REVIEW ARTICLE

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Episodic Muscle Disorders

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ABSTRACT

PURPOSE OF REVIEW: This article reviews the episodic muscle disorders, including benign cramp-fasciculation syndrome, the periodic paralyses, and the nondystrophic myotonias. The core diagnostic criteria for a diagnosis of primary periodic paralysis, including clues to distinguish between the hypokalemic and hyperkalemic forms, and the distinctive elements that characterize Andersen-Tawil syndrome are discussed. Management of patients with these disorders is also discussed.

RECENT FINDINGS: Childhood presentations of periodic paralysis have recently been described, including atypical findings. Carbonic anhydrase inhibitors, such as dichlorphenamide, have recently been approved by the US Food and Drug Administration (FDA) for the treatment of both hypokalemic and hyperkalemic forms of periodic paralysis. Muscle MRI may be a useful outcome measure in pharmacologic trials in periodic paralysis. Genetic research continues to identify additional gene mutations responsible for periodic paralysis.

SUMMARY: This article will help neurologists diagnose and manage episodic muscle disorders and, in particular, the periodic paralyses and the nondystrophic myotonias.

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INTRODUCTION

Episodic muscle disorders are defined as episodes of muscle weakness, muscle pain, or stiffness lasting minutes to hours or days, in general in otherwise healthy-appearing individuals. Patients with episodic muscle disorders may have some degree of muscle atrophy, which is usually proximal; this may be very mild and not associated with functional limitations at rest or between attacks. Muscle strength and deep tendon reflexes are also usually normal in these patients between episodes. Some patients, however, have permanent muscle atrophy and weakness; this is usually proximal and may be disabling.

DIFFERENTIAL DIAGNOSIS OF EPISODIC MUSCLE DISORDERS

Episodic muscle disorders include cramp-fasciculation syndrome, periodic paralyses (including Andersen-Tawil syndrome), and the nondystrophic myotonias (including sodium and chloride channelopathies).

Muscle cramps and fasciculations are the primary symptoms of cramp-fasciculation syndrome. These are usually clearly visible on examination

and are usually confined to the calves at rest and after percussion of the muscle bulk.

During an episode of muscle weakness, patients with periodic paralysis may become totally paralyzed, or, more frequently, weakness may affect one or more limbs, making patients feel that they are unable to lift an arm from the bed, rise from a chair, or hold something in their arms. Although muscles may be of normal bulk, deep tendon reflexes are absent during an attack.

Myotonia is the delayed relaxation after a maximal voluntary contraction; it is usually seen in the hands but may also present in the lower limbs or facial and jaw muscles. Patients with nondystrophic myotonia usually have episodic stiffness, triggered most frequently by changes in temperature or by rest after exercise. In the sodium channelopathies, patients may have episodic pain, and in both sodium and chloride channelopathies, patients may experience episodic weakness.

Hypothyroidism may also be associated with muscle pain and weakness, but it is usually not episodic in nature. Patients may report muscle weakness even if their muscles are bulky and not weak on examination. Some patients may have stiffness and occasional myotonia. If this persists despite normal thyroid function, it is most likely related to a coexistent underlying channelopathy. In fact, reports exist of hypothyroidism unmasking both dystrophic and nondystrophic myotonic disorders.[1,2]

The diagnosis of an episodic muscle disorder is primarily clinical. Muscle strength is usually normal in these patients. Patients with periodic paralysis or nondystrophic myotonia will have episodic weakness involving one or more limbs and usually also loss of deep tendon reflexes during an attack. Patients with nondystrophic myotonia differ from those with periodic paralysis because myotonia is always present in the nondystrophic myotonias involving sodium and chloride channels, while it is absent in the calcium channelopathies resulting in hypokalemic periodic paralysis and in patients with Andersen-Tawil syndrome. Myotonia may be present occasionally in some patients with hypothyroidism.

BENIGN MUSCLE CRAMP-FASCICULATION SYNDROME

Cramp-fasciculation syndrome is a rare condition characterized by persistent muscle cramping and twitching (fasciculations), usually in the legs, in otherwise healthy individuals.[3] Anxiety may also be present. It is an acquired disorder, often associated with signs of mild neuropathy or neurogenic findings on electrophysiologic studies.[4] Rarely, patients may have tingling of the hands and feet. Deep tendon reflexes are usually normal or brisk. Muscle strength examination is normal, creatine kinase may be mildly elevated (up to double the normal level in rare cases), and cramps and fasciculations are usually the only findings on EMG studies. In most cases, patients respond to membrane stabilizers such as pregabalin or carbamazepine. Relatives of patients with a diagnosis of familial amyotrophic lateral sclerosis (ALS) may present with persistent muscle cramps and fasciculations. Whether these symptoms will develop into ALS is unclear, so careful monitoring is warranted for these patients.[5] Limited data are available to provide consensus on the relationship between these two very different conditions in terms of prognosis. However, in ALS, cramps and fasciculations are usually not the only findings on neurologic examination, and EMG usually reveals initial motor neuron dysfunction.

