


## REVIEW OF THE DIAGNOSIS AND TREATMENT OF PERIODIC PARALYSIS

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**ABSTRACT:** Periodic paralyses (PPs) are rare neuromuscular disorders caused by mutations in skeletal muscle sodium, calcium, and potassium channel genes. PPs include hypokalemic paralysis, hyperkalemic paralysis, and Andersen-Tawil syndrome. Common features of PP include autosomal dominant inheritance, onset typically in the first or second decades, episodic attacks of flaccid weakness, which are often triggered by diet or rest after exercise. Diagnosis is based on the characteristic clinic presentation then confirmed by genetic testing. In the absence of an identified genetic mutation, documented low or high potassium levels during attacks or a decrement on long exercise testing support diagnosis. The treatment approach should include both management of acute attacks and prevention of attacks. Treatments include behavioral interventions directed at avoidance of triggers, modification of potassium levels, diuretics, and carbonic anhydrase inhibitors.

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**Abbreviations:** CMAP, compound muscle action potentials; ECG, electrocardiographic; EMG, electromyography; FDA, Food and Drug Administration; IV, intravenous; NKCC, Na-K-2Cl; PMC, paramyotonia congenita; PVC, premature ventricular contraction; VT, ventricular tachycardia

**Key words:** acetazolamide; Andersen-Tawil syndrome; channelopathies; dichlorophenamide; periodic paralyses; review; treatment

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**P**Primary periodic paralyses (PPs) are rare autosomal-dominant genetic neuromuscular disorders associated with mutations in the skeletal muscle sodium, calcium, and potassium channels.<sup>1,2</sup> Common to all PP are attacks of muscle paralysis, which may last minutes to hours or days and cause morbidity and impaired quality of life.<sup>3,4</sup> The attacks are often triggered by behavior or diet, and often are associated with alterations in serum potassium levels. In all forms of PP, ictal paresis is caused by depolarization of the muscle sarcolemma, which in turn causes sodium channel inactivation and reduced fiber excitability.<sup>1,2</sup>

Primary periodic paralyses include hypokalemic paralysis (HypoPP), hyperkalemic paralysis (HyperPP), and Andersen-Tawil syndrome. There are also closely related diseases whose features overlap with HypoPP and HyperPP, including paramyotonia congenita (PMC) and normokalemic PP. In most instances, these diseases are caused by mutations of the sodium channel. The sodium channel mutations present as a spectrum of disorders, ranging from pure myotonic disorders to disorders which primarily have myotonia with episodic weakness (e.g., PMC) to disorders with primary episodic weakness with occasional myotonia (HyperPP and normokalemic PP). There is some overlap, and the determination of whether to classify a disorder as PMC or HyperPP will depend on the predominant symptoms. Estimated prevalences for the periodic paralyses are 1 per 200,000 for HyperPP,<sup>5,6</sup> 1 per 100,000 for HypoPP,<sup>5,7</sup> and 1 per 1,000,000 for Andersen-Tawil syndrome,<sup>8</sup> although a study in the United Kingdom identified a lower prevalence for many of the channelopathies.<sup>9</sup> Nevertheless, these diseases are rare in the general population and as a consequence prospective clinical studies of treatment interventions are limited.

**Table 1.** Clinical presentation of PPPs

Feature	HypoPP	HyperPP	Andersen-Tawil syndrome
Ictal K <sup>+</sup> level	Low	High/normal	Variable
Age at onset	Age 5–35 y	Before age 20 y	Age 2–18 y
Mean duration of episodes	>2h	<2h	1 to 36h
Muscle stiffness	Absent	Moderate	Absent
Episodic weakness	Yes	Yes	Yes
Maximum weakness	Severe	Mild to severe	Moderate
Characteristic facies	Absent	Absent	Present
Arrhythmias	Absent	Absent	Long QT arrhythmia

Treatment options include avoidance of triggers, potassium supplementation to increase potassium levels, and carbonic anhydrase inhibitors. Because of the low prevalence of primary PP and limited treatment options, few prospective studies are available to guide management recommendations, which are primarily based on anecdotal evidence and patient case reports.

This review addresses the diagnosis and treatment of primary PP. The recommendations are based on published literature and on experience of clinicians in managing patients with PP.

#### TYPES OF PRIMARY PERIODIC PARALYSIS

Most individuals with primary PP have inherited autosomal dominant disorders; sporadic cases also occur, although the frequency is unknown.<sup>10</sup> While all of the familial disorders can be attributed to genetic mutations in muscle ion channels, they differ in their genetics, signs and symptoms, and treatment.

