direct effect on mutant channels. **TABLE 11-1** outlines various treatment options in nondystrophic myotonia.

Anecdotal data exists on the benefits of quinine,[65] procainamide,[65,66] carbamazepine,[60] flecainide, tocainide (now withdrawn from the market), and phenytoin[66] in patients with myotonia. Clinical trials of mexiletine in nondystrophic myotonia, at a dosage of 200 mg 3 times a day, demonstrated reduction in muscle stiffness and electrical myotonia, with improvement in quality-of-life measures.[55,67] Gastrointestinal side effects were common. A boxed

KEY POINTS

- **The quality of life of patients with nondystrophic myotonia is comparable to that of some muscular dystrophies, where about one-quarter of patients are disabled or unemployed. About 40% are not on any antimyotonic treatment.**
- **Clinical trials of mexiletine in nondystrophic myotonia, at a dosage of 200 mg 3 times a day, demonstrated reduction in muscle stiffness, electrical myotonia, and quality-of-life measures.**

warning exists on mexiletine regarding the increased chance of having arrhythmias. Given this pro-arrhythmogenic potential, it is recommended that patients on mexiletine should have ECG monitoring at baseline, after 1 month of treatment, and then annually.

Ranolazine, an antianginal drug, demonstrated antimyotonic properties in a myotonia congenita mouse model. In contrast to mexiletine and lamotrigine, which enhance fast inactivation, ranolazine enhances slow inactivation. In open-label studies, ranolazine improved stiffness and weakness, clinical myotonia, and electrical myotonia in patients with myotonia congenita and paramyotonia congenita. Starting dosage was 500 mg 2 times a day and was further increased to 1000 mg 2 times a day.[56,68] Larger studies are needed to confirm the benefits of this treatment.

TABLE 11-1 **Antimyotonic Drugs Used to Treat Symptoms of Nondystrophic Myotonia**[a]

Antimyotonic Drugs	Dosage	Side Effects	Monitoring
Mexiletine[55]	Start 150 mg 2 times a day with slow titration to 200 to 300 mg 3 times a day	Gastrointestinal (GI) distress, tremor, ataxia	Liver function tests, ECG at baseline, 1 month posttreatment, and then annually
Ranolazine[56]	500 to 1000 mg 2 times a day	GI distress, dizziness, headache, prolonged QT interval, vasovagal syncope	Renal function periodically with creatinine clearance less than 60 mL/min; annual ECG
Quinine[57]	200 to 1200 mg/day divided in two to three doses	Cardiac arrhythmias, hypersensitivity reactions, bone marrow suppression, liver damage, GI distress, visual disturbance	Complete blood cell count with platelet count, liver function tests, blood glucose, ECG, ophthalmologic evaluation
Procainamide[57,58]	125 to 1000 mg/day divided in two doses	Rash, GI distress, positive antinuclear antibodies	ECG, creatinine, complete blood cell count, antinuclear antibodies
Phenytoin[57,58]	300 to 400 mg/day divided in three doses	Gingival hypertrophy, agranulocytosis, pancytopenia, rash, cognitive impairment, liver damage	Complete blood cell count, liver function tests
Flecainide[59]	Start 100 mg/day, titrate to 100 mg 2 times a day	Cardiac arrhythmias, dizziness, rash	ECG, periodic drug serum concentrations
Carbamazepine[60,b]	20 mg/kg total daily dose divided 3 times a day	Rash, agranulocytosis, pancytopenia, liver damage	Liver function tests, complete blood cell count, thyroid-stimulating hormone (TSH)
Acetazolamide[57,61]	125 mg 2 times a day with slow titration to goal dose 250 mg 3 times a day	GI distress, electrolyte abnormalities (hypokalemia, hyponatremia), paresthesias, nephrolithiasis, rash, agranulocytosis	Serum electrolytes, liver function tests, complete blood cell count
Lamotrigine[62,63]	Start at 25 mg once a day and titrate slowly to 300 mg daily	Headache, fatigue, and skin rash	Liver and renal function tests as hepatic and renal impairment will drive dose reduction