Neuromyotonia is another presentation of peripheral nerve hyperexcitability. The diagnosis requires a high index of suspicion, support from the physical

KEY POINT

- **Cramp-fasciculation syndrome is a rare condition characterized by persistent muscle cramping and twitching (fasciculations), usually in the legs, in otherwise healthy individuals.**

examination, and recognition of diagnostic EMG features. Neuromyotonia may be hereditary, immune-mediated, or part of other neurologic disorders. When the cause is immune-mediated, neuromyotonia is known as Isaacs syndrome. This is an antibody-mediated potassium channel complex disorder. Not infrequently, this is associated with neoplasm, especially thymoma, and the specific channels affected are the dendrotoxin-sensitive fast potassium channels. These potassium channel complex antibodies are involved in an increasing number of immune-mediated neurologic disorders such as limbic encephalitis and temporal lobe epilepsy as well as in Morvan syndrome, a rare condition involving both peripheral and central nervous system signs with anti–voltage-gated potassium channel complex antibodies.

THE PERIODIC PARALYSES

The primary periodic paralyses are rare autosomal dominant muscle diseases. The estimated prevalence is 1 in 100,000 for hyperkalemic periodic paralysis,[6,7] 1 in 200,000 for hypokalemic periodic paralysis,[6,8] and 1 in 1,000,000 for Andersen-Tawil syndrome.[9] Onset is typically in early childhood, but onset later in life has also been described.

Most adult patients with periodic paralysis have muscles of apparently normal bulk and strength, but careful examination may reveal signs of muscle involvement (FIGURE 9-1 and FIGURE 9-2). Some patients will have proximal muscle atrophy and weakness, especially in the lower limbs, resembling a limb-girdle myopathy because of a fixed weakness.[10,11] Patients with periodic paralysis report that during the course of a day, they may experience episodes of weakness involving one or more limbs (abortive forms) lasting several minutes to several hours. Episodes may sometimes last for days. Frequently, specific factors and situations are identified as triggering the episodes, and episodes may be more frequent at certain times of the day. These abortive episodes may be overlooked by patients because of the transitory nature of the events. Often, the episodes may lead to a complete flaccid tetraparesis (complete adynamia); this severe presentation most often leads to the emergency department and requires prompt diagnosis so that treatment can be started to correct the underlying cause and speed recovery (CASE 9-1). No data have been published on diagnostic delay in these

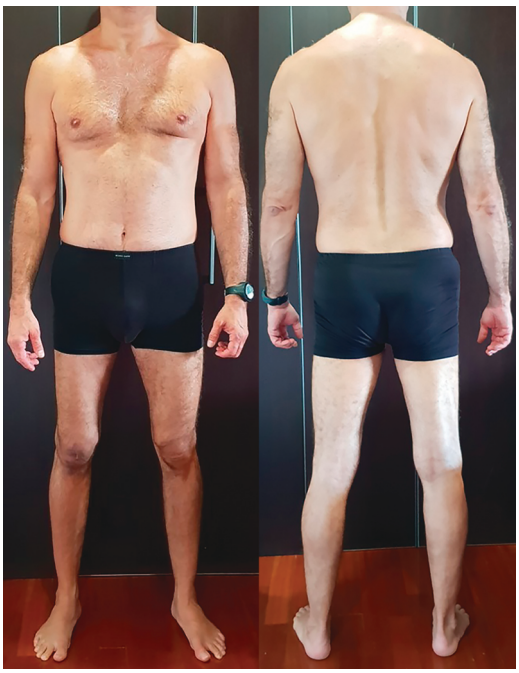

FIGURE 9-1
Hypokalemic periodic paralysis. The patient has asymmetric mild muscular atrophy in the lower limbs, this being more evident in the right thigh especially. He has normal muscle strength between attacks.

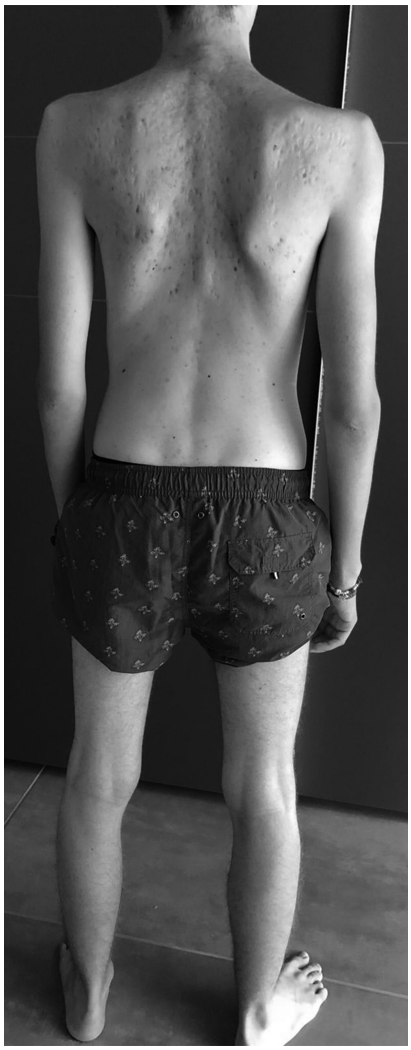

FIGURE 9-2
Hypokalemic periodic paralysis. Note the patient's mild scapular winging and proximal muscle atrophy. Note the difference from the patient described in FIGURE 9-1. In this case, the upper limbs are more involved than the lower limbs.