HypoPP is associated with mutations in calcium channel (*CACNA1S*; 60% of kindreds) and sodium channel (*SCN4A*; 20% of kindreds) genes.<sup>11–15</sup> The clinical presentation is identical for patients with HypoPP caused by calcium or sodium channel mutations because homologous gene defects of either channel cause an anomalous leakage current, which is active at the resting potential and produces susceptibility to paradoxical depolarization of the fiber and inexcitability in the setting of low extracellular K<sup>+</sup> (2.5 to 3.5 Meq/L).<sup>1,12</sup>

HyperPP is associated with mutations in the sodium channel (*SCN4A*) gene on chromosome 17q23.<sup>11–15</sup> These mutations are associated with gain of function changes, usually from impaired channel inactivation or occasionally from enhanced activation.

Andersen-Tawil syndrome in some cases is caused by mutations of the *KCNJ2* gene, which encodes the inward rectifier potassium channel, Kir2.1, stabilizing resting potential of skeletal muscle and cardiac myocytes.<sup>8</sup> Unlike HypoPP and HyperPP, which are limited to mutations in channels expressed almost exclusively in skeletal muscle, the potassium channel mutations leading to Andersen-Tawil syndrome affect multiple tissues, and are associated with a highly variable

phenotype of periodic paralysis, cardiac arrhythmia, and distinctive facial and skeletal anomalies.<sup>2,16</sup>

#### GENERAL CLINICAL PRESENTATION

Patients with PP experience an onset of signs and symptoms typically beginning in the first or second decade of life (Table 1). Patients generally present with intermittent attacks of focal or generalized muscle weakness, often precipitated by triggers.<sup>10,17,18</sup> Patients can develop between-attack weakness of varying severity, and the majority of affected individuals manifest persistent weakness later in life.<sup>19–21</sup>

In addition to its effects on strength, PP is associated with impairments of quality of life due to muscle weakness, myotonia, fatigue, loss of energy, and a reduced ability to participate in social and family life, including school and sporting activities.<sup>3,4</sup>

The effect of PP on quality of life was assessed from patient surveys and a clinical study.<sup>3,4,22</sup> An online survey of 66 patients with HypoPP (46), HyperPP (6), PMC (4), Andersen-Tawil syndrome (6), or unknown cause (4) found permanent weakness in 68%, muscle pain in 82%, and muscle fatigue in 89%.<sup>3</sup> Beginning at age 18–35 years, 83% self-reported that they were moderately to very active compared with 14% at the time of the survey (mean age, 60 years), 67% incurred injuries due to falls, and 49% required mobility aids. Sansone et al<sup>4</sup> assessed quality of life in 66 patients with skeletal muscle channelopathies including 26 patients with periodic paralysis and 4 with Andersen-Tawil syndrome. Quality of life was impaired in all patients, but especially impacted were muscle weakness in HypoPP patients, myotonia in HyperPP patients, fatigue in Andersen-Tawil syndrome, and energy in all patients.

**Clinical Presentation of HypoPP.** HypoPP is characterized by focal or generalized paralytic episodes of skeletal muscle, which can last hours to days and are associated with concomitant hypokalemia (<2.5 mEq/L). A variable myopathy develops in many affected individuals and may result in a progressive muscle weakness predominantly in proximal muscle groups of the lower limbs. The myopathy may occur

independent of paralytic symptoms.<sup>6</sup> Patients with HypoPP are at increased risk for pre- or postanesthetic weakness. Late-onset proximal myopathy may develop in some patients.<sup>2</sup>

The first attack usually occurs between ages 5 and 35 years, but the frequency of attacks is highest between ages 15 and 35 years and subsequently decreases with age.<sup>1,10</sup> Acute attacks occur repeatedly at daily, weekly or monthly intervals and typically last several hours and sometimes days. Attacks can occur both spontaneously, but also in response to triggers such as carbohydrate-rich meals, alcohol, and rest after strenuous exercise.<sup>1,10</sup>

**Clinical Presentation of HyperPP.** Characteristic features of HyperPP are attacks of limb weakness and an increase of serum potassium during an attack, but some patients have normal serum potassium levels during attacks.<sup>23</sup> Administration of potassium may trigger an attack or worsen an ongoing episode.