[a] Reprinted with permission from Statland J, et al. Neurol Clin.[54] © 2014 Elsevier Inc.
[b] Patients of Asian descent should be tested for HLA-B*1502 genotype prior to starting carbamazepine due to an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Lamotrigine, a sodium-channel blocker, has antimyotonic properties.[62] In a double-blind placebo-controlled study in nondystrophic myotonia patients, this drug reduced myotonia and was well tolerated. Maximum dosage was 300 mg daily. The number needed to treat was 2.6 and the number needed to harm was 5.2.[63]

Lacosamide and rufinamide are other sodium-channel blockers found to have antimyotonic effects in vitro but have not yet been studied in clinical trials.[62] Anecdotal reports have also demonstrated benefits of acetazolamide in nondystrophic myotonia.[33]

NONPHARMACOLOGICAL INTERVENTIONS. Identification and regulation of triggers such as cold exposure and potassium are important so that they can be avoided when possible. In general, exercise such as swimming, cycling, and walking is encouraged.[5]

ANESTHETIC CONSIDERATIONS. Succinylcholine should be avoided in nondystrophic myotonia as it can cause myotonic crisis and severe generalized muscle stiffness. Volatile anesthetics and propofol are okay to use.[5,69] Hypothermia should be avoided.

KEY POINT

● Succinylcholine should be avoided in nondystrophic myotonia as it can cause myotonic crisis and severe generalized muscle stiffness. Volatile anesthetics and propofol are okay to use.

PERIODIC PARALYSES

The primary periodic paralyses are autosomal dominant skeletal muscle channelopathies that include hyperkalemic periodic paralysis, hypokalemic periodic paralysis, and Andersen-Tawil syndrome.[70] Overlap may occur with paramyotonia congenita in some patients with hyperkalemic periodic paralysis. The periodic paralyses are caused by mutations in sodium-channel, calcium-channel, and potassium-channel genes that reduce muscle membrane excitability, leading to susceptibility to episodes of paralysis.[64,70] Of these, mutations of the sodium-channel gene are the most common. Patients typically present with episodes of generalized weakness, beginning in the first two decades of life.[2,71,72] The episodes are typically brought on by triggers, which include diet or rest after exercise, and are often associated with changes in extracellular potassium. Many patients develop permanent proximal weakness later in the disease course.[71,73-77] Carbonic anhydrase inhibitors are used to reduce attack frequency and severity.

Clinical Features

While some overlap exists in the clinical features of all forms of periodic paralysis, certain nuances may help distinguish one type from the other.

HYPERKALEMIC PERIODIC PARALYSIS. Hyperkalemic periodic paralysis is caused by mutations in the *SCN4A* gene on chromosome 17. Prevalence is less than 1 per 200,000. Other allelic disorders include paramyotonia congenita and sodium-channel myotonia. Attacks of muscle weakness typically begin in the first decade of life with only one-quarter of patients reporting onset after age 10.[78] Attacks last 1 to 4 hours and are triggered by fasting, rest after exercise, ingestion of potassium-rich foods, stress, and fatigue.[71,72] Respiratory muscles may be rarely affected in severe attacks of paralysis. Some patients experience muscle stiffness due to paramyotonia between attacks of weakness. Strength is preserved between attacks, but a significant number of patients develop fixed

proximal weakness later in life. While electrical myotonia can be seen in a majority of patients,[71,79] clinical myotonia is seen in less than 20%.[79]

HYPOKALEMIC PERIODIC PARALYSIS. Hypokalemic periodic paralysis is the most common periodic paralysis with a prevalence of approximately 0.13 per 100,000.[80] It is caused by mutations of the calcium-channel gene *CACNA1S* and, less frequently, the sodium-channel gene *SCN4A*. Hypokalemic periodic paralysis is characterized by episodic attacks of focal or generalized weakness associated with low serum potassium. Onset is in the first or second decade of life. Patients experience attacks of flaccid paralysis that typically occur upon awakening in the night or early morning. The attacks range from mild weakness to profound paralysis and last hours to days.[71] The initial frequency of attacks is

CASE 11-3

A 55-year-old woman presented with episodes of weakness that started when she was 10 years old. She would notice the episodes when she woke up in the morning or after strenuous physical exertion. Symptoms were worse after she consumed carbohydrates. In some episodes, she was unable to move, whereas in other episodes she had milder weakness. During a severe attack, she could not lift her head off the pillow. The duration of the episodes varied from several hours to 1 to 2 days. Over the years, she developed permanent weakness in her arms and legs. On one occasion she was seen in the emergency department during an episode, during which her potassium was low at 2.5 mmol/L; she was treated with IV potassium and the weakness resolved within a couple of hours. Family history was significant for a daughter who also had similar episodes of weakness.