patients, but it is common for abortive presentations to be attributed to a psychiatric cause. A careful family history, exploration of possible triggers, serum potassium level, and absent deep tendon reflexes during an attack can help in the diagnosis (CASE 9-2). If the initial presentation of periodic paralysis is complete paralysis, the diagnosis of an acute inflammatory polyradiculoneuropathy such as Guillain-Barré syndrome may delay proper diagnosis and management.

Once the diagnosis of periodic paralysis is made, patients can usually identify and thus avoid specific triggers and learn how to handle the abortive episodes (CASE 9-3 and CASE 9-4). Despite avoidance of triggers, episodes may continue; this may contribute to the development of a fixed proximal myopathy. Several authors have investigated the morbidity of these disorders and have demonstrated that quality of life is impaired in these patients as in chronic and progressive muscular dystrophies.[12,13]

The diagnosis of periodic paralysis is usually made after an episode of complete paralysis. If a family member has already been diagnosed with either a hypokalemic or a hyperkalemic periodic paralysis, the diagnosis is rather straightforward. Parents of these children may have had one or two episodes in childhood followed by an improvement in their symptoms, with only one or two abortive episodes a month. Some children may have additional features not usually reported in typical hypokalemic or hyperkalemic periodic paralysis, such as extraocular muscle involvement, foot deformities, leg cramps, and muscle pain.[14] Neurologic examination in pediatric patients is usually also characterized by myotonia in the sodium or chloride channelopathies. Patients with chloride channelopathies may have muscle hypertrophy. Myotonia is the delayed relaxation of a muscle group after a maximum contraction; it can be seen in patients' legs when walking because they appear to be stiff and have an unusual robotic gait.[14] Extraocular myotonia may also be present, leading to fluctuating strabismus and diplopia as well as lid lag, which can be seen as a delayed palpebral descending movement when the eyes rapidly move from upward to downward gaze, leaving the sclera clearly visible to the examiner.

More severe presentations in neonatal forms of hyperkalemic periodic paralysis include laryngeal stridor[14]; this presentation should prompt a diagnostic

KEY POINTS

- Abortive attacks of weakness involving one or more limbs may erroneously suggest a psychogenic (functional) neurologic disorder because of the transitory nature of the event and the anxiety patients experience related to the loss of function, no matter how brief.
- Complete paralysis of all four limbs is the typical presentation that leads to the diagnostic workup for periodic paralysis. The most frequent differential diagnosis is Guillain-Barré syndrome.
- Children presenting with leg stiffness, cramps, muscle pain, and fluctuating extraocular movements should be examined for myotonia to rule out an underlying sodium channelopathy.
- Episodes of muscle weakness may also occur in the nondystrophic myotonias (sodium and chloride channelopathies).

workup for muscle channelopathies. In these patients, episodes of transitory muscle weakness involving one or more limbs may occur, as in periodic paralysis. However, these patients are not classified as having periodic paralysis but nondystrophic myotonias (sodium and chloride channelopathies).

Episodes of weakness may also occur in a distinct, autosomal dominant periodic paralysis known as *Andersen-Tawil syndrome*. In addition to muscle involvement that is comparable to that of the other primary periodic paralyses, patients with Andersen-Tawil syndrome usually have specific facial and skeletal features, such as a small chin (micrognathia), low-set ears, close-set eyes (hypotelorism) (FIGURE 9-3), and double-rowed teeth. These children are usually of small stature and have distinctive features of the hands (short fifth finger, flattened palm, clinodactyly) and toes (usually syndactyly). The most serious

CASE 9-1

A 6-year-old boy experienced an episode of complete weakness on awakening in the morning and was unable to get out of bed. He and his parents were very frightened and recalled the episode quite distinctly. He was taken to the emergency department, where a complete battery of blood tests was obtained. His potassium level was 1.7 mEq/L. With a slow infusion of potassium, he had gradual recovery, and the episode completely resolved within 13 hours, although he had fatigue and general malaise, which completely resolved after an additional 20 hours. He was discharged with the diagnosis of probable hypokalemic periodic paralysis, and an outpatient neurology consultation was recommended. He went back to school after 2 days.

On neurologic evaluation, the patient reported muscle pain and always being tired and unwilling to play with his schoolmates. On examination, his muscles were of normal bulk and tone, and he had normal strength.