Attacks of muscle weakness begin in the first decade of life in approximately 50% of patients, with only 25% reporting their first attack at age  $\geq 10$  years. Attacks may be triggered by potassium-rich food, rest after exercise, fasting, exposure to cold, emotional stress or pregnancy and often begin in the morning lasting up to 2 h.<sup>1,10</sup> Between attacks, approximately half of patients with HyperPP experience muscle stiffness arising from myotonia or paramyotonia that does not impede voluntary movements. More than 80% of patients older than 40 years with HyperPP experience permanent muscle weakness, and one third develop chronic progressive myopathy. Attacks in HyperPP tend to be more frequent and shorter in duration than attacks in HypoPP.<sup>18</sup> Patients with PMC complain of muscle stiffness, often exacerbated by cold temperatures that may progress to weakness.<sup>18</sup>

**Clinical Presentation of Andersen-Tawil Syndrome.** Andersen-Tawil syndrome is characterized by a triad of episodic flaccid muscle weakness (periodic paralysis), cardiac abnormalities (ventricular arrhythmias, prolonged QT interval, and prominent U waves), and distinctive skeletal features (low-set ears, ocular hypertelorism, small mandible, fifth-digit clinodactyly, syndactyly, short stature, scoliosis, and a broad forehead).<sup>16,24</sup> This characteristic triad is present in 58–78% of patients with *KCNJ2* mutations.<sup>25,26</sup> Those affected typically present in the first or second decade with either cardiac symptoms (palpitations and/or syncope) or weakness that occurs spontaneously following prolonged rest or following rest after exertion. Permanent weakness is common. Attacks of muscle weakness can be associated with high, low or normal serum potassium levels.<sup>16</sup>

Andersen-Tawil syndrome is a potentially fatal condition.<sup>27–29</sup> In patients with the *KCNJ2* gene mutation, ventricular arrhythmias are common (Table 1).<sup>27–29</sup> Cardiac manifestations of Andersen-Tawil syndrome include premature ventricular contractions (PVCs), complex ventricular ectopy (bigeminy, consecutive PVCs, or multifocal PVCs), polymorphic ventricular tachycardia (VT), and bidirectional VT.<sup>29</sup> Despite the common occurrence of ventricular arrhythmias, syncope or cardiac arrest is rare.<sup>27,30</sup> Early identification and diagnosis of these patients is important for treatment optimization.

#### DIAGNOSIS

The diagnosis of PP can be confirmed by genetic testing, which we recommend as the first diagnostic step when there is an intermediate-to-high clinical suspicion.<sup>31</sup> All PPs are inherited in an autosomal dominant manner. Genetic testing identifies a heterozygous pathogenic mutation in 60% to 70% of patients meeting clinical criteria.<sup>15,17</sup> For HypoPP, the gene is *CACNA1S* (Ca<sub>v</sub>1) or *SCN4A* and the chromosome is 1q31-32 or 17q23-25; for HyperPP, the gene is *SCN4A* (Na<sub>v</sub>1.4) and the chromosome is 17q23-25; and for Andersen-Tawil syndrome, the gene is *KCNJ2* (Kir2.1) and the chromosome is 17q23. Several mutations have been associated with thyrotoxic HypoPP, most commonly *KCNJ18*, which may be seen in up to 3% of patients with HypoPP,<sup>32</sup> and *KCNE3*, which was originally associated with HypoPP, but whose association is currently controversial.<sup>14</sup> More recently mutations in the gene *KCNJ5* have been implicated in one family with Andersen-Tawil syndrome, and then subsequently found in 1/21 gene negative Andersen-Tawil syndrome, but this will require verification in separate cohorts.<sup>33</sup>

In the absence of an identified genetic mutation in approximately 30% of patients, periodic paralysis subtypes can be distinguished on the basis of clinical presentation, serum potassium levels during attacks, and pattern of abnormalities on long exercise testing.<sup>10,15,23,31,34</sup> If primary PP is suspected but cannot be confirmed by genetic testing, further examination should be undertaken to confirm that the symptoms are not secondary to other conditions such as thyrotoxicosis<sup>35</sup> or secondary causes of blood potassium deficiency or excess (Tables 2 and 3).

Electrodiagnostic testing has been a mainstay to demonstrate evidence of muscle fiber changes in excitability in the muscle channelopathies. On needle electromyography (EMG), positive sharp waves and myotonia, characterized by spontaneous waxing and waning motor unit potential amplitude and frequency, can be seen in PMC and HyperPP.

