PRIMARY PERIODIC PARALYSIS:
MANAGEMENT AND TREATMENT

Rare Opportunities IN NEUROLOGY

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This supplement is sponsored by Strongbridge Biopharma plc.

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Medical writing and editorial support provided by Health & Wellness Partners, LLC.

INTRODUCTION

An Expert Roundtable on Primary Periodic Paralysis (PPP) was sponsored by Strongbridge in January 2019. The meeting brought together a group of expert clinicians and researchers specializing in neuromuscular disorders and representing a variety of academic institutions and teaching hospitals across the United States. The objectives of the Expert Roundtable were to discuss the current state of knowledge about PPP and to identify unmet needs in the diagnostic journey of patients with PPP. With the goal of raising awareness of clinical challenges and best practices related to PPP, the authors present a 3-part series of white papers focusing on different aspects of PPP. This third and final paper in the series explores options for management and treatment of PPP.

BRIEF REVIEW OF PPP PRESENTATION

PPP is a group of rare autosomal dominant neuromuscular disorders that result from malfunctions in the ion channels in skeletal muscle. These disorders arise from mutations in genes that code for voltage-gated ion channels (ie, sodium, calcium, and potassium); however, there is considerable variation in penetrance and manifestations of the disorder within families. The hallmarks of PPP are recurrent attacks of muscle weakness or temporary paralysis, followed by spontaneous recovery.[1]

TABLE 1. PREVALENCE OF THE DIFFERENT PPP SUBTYPES

SUBTYPE	CHARACTERISTICS	PREVALENCE
Hypokalemic periodic paralysis (hypoPP)	• The potassium level is usually low during attacks[2] • Attacks commonly triggered by cold, carbohydrate ingestion, rest after exercise, alcohol, or emotional stress[2]	1/100,000[3]
Hyperkalemic periodic paralysis (hyperPP)	• Elevated serum levels of potassium during attacks as the potassium shifts from the muscle to the extracellular space • Sometimes serum potassium levels can remain normal during attacks • Attacks provoked by rest following exercise, fasting, emotional stress, cold, or ingestion of potassium[2]	1/200,000[3]
Paramyotonia congenita (PMC)	• Attacks of muscle stiffness noted at birth or during early years of life[4] • Notably triggered by cold in addition to exercise[4] • PMC can present with elevated or normal serum potassium levels[6] • Considered to be a related disorder of hyperPPP[3]	1/250,000[5]
Andersen-Tawil syndrome (ATS)	• Cardiac abnormalities such as ventricular arrhythmias, torsades, cardiac arrest, prolonged QT interval, and prominent U waves • Periodic paralysis with low to high ictal potassium[2] • Abnormal skeletal features, including low-set ears, wide-set eyes, small mandible, unusually curved digits or toes, fused digits, short stature, scoliosis, and a broad forehead • Myotonia does not occur in ATS[2]	1/1,000,000[3]

Onset typically occurs before 20 years of age.[2] Some patients with hyperPPP may experience muscle stiffness between attacks.[7] PPP encompasses a variety of subclassifications, with varying prevalence rates **(Table 1)**. The occurrence of episodic attacks of muscle weakness is present in all types of PPP.[2,8] Triggers for episodic attacks are specific to a patient's phenotype, and may vary from patient to patient.[2,6,9]

Over time, progressive, fixed weakness, typically referred to as permanent muscle weakness (PMW) may be present in up to 60% of patients in their 5th or 6th decade.[10] In a survey of patients with hypoPP, hyperPP, PMC, and ATS, the most common sites of weakness were the quads, followed by the hip girdle, and upper arms.[10] While earlier in the disease, muscle strength usually returns to normal between attacks, as patients age into their fifth and sixth decades, up to 60% may experience PMW, impacting their daily functioning and quality of life.[3,10]

IMPACT ON PATIENTS' LIVES

Over time, patients with PPP who develop PMW experience a loss of function that includes reduced strength/stamina and endurance, difficulty performing daily activities or exercising, and, in some cases, difficulty walking even a few steps.[10] PMW can affect work, school, family life, and patients' physical and mental health.[3] A survey of patients with PMW showed that in addition to experiencing pain and fatigue, two-thirds of patients require medical attention for injuries from falls, and nearly half must use a mobility aid, such as a walker or wheelchair.[10]

CONSEQUENCES OF NONTREATMENT

Despite frequent attacks and significant impairment, many patients with PPP receive no treatment.[6]

A major issue is lack of knowledge among general physicians. They are the first line for the diagnosis of these disorders. Many conditions cause weakness—PPP is likely the rarest.

—John C. Kincaid, MD, FAAN

In a randomized, controlled trial of 42 patients with PPP, subjects reported experiencing weekly, sometimes daily, attacks of muscle weakness. At the time of enrollment, nearly 60% were not receiving any treatment other than potassium supplements.[11]

Because PPP is considered by many providers to be a "benign" disease, since it does not usually result in death, some clinicians may treat acute attacks but not consider chronic treatment. However, frequent attacks can have a substantial impact on a patient's ability to work and perform daily activities, so it makes sense to do whatever is possible to minimize the frequency and severity of attacks. Moreover, these patients frequently develop PMW over time.

—Carlayne E. Jackson, MD

In a survey of almost 100 patients with genetically confirmed hyperPP who were older than 18 years, those with no long-term treatment regimen had twice the risk for inadequate disease control ($P<0.0001$) compared with those taking long-term medication.[6]

"Inadequate disease control" means that patients are having attacks of weakness that interfere with their activities of daily living and/or affect their ability to go to work and/or school.