He was started on dichlorphenamide 50 mg 1 time a day. A low-carbohydrate diet and potassium-rich foods were recommended. Genetic testing revealed a common mutation in the *CACNA1* gene.

Over the next 16 years, the patient experienced only five episodes of complete weakness that led him to the emergency department; all were triggered by exercise or after a high-carbohydrate meal. Other minor and abortive episodes occurred before school tests or other situations that caused anxiety for him. He learned to overcome the episodes by moving around at the onset of symptoms and increasing his potassium intake as needed. Between episodes, he stated that he was in good health; when specifically inquired about his muscle strength, he described his muscle strength as 2 on a scale from 0 to 9 (0 = normal strength; 9 = no strength, extreme weakness) and stated that a score of 2 was his normal functional muscle state.

COMMENT

This case describes a typical onset of periodic paralysis in childhood. The severity is such that the young patients are completely unable to move but remain awake and alert; they are, therefore, very frightened. Usually breathing, heartbeat, and blood pressure are unaffected.

feature of Andersen-Tawil syndrome is cardiac involvement,[15–19] which is characterized by severe arrhythmias such as sustained ventricular arrhythmias, torsade de pointes, and prolonged QT interval. The prolonged QT interval justifies the classification of Andersen-Tawil syndrome as a variant of the many long QT syndromes and designated as LQT7. Despite the general concept that this is a less severe form of long QT syndrome, natural history

CASE 9-2

A 3-year-old boy had an episode of complete paralysis in the evening, when he was unable to rise from the couch. His parents described him as being "floppy." Earlier that day he was at a school party at which he had played ball, had a soft drink, and ate chips and candy with his schoolmates.

He was taken to the emergency department, where his potassium level was 1.2 mEq/L, and his creatine kinase level was 3 times the normal level. After potassium replacement, his muscle strength gradually recovered, and he was again able to walk and run. However, his parents noticed that he had difficulty going up and down stairs and depended on a railing. Getting up from the floor was also difficult for him, and he needed to hold on to the furniture to stand from a sitting position. A neurologic consultation was recommended.

On neurologic examination, the patient was found to have mild scapular winging, hyperlordosis, and a waddling gait resembling a muscular dystrophy. Genetic testing for mutations in the *CACNA1* gene and muscle biopsy for dystrophin immunostaining were performed. A common mutation in the *CACNA1* gene was found. Dystrophin and dystrophin-associated proteins were normally distributed in this patient's muscle fibers. The patient was started on 50 mg dichlorphenamide 1 time a day and potassium tablets as needed and discharged with the diagnosis of hypokalemic periodic paralysis.

Twenty years later, on neurologic evaluation, the patient walked independently, but his gait was waddling, and he was unable to rise from a chair or climb stairs unaided. Proximal muscle weakness was present in the upper limbs, and his distal strength was normal. He had experienced only two complete episodes of weakness since the first episode at age 3, but he continuously experienced fluctuations in his muscle strength and episodes of paralysis that overlapped with the permanent weakness.

COMMENT

This case illustrates the typical triggers, which patients learn to avoid as they grow up, that may cause a complete paralysis in patients with either hypokalemic or hyperkalemic periodic paralysis. Clinicians should counsel patients to avoid developing obsessions with diet, carbohydrate intake, and potassium intake. Although not specifically exemplified in this case, patients may fear an episode will occur and become excessively worried about eating certain foods, completely avoiding carbohydrates and increasing intake of high-potassium foods. A diet with fewer carbohydrates that is high in potassium is recommended but must be balanced.

data on cardiac involvement and specifically on cardiac death and implantable cardioverter-defibrillator implantations in these patients are missing, and close monitoring and caution are warranted even in patients who are apparently asymptomatic.

In the primary periodic paralyses, episodes of weakness may occur because serum potassium levels fall below the normal range (as low as 1.2 mEq/L), termed *hypokalemic periodic paralysis*, or rise above the normal range (as high as 5.6 mEq/L), termed *hyperkalemic periodic paralysis*. In Andersen-Tawil syndrome, episodes can occur in both settings.[18–25] In the nondystrophic myotonias, serum potassium levels are unaffected during episodes of muscle weakness and exacerbation of myotonia.

Hypokalemic periodic paralysis is primarily caused by mutations in the calcium channel *CACNA1S*[21–25] and rarely due to mutations in the sodium channel *SCN4A*.[26–30] Hyperkalemic periodic paralysis is associated with mutations in the sodium channel *SCN4A* gene on chromosome 17.[31–35] Andersen-Tawil syndrome is most commonly caused by mutations of the

CASE 9-3

A 29-year-old man presented to the emergency department following an attack of paralysis that occurred after a football game and drinking several beers with his friends. In the emergency department, his potassium level was 1.3 mEq/L, and his creatine kinase level was in the thousands. His history revealed that he had experienced other attacks during adolescence that had never been diagnosed because they had always been only partially limiting and had always resolved spontaneously after several hours. He had since learned to avoid high-carbohydrate meals and exercise to avoid recurrence of the episodes.