**Table 2.** Supportive diagnostic criteria for HypoPP

1. Two or more attacks of muscle weakness with documented serum K <3.5 mEq/L
2. One attack of muscle weakness in the proband, and 1 attack of weakness in 1 relative with documented serum K <3.5 mEq/L in at least 1 attack
3. Three of 6 clinical or laboratory features:
  - a. Onset in the first or second decade
  - b. Attack duration (muscle weakness involving 1 or more limbs) > 2 hours
  - c. Positive triggers (high carbohydrate rich meal, rest after exercise, stress)
  - d. Improvement with potassium intake
  - e. Positive family history or genetically confirmed skeletal calcium or sodium channel mutation
  - f. Positive McManis long exercise test
4. Exclusion of other causes of hypokalemia (renal, adrenal, thyroid dysfunction; renal tubular acidosis; diuretic and laxative abuse)
5. Absence of myotonia (clinically or latent detected by needle EMG), except eye lids

In PP, long exercise testing has largely replaced provocative maneuvers, which induce full body attacks of paralysis. In the long exercise test a focal attack of paralysis is induced by exercise of a single muscle. The patient is instructed to perform repeated isometric contractions of the abductor digiti minimi muscle over 5 min (in 15-s blocks alternating with 3–4 s of rest), and compound muscle action potentials (CMAPs) are recorded after supramaximal stimulation of the ulnar nerve every minute or every other minute for 40–60 min postexercise. A reduction in CMAP amplitude of 40% or more from the maximal during exercise or post exercise is considered abnormal and is typically seen in >70% of patients.<sup>31,36,37</sup>

Several symptoms or signs, or test results, can suggest an alternative diagnosis.<sup>7,38</sup> The first attack most commonly occurs in the first 2 decades of life, and rarely after 30 years of age. Prominent sensory symptoms or pain or autonomic symptoms during the attacks may indicate Guillain-Barré syndrome or spinal cord injury. Alteration of consciousness or abnormal movements may be indicative of seizure or stroke. Symptoms such as double vision, ptosis, or difficulty swallowing might point to a neuromuscular junction disorder. During the attacks, the motor exam should reveal a flaccid paralysis, so preservation of reflexes in a paralyzed limb should raise the possibility of a different cause. When interpreting genetic testing it

is important to put the results in the clinical context. A known pathological mutation in the typical clinical context is confirmatory. Variants of unknown significance may require testing of additional family members, or further functional testing of the mutation in vitro to fully resolve its significance.

**Andersen-Tawil Syndrome.** Andersen-Tawil syndrome occurs with a high degree of phenotypic variability rendering diagnosis very difficult. Mutations in the *KCNJ2* gene are identified in approximately 60% of all individuals with the disorder; a genetic mutation is not identified in the remaining 40% of cases where the cause is unknown. In those with *KCNJ2* mutations, hyperkalemic episodes occur in approximately 15% of patients, normokalemic episodes in approximately 20% of patients, and the remainder have hypokalemic episodes of paralysis that are similar to those seen in HypoPP.<sup>8</sup>

The presence of characteristic physical features and/or electrocardiographic (ECG) abnormalities is consistent with a diagnosis of Andersen-Tawil syndrome.<sup>18,24</sup> Typical resting ECG abnormalities include a long QTc or long QU interval in the absence of hypokalemia. When the diagnosis of Andersen-Tawil syndrome is suspected, electrophysiological studies including the long exercise protocol may help support the diagnosis.<sup>31,39</sup>

The primary diagnostic criterion is documentation of the *KCNJ2* mutation. In the absence of an

**Table 3.** Supportive diagnostic criteria for HyperPP

1. Two or more attacks of muscle weakness with documented serum K >4.5 mEq/L
2. One attack of muscle weakness in the proband, and 1 attack of weakness in 1 relative with documented serum K >4.5 mEq/L in at least 1 attack
3. Three of 6 clinical or laboratory features:
  - a. Onset before third decade
  - b. Attack duration (muscle weakness involving 1 or more limbs) < 2 hours
  - c. Positive triggers (exercise, stress)
  - d. Myotonia
  - e. Positive family history or genetically confirmed skeletal sodium channel mutation
  - f. Positive McManis long exercise test
4. Exclusion of other causes of hyperkalemia (renal, adrenal, thyroid dysfunction; potassium-sparing diuretics use)