—Carlayne E. Jackson, MD

The root causes of inadequate disease control are underdiagnosis and undertreatment.

—John C. Kincaid, MD, FAAN

Generally, PPP is treated empirically,[3] and the goals of treatment are to prevent or decrease the frequency and severity of PPP attacks and to treat major paralytic attacks once they occur.[2] Most patients with PPP require prophylactic therapy to prevent acute attacks and potentially the development of PMW.[2] When PMW develops, it can be improved but not reversed.[2]

ACUTE MANAGEMENT OF PPP

For hypoPP, recommended treatment **(Table 2)** of acute attacks involves mild exercise, such as walking around the room or shaking arms at attack onset,[3] and oral potassium 0.2-0.4 mEq/kg every 30 minutes, up to 200-250 mEq in 24 hours (avoiding slow-release formulations) until weakness improves.[3] Intravenous (IV) potassium is generally reserved for patients who are hospitalized and cannot take oral medications.[3] The recommended dose is 40 mEq/liter in 5% mannitol infused at 20 mEq per hour to a maximum dose of 200 mEq.[3] For patients who require IV potassium, hospitalization is recommended so that the ECG can be monitored.[3]

The acute treatment of mild to moderate attacks of hyperPP involves mild exercise, β-adrenergic agonists, and a carbohydrate snack.[2,3,8] For severe attacks of hyperkalemia, in particular with ECG changes, treatment may require IV sodium bicarbonate, glucose and insulin, and calcium gluconate that is administered under cardiac monitoring.[2]

Treatment of acute attacks of weakness in ATS depends on whether the attack is associated with high or low levels of potassium, and treatment should be individualized for each patient.[3]

PREVENTATIVE TREATMENT OF PPP

Patients with PPP can help manage their conditions nonpharmacologically by learning and avoiding their own specific triggers—through lifestyle and dietary modification.[2] In the case of hypoPP, the patient should avoid high-carbohydrate and high-salt meals as well as alcohol and stress.[3] Patients with hyperPP should consider consuming multiple small carbohydrate snacks and avoiding potassium-rich foods.[3] However, as noted earlier, triggers vary from patient to patient, so it is important for individuals to learn and avoid their own triggers.[6]

In the case of ATS, pharmacologic treatment focuses on preventing cardiac arrhythmias.[2] Specific types of antiarrhythmic agents including β-blockers, calcium-channel blockers, and flecainide can be used to prevent cardiac arrhythmias.[3]

Pharmacologic treatment of PPP is recommended to prevent or reduce the frequency and severity of attacks.[2] CAIs have been used for nearly 50 years as empiric treatment for both hypoPP and hyperPP, but only one treatment, dichlorphenamide (DCP), is FDA-approved for hypoPP, hyperPP, and related variants.[3] Common adverse events with CAIs include paresthesia, fatigue, and mild, reversible, cognitive cognitive disturbances. Nephrolithiasis has also been reported with some CAIs.[3]

The mechanism of action of CAIs is not fully understood but may be related to the development of kaliuresis and nonanion gap acidosis as a result of increased urinary excretion of bicarbonate.[3] The resulting acidosis may reduce the likelihood of PP attacks.[3] An alternative hypothesis involves enhanced opening of calcium-activated potassium channels.[3]

TABLE 2. GENERAL APPROACH TO TREATMENT OF PPP[3*]

	HYPER PP	HYPOPP	ATS
ACUTE ATTACK			
Nonpharmacological	Mild exercise; carbohydrates	Mild exercise at attack onset; potassium supplements	Mild exercise; carbohydrates if attacks associated with hyperkalemia
Potassium supplement[†]	Not applicable	Oral K+ 0.2-0.4 mEq/kg every 30 minutes up to 200-250 mEq every 24 hours; avoid slow release formulations	If attacks associated with low K+, 1 mEq/kg up to 200 mEq/12 h[‡] to normalize
Beta-2 agonist--salbutamol	2 puffs 0.1 mg	Not applicable	Not applicable
PREVENTION			
Nonpharmacological	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/day Children: 5-10 mg/kg/day	Adults: 125-1000 mg/day Children: 5-10 mg/kg/day	Adults: 125-1000 mg/day Children: 5-10 mg/kg/day
Dichlorphenamide	50-200 mg/day	50-200 mg/day	50-200 mg/day[§]
Potassium supplement[†]	Not applicable	Oral K+ 30-60 mEq/day; sustained release formulation may be preferred	Not applicable
K+ sparing diuretic	Not applicable	Triamterene 50-150 mg/day Spironolactone 25-100 mg/day Eplerenone 50-100 mg/day	Not applicable
Hydrochlorothiazide	25-75 mg daily	Not applicable	Not applicable[‖]
Antiarrhythmics	Not applicable	Not applicable	Flecainide, beta blockers, or calcium-channel blocker to prevent ventricular arrhythmias

[*]Adapted from Statland, et al. *Muscle Nerve*. 2018;57(4):522-530.

[†]Total body potassium is not depleted in hypoPP; use caution with acute K+ administration to avoid overshoot

[‡]Monitor ECG and potassium levels

[§]ATS was not studied in controlled trials of DCP

[‖]Use of K-sparing diuretics should be individualized based on patient need

SUMMARY

PPP comprises a group of rare channelopathies that cause attacks of muscle weakness or temporary paralysis. Both acute and long-term manifestations of PPP adversely affect patients' lives and functioning. There are currently no consensus treatment guidelines for any PPP subtype. It is important for patients to receive treatment for their PPP. Identification and avoidance of triggers plays an important role in managing these disorders. Nonpharmacologic and pharmacologic approaches should be individualized.

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