On examination, his muscles appeared to be of normal bulk, tone, and strength except for mild scapular winging. ECG showed normal findings except for flattening of T waves. Serum potassium levels rose to normal 4 hours after oral potassium supplementation.

During an outpatient visit 1 month later, the clinical suspicion of hypokalemic periodic paralysis was confirmed by genetic testing, which showed a common calcium channel mutation R528H on *CACN1A*. No preventive treatment was initiated, but the patient was asked to report his episodes in a diary, including the times at the beginning and end of the attack and a score of its severity from 0 to 9, to clarify the frequency and severity of the attacks. It was agreed that if he had four or five episodes per month, no matter how minor, treatment with a carbonic anhydrase inhibitor would be discussed.

COMMENT

This case illustrates that exercise may be a trigger for a paralytic episode. Potassium may reach very low levels, but cardiac function is usually unaffected except for the appearance of abnormal U waves on ECG, which is a typical finding in patients with Andersen-Tawil syndrome. This patient did not have Andersen-Tawil syndrome but rather a primary hypokalemic periodic paralysis.

KCNJ2 gene. Functional and clinical characterization of mutations of this gene on chromosome 17 result in loss or suppression of the function of the channel Kir2.1, an inward rectifier associated with LQT7.[17] These mutations result in a reduction in the function of the channel (TABLE 9-1).[28,36]

Diagnostic Criteria

Diagnostic criteria for primary periodic paralyses were proposed by an expert committee at the 87th European Neuromuscular Centre International Workshop in 2000 and were recently revised.[37]

In general, the diagnosis of periodic paralysis is a clinical one, and genetic testing should be targeted to confirm the clinical suspicion based on the clinical criteria. Genetic testing (whole-genome sequencing) identifies mutations in about 60% to 70% of patients who meet clinical criteria.[35,38] In the absence of an identified genetic mutation (about 30% of patients), periodic paralysis subtypes can be differentiated on the basis of clinical presentation, serum potassium levels during attacks, and decremental responses after repetitive stimulation during long-term exercise.[37,39] If periodic paralysis is suspected but cannot be confirmed genetically, further assessment should be conducted to exclude other conditions (eg, thyrotoxicosis or secondary causes of blood potassium deficiency or excess). If secondary causes are ruled out and the clinical suspicion of a muscle channelopathy is still high, patients should be subjected to further genetic workup (FIGURES 9-4A and 9-4B).

CASE 9-4

A 15-year-old girl with hyperkalemic periodic paralysis due to a common mutation in the *SCN4A* gene presented to the emergency department with weakness that began in one arm after exercise and spread to all four limbs. She loved aerobics and trained for an hour and a half every day. Her attacks of weakness typically occurred after training, never during training, and lasted for no longer than a couple of hours before resolving spontaneously.

In the emergency department, her potassium level was 5.7 mEq/L, and her creatine kinase level was elevated to twice the normal level. No ECG abnormalities were recorded except for sharp T waves. On examination between attacks, her muscles were of normal tone, bulk, and strength. Myotonia was clearly evident in her eyelids and hands.

She was started on acetazolamide 125 mg 2 times a day. No further episodes occurred, and she continued to train.

COMMENT

This case shows the presentation of the hyperkalemic form of periodic paralysis. In hyperkalemic periodic paralysis, attacks are usually shorter than those experienced by patients who have hypokalemic periodic paralysis; the triggers may be different between the two groups of patients, as well. The attacks may be more frequent during the day. Treatment can be very effective, and in some cases, patients may have no significant limitations.

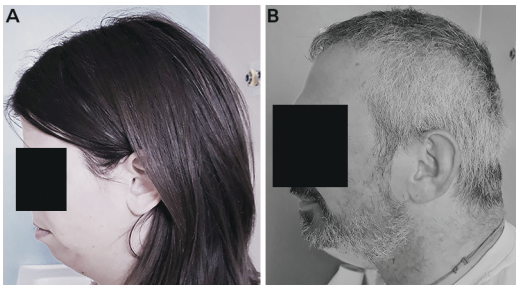

FIGURE 9-3
Andersen-Tawil syndrome. Note the typical facial appearance (low-set ears and small chin in *A*, small chin in *B*).

Blood tests are useful only during an acute episode of weakness because the serum potassium level during an attack is a crucial criterion for the diagnosis of either hypokalemic or hyperkalemic periodic paralysis. Creatine kinase levels are usually normal or mildly elevated (2 to 3 times the normal level) even during an attack, although some patients may have occasional levels in the thousands (10 times the normal level).