**Table 4.** Supportive diagnostic criteria for Andersen-Tawil syndrome.<sup>24</sup>

- A. Presence of 2 of the following 3 criteria:
- Periodic paralysis
  - Symptomatic cardiac arrhythmias or ECG evidence of enlarged U-waves, ventricular ectopy or a prolonged QTc or QUc interval
  - Characteristic facies, dental anomalies, small hands and feet, and at least 2 of the following:
    - Low-set ears
    - Widely spaced eyes
    - Small mandible
    - Fifth-digit clinodactyly
    - Syndactyly of toes 2 and 3
- B. One of the above 3 in addition to at least 1 other family member who meets 2 of the 3 criteria.<sup>18,24,30</sup>

identified genetic mutation, Andersen-Tawil syndrome should be suspected in individuals with either A or B in Table 4.<sup>24</sup>

#### GENERAL TREATMENT CONSIDERATIONS

A progressive strategy should be used beginning with patient education and lifestyle changes to minimize triggers of PP, and then potassium therapy (supplement or avoidance) followed by use of carbonic anhydrase inhibitors. As an initial step, discussion of triggering factors, especially diet, may be of benefit to decrease the number of attacks. Professional advice from a dietician may be beneficial. An understanding of the episodic nature of the disease is important for children, and health officials should be informed at schools where children with periodic paralysis are enrolled. If the potassium level during attacks is unknown, behavioral strategies for acute attacks should be used (e.g., mild exercise at attack onset).

Pharmacological interventions consist of therapy to abort acute attacks and chronic preventive therapy to reduce attack frequency.<sup>18</sup> Treatment options for periodic paralyses are limited, and aside from the recent Food and Drug Administration (FDA) approval of dichlorphenamide, are based largely on anecdotal experience (Table 5).<sup>22,40,41</sup>

Carbonic anhydrase inhibitors (in particular acetazolamide and dichlorphenamide) have been used for almost 50 years as empiric treatment for both HypoPP and HyperPP.<sup>1,40,42</sup> The mechanism of action in periodic paralyses is incompletely understood. Carbonic anhydrase inhibitors promote kaliuresis and a nonanion gap acidosis by increasing urinary bicarbonate excretion. The systemic acidosis may reduce the susceptibility to periodic paralysis.<sup>1,34,43</sup> An alternative proposal is enhanced opening of calcium-activated K channels.<sup>44</sup> In addition, carbonic anhydrase inhibitors also may be effective for treating permanent weakness in HypoPP by reducing intracellular sodium accumulation.<sup>45</sup> This lessens damage to the structure of muscle fiber, thus allowing the remaining

muscle fibers to regenerate. However, whether these pharmacological effects are directly responsible for the benefits of carbonic anhydrase inhibitors in PP remains poorly understood.<sup>42</sup> The interval between attacks varies widely, and the interval may be prolonged by treatment with potassium or carbonic anhydrase inhibitors.

Those with HypoPP caused by an *SCN4A* mutation are less responsive to carbonic anhydrase inhibitors or may even experience worsening of symptoms. In a study of 74 patients with HypoPP who were genotyped, the overall response to acetazolamide was 46%, but the response differed by genotype.<sup>40</sup> Among those with the *CACNA1S* mutation, the response was 56% (31/55), but among those with the *SCN4A* mutation the response was 16% (3/19). Exacerbation of HypoPP with acetazolamide has been reported in patients with the *SCN4A* mutation.<sup>46,47</sup> Specific gene defects have been associated with clinical worsening on carbonic anhydrase inhibitors. Acetazolamide caused worsening for several patients with the *SCN4A* HypoPP mutations R672G or R672S and in one patient with the *CACNA1S* mutation R1239H.<sup>48,49</sup> Another report describes 3 patients with HypoPP who worsened with acetazolamide treatment but subsequently responded to treatment with dichlorphenamide.<sup>19</sup>

Acetazolamide is routinely used for treating PP. No randomized, controlled studies have been performed with acetazolamide in PP, but rather its use is based on the results of nonrandomized, single-blind trials and anecdotal reports.<sup>23</sup> Overall, approximately 50% of patients respond to acetazolamide.<sup>40</sup>

Common side effects of carbonic anhydrase inhibitors include paresthesia, fatigue, and mild, reversible cognitive disturbances.<sup>22,50</sup> An additional concern with carbonic anhydrase inhibitors is an increased risk of nephrolithiasis. In 1 report, 3 of 20 (15%) patients receiving long-term treatment with acetazolamide for myotonia experienced nephrolithiasis.<sup>51</sup> Nephrolithiasis has been widely reported with acetazolamide when used for other