On examination, the patient had mild weakness in her proximal muscles. She did not have clinical myotonia. On laboratory testing, renal function and thyroid-stimulating hormone (TSH) were normal. ECG and EMG were normal. Prolonged exercise test of the ulnar nerve with recording over the abductor digiti minimi muscle revealed a 45% decrement in the compound muscle action potential (CMAP) postexercise. Genetic testing confirmed a mutation in the *CACNA1S* gene.

For abortive therapy, she was treated with oral potassium. Prophylactically, she was treated with acetazolamide 500 mg 2 times daily with significant reduction in the frequency of her episodes of weakness. She was advised to avoid triggers, especially a high-carbohydrate diet.

COMMENT

This is a typical presentation of hypokalemic periodic paralysis. While patients have episodes of weakness, many patients also develop permanent weakness over time. Carbonic anhydrase inhibitors help in reducing attacks; however, treatment response may not be complete. Treatment strategy should also include patient education and lifestyle changes to minimize triggers of weakness. Genetic counseling is important and family members should be evaluated as indicated.

daily, weekly, or monthly and decreases after age 40.[72,78] Triggers include carbohydrates, alcohol, menstruation, rest after exercise, stress, and medications such as corticosteroids, insulin, and β-agonists. During an attack, potassium can drop to less than 3.0 mmol/L. **CASE 11-3** describes a typical example of hypokalemic periodic paralysis. Ocular, bulbar, and respiratory muscle involvement is seen rarely in association with severe attacks. Morbidity is due to the attacks of paralysis and the permanent weakness that develops over the years.[74,76]

ANDERSEN-TAWIL SYNDROME. Andersen-Tawil syndrome is a rare autosomal dominant disorder with a prevalence of approximately 1 per 1,000,000. Approximately two-thirds of patients with Andersen-Tawil syndrome will have a mutation in the *KCNJ2* gene on chromosome 17 which encodes an inwardly rectifying potassium channel (Kir2.1).[72] Andersen-Tawil syndrome is characterized by a triad of episodic weakness, cardiac abnormalities, and distinctive skeletal features. Symptoms usually start in the first or second decade of life with either palpitations, syncope, or episodic weakness; duration and frequency are variable and potassium levels are either low, high, or normal during attacks.[72] The cardiac abnormalities include ventricular arrhythmias, prolonged QT interval, and prominent U waves. Most cardiac arrhythmias will remain asymptomatic; however, some patients experience syncope or, very rarely, sudden cardiac death.[81] Characteristic skeletal features include short stature, low-set ears, hypertelorism, broad nasal bridge, micrognathia, clinodactyly, syndactyly, scoliosis, and toes joined at the base.[78,82] Permanent weakness occurs commonly in Andersen-Tawil syndrome patients.

THYROTOXIC HYPOKALEMIC PERIODIC PARALYSIS. Thyrotoxic hypokalemic periodic paralysis is most prevalent in Asian and Latin American men. About one-third of patients have a mutation in the *KCNJ18* gene which encodes an inwardly rectifying KCN channel (Kir2.6).[83] The disease is characterized by hypokalemia, episodic weakness, and thyrotoxicosis. Episodes of weakness resolve with treatment of the underlying thyrotoxicosis.

***RYR1* MUTATIONS.** Recently, *RYR1* mutations have been linked to late-onset episodic weakness or paralysis, with or without associated myopathy. Patients can also have myalgia or cramps and the long-exercise test can be abnormal in these patients. It is advisable to test for *RYR1* mutations when *SCN4A*, *CACNA1S*, or *KCNJ2* mutations are not identified.[84]

Diagnosis

When a patient presents with episodic weakness, diagnostic testing for primary periodic paralyses includes (1) ictal potassium, which may be high, normal, or low with normal interictal potassium; (2) thyroid function to evaluate for thyrotoxicosis-related hypokalemic periodic paralysis; (3) long-exercise test; (4) exclusion of secondary causes of hypokalemia or hyperkalemia; (5) evaluation for cardiac involvement; (6) thorough physical examination to assess for characteristic skeletal features of Andersen-Tawil syndrome described previously; and (7) genetic testing. A positive family history would support a diagnosis of periodic paralysis; however, a negative history should not be exclusionary. It is also important to note that, while genetic testing is the gold

KEY POINTS

- In hypokalemic periodic paralysis, patients experience attacks of flaccid paralysis that typically occur upon awakening in the night or early morning. The attacks range from mild weakness to profound paralysis and last hours to days.
- Andersen-Tawil syndrome is characterized by a triad of episodic weakness, cardiac abnormalities, and distinctive skeletal features.

standard to confirm definite periodic paralysis, a significant number of patients do not have an identifiable mutation.