EMG is a useful diagnostic test in the periodic paralyses and may help to confirm the clinical suspicion in cases in which the family history is unclear and serum potassium levels during an attack are unavailable. A specific protocol (Fournier protocol[40]) including repetitive stimulation before and after short and long exercise is required and should be performed by an experienced neurophysiologist.[40]

Muscle biopsy should not be routinely done in patients with periodic paralysis. Tubular aggregates may be found in some cases and can contribute to the diagnosis in patients with negative genetic testing but with clear clinical criteria for probable periodic paralysis.[41] However, these are not specific and can be present in other conditions.[42]

Muscle MRI is not routinely performed in patients with periodic paralysis, but some reports have shown preclinical abnormalities in patients with hypokalemic periodic paralysis,[43,44] and evidence is growing that muscle MRI may be used to monitor disease progression and response to therapy (refer to the Trends section).

Treatment of Periodic Paralysis

Management of periodic paralysis is essentially based on three principles. The first is to avoid known triggers, such as high-carbohydrate meals and prolonged rest after exercise for patients with hypokalemic periodic paralysis and to reduce stressful situations, such as nightshift work, irregular meals, and abnormal sleep-wake cycles, that may precipitate hypokalemic paralytic episodes.

The second principle is that patients' serum potassium levels should be stabilized. For patients with hypokalemic periodic paralysis, this can be done by increasing potassium intake by following a diet high in potassium-rich foods. However, even regular potassium intake and adherence to the prescribed diet may fail to prevent attacks, and escalating potassium intake may cause gastrointestinal problems. In patients with hyperkalemic periodic paralysis, serum potassium levels can be stabilized by adhering to a diet low in potassium-rich food and the use of diuretics, but all the same, these attempts may fail to prevent attacks in the hyperkalemic form in some patients.[45]

Third, patients should be made aware that episodes of weakness, no matter how brief, may lead to muscle damage and permanent weakness, so if episodes

continue, a more aggressive pharmacologic therapeutic approach should be applied.[46]

The serum potassium abnormalities seen in the periodic paralyses and the response to potassium administration provide a rationale for the use of drugs capable of affecting serum potassium levels, such as carbonic anhydrase inhibitors.[47,48] In general, studies have aimed to reduce the frequency and severity of the attacks primarily with the use of two drugs: acetazolamide[28,47–50] and dichlorphenamide.[10,51,52] Dichlorphenamide is an alternative carbonic anhydrase inhibitor with side effects similar to acetazolamide but milder. In August 2015, the US Food and Drug Administration (FDA) approved dichlorphenamide as a pharmacologic treatment for hypokalemic and hyperkalemic periodic paralysis. Although some patients respond to acetazolamide, clinical experience indicates that side effects are more common with acetazolamide compared to dichlorphenamide.[51] Common side effects of carbonic anhydrase inhibitors include paresthesia, fatigue, and mild reversible cognitive disturbances.[52] A study by Sansone and colleagues[52] did not allow direct comparison of the two drugs; however, the fact that the initial study design, which included an arm with acetazolamide in addition to an arm with dichlorphenamide, failed to recruit patients, may be an indirect indication of patient preferences. The study was redesigned and amended to include only the dichlorphenamide arm and a placebo arm.

In patients with Andersen-Tawil syndrome, close monitoring of cardiac function, even in patients who are asymptomatic, is recommended. Paralytic attacks in Andersen-Tawil syndrome may be managed similarly to hypokalemic or hyperkalemic primary periodic paralysis, and carbonic anhydrase inhibitors are used to prevent attacks based on expert clinical experience,[37,51,52] although no randomized controlled clinical trial has been performed in patients with Andersen-Tawil syndrome.

NONDYSTROPHIC MYOTONIAS

The nondystrophic myotonias include sodium and chloride channelopathies. They are caused by mutations in voltage-gated ion channels on the skeletal muscle membrane resulting in episodic muscle weakness or myotonia.[53] The skeletal muscle sodium channelopathies are autosomal dominant allelic disorders that include hyperkalemic periodic paralysis and paramyotonia congenita, resulting from mutations occurring in the α-subunit of the channel that is expressed by the *SCN4A* gene located on chromosome 17q23.1-25.3.[54] They are characterized by episodes of stiffness and weakness, usually triggered by rather typical stimuli. From a clinical point of view, episodes of paralysis are typical of hyperkalemic periodic paralysis due to *SCN4A* mutations. They usually last a few minutes and are triggered by fasting or by rest following exercise. Weakness primarily affects the lower limbs, while myotonia in these patients mostly affects the face and hands. Muscle pain may be frequently reported in these channelopathies and is not always related to myotonia. Symptoms of myotonia and muscle pain may worsen with low external temperatures or with temperature changes. In paramyotonia (ie, paradoxical myotonia), changes in temperature cause myotonia. In contrast to what normally happens in other forms of myotonia, myotonia worsens with repeated exercise; this is known as paramyotonia. Episodes of paralysis may or may not be associated.