**Table 5.** General approach to treatment for primary periodic paralyses.<sup>1,4,6,24</sup>

	HyperPP	HypoPP	Andersen-Tawil syndrome
<b>Acute attack</b>			
Non-pharmacological	Mild exercise; carbohydrates	Mild exercise at attack onset; potassium supplements	Mild exercise; carbohydrates (if attacks associated with hypokalemia)
Potassium supplement <sup>†</sup>	Not applicable	Oral K + 1 mEq/kg up to 200 mEq/24h* Avoid slow release formulations	If attacks associated with low K+, oral K + 1 mEq/kg up to 200 mEq/12h* to normalize
Beta-2 agonist – salbutamol	2 puffs 0.1 mg	Not applicable	Not applicable
<b>Prevention</b>			
Non-pharmacological	Frequent high carbohydrate meals; Avoid: fasting; strenuous exercise; cold exposure; K + rich foods	Low sodium and carbohydrate diet; potassium supplements; avoid hyperosmolar states (dehydration, hyperglycemia)	
Acetazolamide	Adults: 125-1000 mg daily Children: 5-10 mg/kg/d	Adults: 125-1000 mg daily Children: 5-10 mg/kg/d	Adults: 125-1000 mg daily Children: 5-10 mg/kg/d
Dichlorphenamide	50-200 mg daily	50-200 mg daily	50-200 mg daily
Potassium supplement <sup>†</sup>	Not applicable	Oral K + 30-60 mEq/day; sustained released formulation may be preferred	Not applicable
K + sparing diuretic	Not applicable	Triamterene 50-150 mg/d Spironolactone 25-100 mg/d Eplerenone 50-100 mg/d	Not applicable <sup>‡</sup>
Hydrochlorothiazide	25-75 mg daily	Not applicable	Not applicable
Antiarrhythmics	Not applicable	Not applicable	Flecainide, beta-blockers or calcium channel blockers to prevent ventricular arrhythmias

\*Monitor ECG and potassium levels.

<sup>†</sup>Total body potassium is not depleted in HypoPP, use caution with acute K<sup>+</sup> administration to avoid overshoot.

<sup>‡</sup>Use of K-sparing diuretics should be individualized based on patient needs.

conditions,<sup>52</sup> and may be managed by removal of renal calculi without necessitating discontinuation of carbonic anhydrase inhibitor treatment.<sup>51</sup>

Dichlorphenamide was recently approved by the FDA for the treatment of PP. Dichlorphenamide has been evaluated in four randomized, placebo-controlled studies, two each in patients with HypoPP and HyperPP (Supplementary Table 1, which is available online).<sup>22,53</sup> The dose of dichlorphenamide was 50 mg twice daily for treatment-naïve patients. Patients already on dichlorphenamide before the study continued on the same dose during the study. In patients taking acetazolamide before the study, the dose of dichlorphenamide was set at 20% of the acetazolamide dose. Dose reduction for tolerability was permitted. The mean dose of dichlorphenamide at Week 9 was 82 mg/day. While randomized controlled trials of dichlorphenamide were performed in adults, the same approach is taken for children. Dose adjustments may be required based on age.

These studies demonstrated a significant reduction in the frequency and severity of the attacks. The most common side effects with dichlorphenamide were paresthesias, cognitive disorder, dysgeusia, headache, fatigue, hypoesthesia, and muscle spasms,<sup>22</sup> generally not requiring discontinuation

of dichlorphenamide, and reversible with drug discontinuation. During a 52-week extension, in which all remaining patients received open-label dichlorphenamide, continued improvement in outcomes was observed in both placebo and dichlorphenamide groups (Supplementary Table 2).<sup>22</sup>

In one of the studies of dichlorphenamide, quality of life was assessed at 9 weeks with the SF-36.<sup>22</sup> No significant improvement was observed in patients with HyperPP, but significant improvement was reported for the physical component and physical functioning, role physical, bodily pain, vitality, and social functioning in those with HypoPP.

Other pharmacological treatments for periodic paralyses depend on serum potassium levels and the specific diagnosis but include potassium supplementation, thiazide or potassium-sparing diuretics or beta-adrenergic agents.<sup>42,54</sup> For patients receiving chronic potassium supplementation for HypoPP, providers can consider adding magnesium, which can be helpful to promote renal retention of K<sup>+</sup> and, therefore, reduce the potassium dose.