During an acute attack, neurologic examination will reveal flaccid muscle paralysis and loss of deep tendon reflexes in affected limbs. Ictal potassium is low in primary hypokalemic periodic paralysis, often less than 3.0 mmol/L; in hyperkalemic periodic paralysis, elevations in potassium greater than 5 mmol/l or increases greater than 1.5 mmol/L are often seen. In about half of primary hyperkalemic periodic paralysis patients, potassium level is within the normal range during an attack.[79,85] In Andersen-Tawil syndrome, potassium can be low, normal, or high. It is crucial to evaluate for secondary causes of hypokalemia or hyperkalemia as these can mimic primary periodic paralysis in their clinical presentation (TABLE 11-2). Creatine kinase can be mildly elevated during attacks and this is nonspecific. Diagnosis of Andersen-Tawil syndrome is made with the presence of two of the three cardinal features: episodic weakness, ventricular arrhythmia, and the typical skeletal features. However, Andersen-Tawil syndrome should be considered even in cases of isolated periodic paralysis or polymorphic ventricular ectopy.[81,86,87] Nonspecific myopathic changes can be seen on muscle biopsy and some patients with hypokalemic periodic paralysis or hyperkalemic periodic paralysis may have a vacuolar myopathy.[71] Tubular aggregates can be seen in patients with hypokalemic periodic paralysis and Andersen-Tawil syndrome.

Electrodiagnostic testing is an important diagnostic tool in periodic paralysis. Electrical myotonia can be seen on EMG in hyperkalemic periodic paralysis. The long-exercise test mentioned previously is useful in diagnosing periodic

TABLE 11-2 **Conditions Associated with Secondary Periodic Paralysis**[a]

Low potassium

- Thyrotoxic
- Primary hyperaldosteronism
- Renal tubular acidosis
- Juxtaglomerular apparatus hyperplasia
- Gastrointestinal potassium wastage
- Laxative abuse
- Licorice consumption
- Corticosteroids
- Potassium depleting diuretics

High potassium

- Addison disease
- Hypoaldosteronism
- Potassium-sparing diuretics
- Excessive potassium supplementation

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paralysis. During testing, patients are instructed to contract the abductor digiti minimi muscle in an isometric fashion (usually alternating between 15-second contractions and 3 to 4 seconds of rest) for up to 5 minutes against fixed resistance; then, CMAPs are recorded every 1 to 2 minutes for up to 50 minutes postexercise. Characteristic reduction in CMAP amplitude of 40% or more from the maximum CMAP during exercise or postexercise is considered abnormal. The sensitivity of this test in diagnosing periodic paralysis is 70%.[40,42,43]

Genetic testing is required for confirmation of periodic paralysis and will identify a mutation in approximately 60% to 70% of patients who meet clinical criteria.[78] Variants of unknown significance should be interpreted with caution and may require testing of family members or functional testing of the variant to understand its significance.

Pathophysiology

Aberrant depolarization inactivates sodium channels, leading to sarcolemmal inexcitability in all forms of primary periodic paralysis.[88] Patients with hyperkalemic periodic paralysis develop myotonia as well as paralysis; this occurs due to missense mutations in the α-pore-forming subunit of the *SCN4A* gene. The development of myotonia and paralysis depends on the extent of persistent inward sodium currents.[4] The rate of sodium-channel inactivation is altered in most mutations; however, in mutations causing hyperkalemic periodic paralysis, incomplete inactivation with subsequent large persistent inward depolarizing currents also occurs. When these currents are large, they shift the resting membrane to depolarizing potentials and the sodium channels then become inactive, leading to paralysis.