The chloride channelopathies are due to mutations in the skeletal muscle chloride channel (type 1), encoded on chromosome 7q35.[55–57] Mutations result in

KEY POINTS

- Cardiac involvement in Andersen-Tawil syndrome warrants close monitoring, even in patients who are asymptomatic.
- Testing the patient's serum potassium level during an attack of weakness is crucial to the diagnosis of periodic paralysis.
- Creatine kinase levels are not diagnostic in periodic paralysis.
- EMG may contribute to the diagnosis of periodic paralysis in patients in whom family history and potassium levels during an attack are unavailable or not informative.
- Muscle biopsy is not diagnostic in periodic paralysis; although tubular aggregates may be found in some patients, they are not specific to periodic paralysis.
- Patients can manage their episodes of periodic paralysis by learning to avoid triggers, following a diet based on the type of periodic paralysis, and stabilizing their serum potassium levels by taking oral potassium or diuretics according to the type of periodic paralysis.
- When managing patients with periodic paralysis, clinicians should consider more aggressive pharmacologic treatment with carbonic anhydrase inhibitors (preferably dichlorphenamide), if needed, and closely monitor cardiac function in Andersen-Tawil syndrome, even when no symptoms are present.

an autosomal dominant form (Thomsen disease) or an autosomal recessive form (Becker type). The autosomal dominant variant is usually present at birth, whereas the recessive form develops during the first or second decade, beginning in the legs and progressing to the arms, neck, and facial muscles. It is less prominent in the eyes, except for lid lag, which may be clearly evident. Lid lag is most frequent in the nondystrophic myotonias but may be seen in patients with myotonic dystrophy type 2 (DM2).

Patients with Thomsen disease are typically very muscular in appearance and have diffuse myotonia in the trunk and limbs and usually not in the facial or jaw muscles. DM2 needs to be ruled out. Patients with myotonic dystrophy, in fact, may have muscles of normal bulk at onset, and there may be calf hypertrophy; this appearance and myotonia may remind clinicians of the nondystrophic autosomal dominant form of Thomsen disease. However, the multisystem nature of the dystrophic form and the early-onset cataracts are characteristic of DM2 only.

TABLE 9-1 **Main Genes and Channels Involved in Major Types of Periodic Paralysis**

Type of Periodic Paralysis	Chromosome Number	Gene Lesion	Protein Involved	Physiologic Functional Consequences	Main Clinical Characteristics
Hypokalemic periodic paralysis					
Type 1	1q32	*CACNA1S*	Cav1.1 on the transverse tubules of skeletal muscle	Reduced excitability and increased sodium conductance, aggravated by reduced extracellular potassium concentration	Autosomal dominant Episodes of muscle weakness triggered by carbohydrate-rich meals or prolonged resting No myotonia Onset usually in childhood Usually acetazolamide or dichlorphenamide responsive A permanent proximal myopathy may be present
Type 2	17q23.1q25.3	*SCN4A*	Nav1.4 on the neuromuscular junction	Similar to type 1 but further aggravated by a decreased density of membrane sodium channels, decreasing overall current	Autosomal dominant Similar to type 1 but usually episodes of weakness worsen with acetazolamide or dichlorphenamide

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Mexiletine is the drug of choice for myotonia in both nondystrophic and dystrophic myotonias. Cardiac monitoring with the use of mexiletine often involves a baseline ECG and a follow-up ECG in the first 3 months of treatment. Cardiac monitoring for myotonic dystrophy type 1 and type 2 is discussed in the article, "Myotonic Muscular Dystrophies," by Nicholas E. Johnson, MD, MSc, FAAN,[58] in this issue of *Continuum*. For the nondystrophic myotonias, regular cardiac monitoring is not indicated. For other channelopathies, it is only in Andersen-Tawil syndrome that serial ECGs or Holter monitoring is indicated.

TRENDS

Dichlorphenamide has been approved by the FDA, but it is only available in Europe on an individual basis; the cost currently limits its use to patients who do not respond to acetazolamide. Despite the favorable profile of dichlorphenamide compared to acetazolamide, debate on whether it should always be preferred to acetazolamide given the apparently reduced number and

CONTINUED FROM PAGE 1706

Type of Periodic Paralysis	Chromosome Number	Gene Lesion	Protein Involved	Physiologic Functional Consequences	Main Clinical Characteristics
Hyperkalemic periodic paralysis	17q23.1q25.3	*SCN4A*	Nav1.4 on the neuromuscular junction	Increased sodium influx into the cells, which triggers the release of potassium from muscle cells, which in turn causes more sodium channels to open and stimulates the flow of more sodium ions into the cells, reducing the overall ability of skeletal muscles to contract	Autosomal dominant Episodes of muscle weakness triggered by fasting or exercise Myotonia in the eyes and hands Often painful Onset may be in later childhood
Andersen-Tawil syndrome	17q24.3	*KCNJ2*	Kir2.1	Loss of function or suppression of the inward rectifying potassium current and, therefore, loss of function of the channel protein	Autosomal dominant Episodes of muscle weakness usually associated with hypokalemia, but normokalemia and hyperkalemia may also occur Characteristic facial and skeletal features, often diagnostic Potentially severe cardiac arrhythmias (long QT syndrome 7) Incomplete penetrance Onset may be in childhood