**Management of HypoPP.** *Acute management.* Mild exercise (e.g., nonresistance activities such as walking around a room or shaking the arms) at the onset

of the attack may be of benefit. Low serum potassium is not due to low total body potassium but rather shifts of potassium from the blood compartment into the intracellular muscle compartment. Therefore, correction of serum potassium should not be undertaken with the goal of correcting low total body potassium. Treatment options include oral or intravenous (IV) potassium administration.<sup>18,19</sup> Oral potassium is recommended for outpatient treatment. Slow-release formulations usually should be avoided for acute management. The dose of oral potassium is 0.2–0.4 mEq/kg every 30 min not to exceed 200–250 mEq/day. Administering potassium by IV infusion usually requires hospitalization for ECG monitoring but is only necessary if the patient cannot take oral potassium. The dose of IV potassium is 40 mEq/L in 5% mannitol solution infused at a maximum of 20 mEq/h, not to exceed 200 mEq/day. A potassium chloride IV bolus of 5 mEq can be used as an alternative. Use of glucose- and saline-containing IV solutions for administering potassium should be avoided, as this may worsen muscle weakness.<sup>55</sup>

*Prevention.* The patient should be advised to avoid triggers such as high-carbohydrate and/or high-salt meals, alcohol, and stress.<sup>2</sup> Although no randomized controlled studies are available to inform dosing, a daily slow-release potassium salt formulation may be considered the standard of care for chronic therapy.

Dichlorphenamide is approved for HypoPP, and has been associated with reductions in attack frequency, severity, and duration during chronic treatment.<sup>22,53</sup> Based on anecdotal reports, acetazolamide 125–1000 mg/day may be effective chronic treatment of HypoPP.<sup>15,20,23,56–58</sup> In a double-blind crossover study, acetazolamide 125 mg three times daily or placebo given for 2 weeks each was evaluated in 8 patients with HypoPP.<sup>59</sup> Muscle strength was measured in muscle groups every week and improved significantly in seven of eight patients. Mean strength was significantly greater with acetazolamide ( $P = 0.05$ ), and total muscle strength increased by a mean of 10% with treatment.

Potassium-sparing diuretics are a potential option for chronic treatment of HypoPP.<sup>6,18</sup> Recommended doses are triamterene 50–150 mg/day, spironolactone 25–100 mg/day or eplerenone 50–100 mg daily. Spironolactone may be poorly tolerated because of androgenic side effects, and eplerenone may be substituted because it causes fewer hormonal issues. For patients with HypoPP, potassium supplementation and a potassium-sparing diuretic may be used concomitantly, but potassium levels should be routinely monitored.

Recent studies in mouse models of HypoPP with both *SCN4A* mutations and *CACNA1S* mutations

show that maneuvers to reduce the activity of the Na-K-2Cl (NKCC) co-transporter can reverse an acute attack of HypoPP and protect against an attack triggered by low  $K^+$  exposure.<sup>60,61</sup> The beneficial effect is the result of biasing intracellular chloride to be low, which promotes hyperpolarization of the resting potential. The NKCC co-transporter is activated by hyperosmolarity (hence the importance of avoiding high sodium diet, dehydration or hyperglycemia) and is inhibited by loop diuretics such as bumetanide. Pharmacologic inhibition of NKCC as an acute therapy for HypoPP is under study.

**Management of HyperPP.** *Acute Management.* Acute management may include mild exercise at attack onset and a carbohydrate snack. Beta agonists can be an effective acute potassium-lowering therapy for HyperPP.<sup>1</sup> In case reports, salbutamol 1–2 puffs (0.1 mg) and other beta-agonists have shown benefits.<sup>62–64</sup> While severe hyperkalemia during attacks is typically not seen, the treatment for acute hyperkalemia which is severe or life-threatening should match institutions' established protocols.

*Prevention.* In individuals with HyperPP, consider recommending consumption of multiple small carbohydrate snacks and avoid potassium-rich foods.<sup>10</sup>

Dichlorphenamide can be effective for chronic treatment and is approved for HyperPP.<sup>22,53</sup> In randomized, placebo-controlled studies, dichlorphenamide reduced attack frequency and severity among patients.<sup>22,53</sup> The initial dose is 50 mg twice daily, which may be increased or decreased at weekly intervals based on individual response or the occurrence of adverse events. The maximum recommended dose is 200 mg daily.<sup>22,53</sup> Acetazolamide 125–1000 mg/day may be effective for chronic treatment of HyperPP.<sup>15,23</sup>

Thiazide diuretics are an option for chronic treatment of HyperPP.<sup>1,42</sup> The drug of choice is hydrochlorothiazide 25 mg to 75 mg daily.<sup>41,54</sup> Potassium-sparing diuretics should be avoided.