Most mutations in sodium and calcium channels in hypokalemic periodic paralysis occur at the arginine residue in the S4 segment of the voltage sensor domains.[89] As the membrane potential changes, the S4 segment translocates through a gating pore. In hypokalemic periodic paralysis, mutations in the S4 segment lead this gating pore to conduct ions in a resting state. Usually, this depolarizing current is small; however, when potassium is low, the repolarizing current decreases with a net shift to depolarization. The membrane then depolarizes, and sodium channels become inactive, leading to sarcolemmal inexcitability. This gating pore current anomaly has been observed in mouse models of hypokalemic periodic paralysis related to both sodium- and calcium-channel mutations.[90,91]

With regard to Andersen-Tawil syndrome, the pathophysiology is not clearly understood. The role of the potassium inward rectifier (Kir2.1) is to set the resting membrane potential in cardiac and skeletal muscles; it also helps in the terminal repolarization of the cardiac action potential.[81,82] Mutations of the Kir2.1 channel cause sustained depolarization, which leads to failure of propagation of the action potential and subsequent paralysis.[82]

Therapeutic Options in Periodic Paralysis

The treatment strategy for periodic paralysis includes patient education about triggers, lifestyle modifications, targeted therapy during an attack, and prophylactic treatment.

GENERAL GUIDELINES. The treatment of periodic paralyses includes a multipronged approach to reduce episodes of weakness, including lifestyle and behavioral

KEY POINTS

- Ictal potassium is low in primary hypokalemic periodic paralysis, often less than 3.0 mmol/L; in hyperkalemic periodic paralysis, elevations in potassium greater than 5 mmol/l or increases greater than 1.5 mmol/L are often seen.
- Genetic testing is required for confirmation of periodic paralysis and will identify a mutation in approximately 60% to 70% of patients who meet clinical criteria of periodic paralysis.

TABLE 11-3 Treatment Strategies for Primary Periodic Paralyses[a]

Treatment	Hypokalemic periodic paralysis	Hyperkalemic periodic paralysis	Andersen-Tawil syndrome
Acute therapy			
Behavioral	Mild exercise at attack onset	Mild exercise at attack onset	Mild exercise at attack onset
Oral potassium	0.2 to 0.4 mEq/kg every 30 minutes; not to exceed 200 to 250 mEq/day	Not indicated	If potassium low during attacks: 0.2 to 0.4 mEq/kg every 30 minutes; not to exceed 200 to 250 mEq/day
Oral carbohydrate	Not indicated	Oral carbohydrate up to 2.0 gm/kg	Not typically indicated
IV potassium	Only if cannot take orally: 40 mEq/L in 5% mannitol solution to run at maximum rate of 20 mEq/hour; not to exceed 200 to 250 mEq/day	Not indicated	If potassium low during attack and cannot take orally: 40 mEq/L in 5% mannitol solution to run at maximum rate of 20 mEq/hour; not to exceed 200 to 250 mEq/day
β-agonist	Not indicated	Two 100 mcg metered inhalations salbutamol	Not typically indicated
IV calcium gluconate	Not indicated	If attack severe and associated with high potassium: 0.5 to 2.0 gm	Not typically indicated
Chronic therapy			
Diet	Low salt, low carbohydrate; avoid alcohol	Avoid potassium-rich foods	If potassium is low during attacks: low salt, low carbohydrate; avoid alcohol
Oral potassium	10 to 20 mEq up to 3 times a day	Not indicated	If potassium is low during attacks: 10 to 20 mEq up to 3 times a day
Carbonic anhydrase inhibitor	Acetazolamide 125 to 1000 mg/day, or dichlorphenamide 50 to 200 mg/day, both divided into two doses	Acetazolamide 125 to 1000 mg/day, or dichlorphenamide 50 to 200 mg/day, both divided into two doses	Acetazolamide 125 to 1000 mg/day, or dichlorphenamide 50 to 200 mg/day, both divided into two doses
Potassium sparing diuretic	Triamterene 50 to 150 mg/day in either a single dose or two divided doses; spironolactone 25 to 100 mg/day in either a single dose or two divided doses; eplerenone 50 to 100 mg/day once daily	Not indicated	If potassium is low during attack: Triamterene 50 to 150 mg/day in either a single dose or two divided doses; spironolactone 25 to 100 mg/day in either a single dose or two divided doses; eplerenone 50 to 100 mg/day once daily
Oral hydrochlorothiazide	Not indicated	25 to 50 mg/day; monitor potassium	Not typically indicated