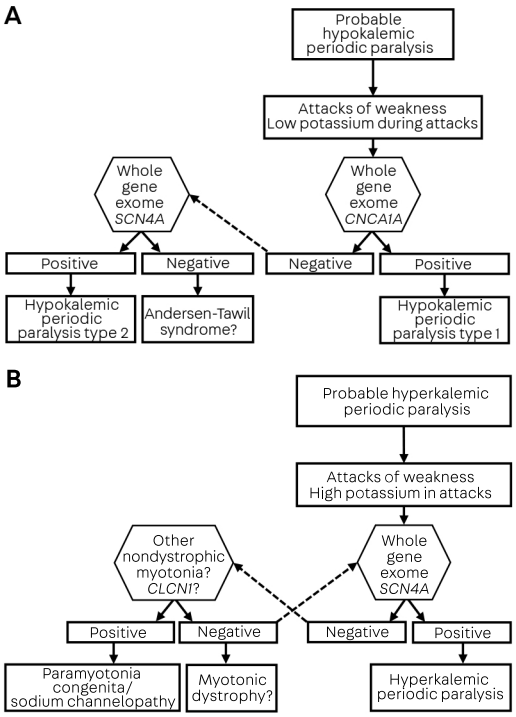

FIGURE 9-4
Suggested genetic workup for hypokalemic (*A*) and hyperkalemic (*B*) periodic paralysis.

severity of side effects is ongoing. How and to what extent both these drugs reduce and affect the development of permanent muscle weakness requires more study. Although expert opinion supports the use of carbonic anhydrase inhibitors in patients with Andersen-Tawil syndrome, more evidence is needed in this patient population.

Muscle MRI is increasingly important in neuromuscular disorders. Previous findings suggesting that muscle tissue is replaced by fibrous and fat tissue even in apparently strong muscles suggest that abnormalities in skeletal muscle may occur early in the course of the disease. In addition to fatty and fibrous replacement, preliminary reports suggest that "edema-type" abnormalities may be seen that are transitory and can respond to treatment. This suggests that muscle MRI may be a useful outcome measure in pharmacologic trials in periodic paralyses.

A number of patients (20%) with a clinical suspicion of periodic paralysis or a channelopathy, in general, do not have any known genetic mutation. Additional genetic mutations may yet be identified in the muscle channelopathies.

CONCLUSION

Episodic muscle disorders include a variety of disorders ranging from benign muscle cramps and fasciculations to more severe forms of paralysis, such as Andersen-Tawil syndrome, in which life-threatening cardiac arrhythmias may occur. Although all these disorders share the episodic nature of symptoms such as muscle pain, stiffness, or muscle weakness and thus have overlapping features, distinct clues to the diagnosis exist for each type, which may help physicians in the management of these patients. Episodes of muscle weakness are characteristic of the primary periodic paralyses and can occur in patients having either the hypokalemic form or the hyperkalemic form or the distinct form known as Andersen-Tawil syndrome. Patients with nondystrophic myotonias may experience episodes of transitory muscle weakness in the predominantly myotonic phenotype. Age at onset of the periodic paralyses is typically in childhood, but later onset has been described. Children may have additional clinical features that may be indicative of an underlying periodic paralysis that should be initially considered if unclear abnormalities in gait, muscle pain, and

cramps are present or when extraocular impairment appears to be fluctuating and is not clearly suggestive of another specific muscle or nerve disorder.

Although often considered "benign" disorders compared to other chronic and progressive disorders, morbidity is high, and quality of life is impaired in patients with episodic muscle disorders. Moreover, the cardiac involvement in Andersen-Tawil syndrome should not be underestimated because, although natural history data are missing, cardiac arrest may occur; implantable cardioverter-defibrillators may need to be considered to prevent severe and life-threatening ventricular arrhythmias. Close monitoring is recommended, even in patients who are apparently asymptomatic, and may prevent potentially life-threatening conditions.

Treatment of these episodic muscle disorders depends on the severity of the phenotype. Muscle membrane stabilizers, such as pregabalin or carbamazepine, are usually effective for myotonia or muscle stiffness and have an indirect action on anxiety and muscle tension, which aggravate the clinical picture. Treatment for periodic paralysis should include both preventive measures (avoiding triggers, complying to dietary recommendations) and pharmacologic treatments, especially considering that permanent muscle weakness is thought to become more likely if the episodes of paralysis are untreated. General consensus exists that pharmacologic treatment should probably be limited to patients having four or more episodes of weakness a month, similar to the criteria applied during randomized controlled trials of dichlorphenamide. Patients should be informed that even short and mild episodes should be included in their reports of the number of episodes per month to avoid potentially harmful underestimations.

The best management approach should be discussed with individual patients and tailored according to the type of episodic muscle disorder. Natural history studies addressing both muscle and cardiac progression over time will be very useful to improve communication and decision making among patients and physicians.

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