There are no rigorously controlled data on the treatment of PMC, normokalemic PP, and other atypical PPs, but in general, the same treatment strategies used for HyperPP are appropriate.

#### **Management of Andersen-Tawil Syndrome.**

Management of individuals with Andersen-Tawil syndrome requires the coordinated input of a neurologist familiar with the treatment of periodic paralysis and a cardiologist familiar with the treatment of cardiac arrhythmias. Treatment for acute attacks of weakness or for chronic suppression of attacks of weakness in individuals with Andersen-Tawil syndrome depends on whether the attack is associated with high or low levels of potassium, and treatment needs to be individualized for each

**Table 6.** Evaluations recommended to establish the diagnosis of Andersen-Tawil syndrome

- Baseline assessments by a neurologist familiar with periodic paralyses and a cardiologist familiar with long QT syndrome
- Syncope in patients with Andersen-Tawil syndrome requires a cardiology assessment<sup>65</sup>
- Assess serum potassium concentrations at baseline and during attacks of weakness
- Obtain 12-lead ECG and perform 24-hour Holter monitoring
- Confirm that serum thyroid stimulating hormone concentration is within normal limits
- Obtain a medical genetics consultation

patient (see sections above for HypoPP and HyperPP for specific recommendations).<sup>10</sup> Evaluations recommended to establish the extent of disease and needs in a patient diagnosed with Andersen-Tawil syndrome are summarized in Table 6.<sup>65</sup> For asymptomatic patients with a *KCNJ2* mutation, annual screening should include a 12-lead ECG and 24-h Holter monitoring.

**Treatment of Manifestations.** *Cardiac considerations.* Empiric treatment with an antiarrhythmic agent should be considered for significant, frequent ventricular arrhythmias in the setting of reduced left ventricular function.<sup>27,66</sup> A prospective open label study in 10 individuals with Andersen-Tawil syndrome and a confirmed *KCNJ2* mutation tested the effect of flecainide, a type 1c antiarrhythmic, for the prevention of cardiac arrhythmias.<sup>67</sup> Assessments included 24-h Holter monitoring before and after treatment, and a treadmill exercise test. Flecainide significantly reduced the number of ventricular arrhythmias observed on Holter monitor and suppressed exercise-induced ventricular arrhythmias. After a mean follow-up of 23 months, no syncope or cardiac arrest was documented. Thus, flecainide may reduce cardiac arrhythmias in Andersen-Tawil syndrome, although further evaluation is needed. Others have reported beneficial effects with flecainide.<sup>68–70</sup> Others report beneficial effects for suppressing ventricular arrhythmias with the use of beta-blockers, calcium channel blockers, or amiodarone.<sup>27,28</sup>

*Prevention of secondary complications.* Some antiarrhythmic drugs (e.g., lidocaine, mexiletine, propafenone, quinidine) may paradoxically exacerbate neuromuscular symptoms and should be used cautiously in individuals with Andersen-Tawil syndrome.<sup>8,24</sup> Although malignant hyperthermia has not been reported in Andersen-Tawil syndrome, appropriate precautions should be undertaken when using anesthesia for surgical procedures. Patients should be instructed about medications known to prolong QT intervals and avoid their use. Inhaled salbutamol, which may be used for

the treatment of HyperPP, should be avoided because of the potential to exacerbate cardiac arrhythmias. Thiazide diuretics should be avoided, because they may induce drug-induced hypokalemia and could aggravate the QT interval.

#### CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE STUDIES

Because of their low prevalence in the general population, most experience with treatment for these patients is obtained from anecdotal reports. The present recommendations are based on a review of published literature with the exception of the Level I evidence supporting the use of dichlorphenamide in the long-term management of HypoPP and HyperPP.

Despite the rarity of these disorders, which creates many challenges in conducting studies in periodic paralyses, more prospective studies are needed, in particular comparing acetazolamide and dichlorphenamide as well as other interventions for managing patients. Studies should include long-term follow-up, cost benefits of treatment, effects of treatment on permanent muscle weakness, adverse events, as well as efficacy. In the future, a better understanding of the genetics of these disorders may lead to improved treatment options.

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