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modifications such as the recognition and avoidance of triggers, which are critical in reducing paralytic attacks. Patients with hypokalemic periodic paralysis should avoid large amounts of carbohydrates as these stimulate insulin secretion, which in turn drives potassium intracellularly and triggers the episodes of weakness. Meals should be small but frequent and salt intake should be low. In contrast, hyperkalemic periodic paralysis patients benefit from carbohydrate snacks, but should avoid potassium-rich foods, fasting state, and medications that increase potassium (eg, spironolactone). For all the periodic paralyses, mild exercise at the onset of an episode of weakness can help prevent a full-blown attack of paralysis.

Pharmacologic options for periodic paralyses are limited and often involve off-label use of drugs. The only FDA-approved treatment is dichlorphenamide. Carbonic anhydrase inhibitors (eg, acetazolamide and dichlorphenamide) have been used for decades in empiric treatment of hypokalemic periodic paralysis and hyperkalemic periodic paralysis; however, the mechanism of action is not well understood. These drugs promote kaliuresis and increase urinary bicarbonate excretion, thereby leading to nonanion gap acidosis, the latter of which may reduce susceptibility to periodic paralyses.[92] An alternative proposed mechanism is the enhanced opening of calcium-activated potassium channels and mild diuretic effects.[93] Common side effects of carbonic anhydrase inhibitors include paresthesia, fatigue, mild reversible cognitive disturbance, and nephrolithiasis.[94-96] In a randomized placebo-controlled trial, dichlorphenamide reduced the median attack rate in hypokalemic periodic paralysis compared to placebo (0.3 versus 2.4, P = 0.02). It was found to be safe and improved quality of life in patients with hypokalemic periodic paralysis. In the hyperkalemic periodic paralysis cohort, while the attack rate was lower, it did not reach statistical significance. Dichlorphenamide dosing was 50 mg 2 times a day in treatment-naive patients and the mean dose was 82 mg per day.[94] Alternative treatments include potassium-sparing diuretics in hypokalemic periodic paralysis patients and hydrochlorothiazide in hyperkalemic periodic paralysis. TABLE 11-3 lists the abortive and preventive therapies to reduce attack frequency and severity.

KEY POINTS

- Patients with hypokalemic periodic paralysis should avoid large amounts of carbohydrates as these stimulate insulin secretion, which in turn drives potassium intracellularly and triggers the episodes of weakness.
- In a randomized placebo-controlled trial, dichlorphenamide reduced the median attack rate in hypokalemic periodic paralysis compared to placebo.
- Patients with hypokalemic periodic paralysis with *SCN4A* mutations may respond less favorably to carbonic anhydrase inhibitors or may have worsening of symptoms.

MANAGEMENT OF HYPOKALEMIC PERIODIC PARALYSIS OR ANDERSEN-TAWIL SYNDROME DUE TO HYPOKALEMIA. Management of hypokalemic periodic paralysis or Andersen-Tawil syndrome due to hypokalemia is twofold, including abortive treatment as well as prophylactic treatment.

ABORTIVE THERAPY. Potassium supplementation can be effective in treating acute attacks of paralysis in hypokalemic periodic paralysis and Andersen-Tawil syndrome due to hypokalemia.[2,71] Oral potassium administration is preferred at doses of 0.2 to 0.4 mEq/kg every 30 minutes, up to a maximum dose of 200 to 250 mEq per day. IV potassium is only needed when patients cannot take oral potassium, with a dosing of 40 mEq/L in 5% mannitol solution infused at a maximum rate of 20 mEq/h, not to exceed 200 to 250 mEq per day. Glucose- or saline-containing solutions can worsen weakness and should be avoided.[97] Cardiac monitoring is recommended as arrhythmias may occur during an acute paralytic attack as well as during treatment of hypokalemia.[98]

PROPHYLACTIC THERAPY. Carbonic anhydrase inhibitors are generally beneficial in reducing attacks of paralysis, although patients with hypokalemic periodic

paralysis with *SCN4A* mutations may respond less favorably to carbonic anhydrase inhibitors or may have worsening of symptoms. In a cohort of 74 genotyped patients with hypokalemic periodic paralysis, only 46% reported benefit from acetazolamide. Benefit was more evident in patients who had *CACNA1S* mutations (31/55) compared to those with mutations in the *SCN4A* gene (3/9). It was also found that patients with mutations that result in amino acids being substituted by glycine in either gene are less likely to benefit from acetazolamide.[99] Exacerbation has been reported with acetazolamide in select sodium-channel mutations.[100-102]

Dietary prophylaxis includes a low-sodium and low-carbohydrate diet and daily slow-release potassium salt. Pharmacologic prophylaxis includes acetazolamide (125 to 1000 mg per day in two divided doses[103,104]) or dichlorphenamide (50 mg 2 times a day; maximum total daily dosage 200 mg per day).[94] Potassium-sparing diuretics can be used as an alternative or as adjuvant therapy. Recommended doses are triamterene 50 to 150 mg per day, spironolactone 25 to 100 mg per day, or eplerenone 50 to 100 mg per day.[2,105] Spironolactone can cause gynecomastia, in which case eplerenone may be preferred.

MANAGEMENT OF HYPERKALEMIC PERIODIC PARALYSIS OR ANDERSEN-TAWIL SYNDROME DUE TO HYPERKALEMIA. Management of hyperkalemic periodic paralysis or Andersen-Tawil syndrome due to hyperkalemia is twofold, including abortive treatment as well as prophylactic treatment.

ABORTIVE THERAPY. Mild exercise or oral carbohydrate snacks will usually help abort attacks. An inhaled β-agonist like salbutamol or IV calcium gluconate can be used if attacks persist or are severe. Salbutamol dosage is two 100 mcg metered inhalations.[106] As in hypokalemic periodic paralysis, severe attacks should be monitored on telemetry.

PROPHYLACTIC APPROACH. Dietary prophylaxis includes avoidance of potassium-rich foods, and multiple carbohydrate snacks during the day. Pharmacologic options include acetazolamide (125 to 1000 mg per day in two divided doses[103,104]) or dichlorphenamide (50 mg 2 times a day); the latter can be increased weekly to a maximum dosage of 200 mg total daily dose per day.[94] Thiazide diuretics can be used as alternatives or as adjuvant therapy. This includes hydrochlorothiazide at a dosage of 25 to 50 mg per day.[107]

MANAGEMENT OF ANDERSEN-TAWIL SYNDROME. Abortive and prophylactic therapy depends on whether the attacks of weakness are due to hypokalemia or hyperkalemia. Treatment suggestions are described previously for hypokalemic periodic paralysis and hypokalemic periodic paralysis. Additionally, Andersen-Tawil syndrome patients require a multidisciplinary approach with yearly follow-up with a cardiologist who is familiar with treating cardiac arrhythmias. Patients may require annual monitoring with an ambulatory ECG, and if symptomatic arrhythmias develop they may require implantable cardioverter-defibrillators.

ANESTHETIC CONSIDERATIONS. Succinylcholine can trigger myotonia and cause hyperkalemia and so it should be avoided in hyperkalemic periodic paralysis. It is

preferable to use short-acting nondepolarizing neuromuscular blockers for all forms of periodic paralysis. Anticholinesterases should be avoided in hyperkalemic periodic paralysis due to potential risk of exacerbation of myotonia. Carbohydrate load can cause attacks of paralysis in hypokalemic periodic paralysis and glucose solutions should thus be avoided. In contrast, IV dextrose is useful in covering the fasting period in hyperkalemic periodic paralysis patients.[69] An association of malignant hyperthermia in hypokalemic periodic paralysis is possible, so it is advisable to avoid anesthetics that trigger malignant hyperthermia.[69,108]

KEY POINT

- **Succinylcholine can trigger myotonia and cause hyperkalemia and so it should be avoided in hyperkalemic periodic paralysis. It is preferable to use short-acting nondepolarizing neuromuscular blockers for all forms of periodic paralysis.**

CONCLUSION

Despite the rarity and heterogeneity of muscle channelopathies, significant advances in the understanding of these disorders have led to expanded treatment options based on randomized clinical trials. However, more prospective studies are needed and should include long-term follow-up efficacy studies. Patients benefit from a dedicated multidisciplinary approach to managing their conditions. Besides pharmacologic intervention, patients should also be educated about lifestyle and dietary interventions in managing their diseases.

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