Primary Periodic Paralysis

THE DIAGNOSTIC JOURNEY

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A SUPPLEMENT TO

NEUROLOGY REVIEWS

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INTRODUCTION

An Expert Roundtable on Primary Periodic Paralysis (PPP) was sponsored by Strongbridge Biopharma plc in January 2019. The meeting brought together a group of expert clinicians and researchers specializing in neuromuscular disorders, representing a variety of academic institutions and teaching hospitals across the nation. 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 these conditions. 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 first-in-series paper provides an overview on PPP clinical characteristics, subtype classification, neurophysiology, and genetics necessary to guide the diagnosis of PPP. The authors introduce a new diagnostic algorithm that addresses history, symptomology, laboratory workup, genetic testing, and electrodiagnostic studies to guide diagnosis of PPP.

> A person may delay investigating their condition because they've had fixed weakness for a long time. Fixed weakness is reason for suspicion of PPP.
>
> **-Jeffrey Rosenfeld, MD, PhD, FAAN, FANA**

CLINICAL CHARACTERISTICS OF PPP

PPP is a group of rare genetic neuromuscular disorders characterized by recurrent attacks of muscle weakness—ranging in duration from minutes to hours or even days—followed by spontaneous and full recovery.[1] Some patients may also experience muscle stiffness between attacks, which may be exacerbated by cold temperatures or exercise in some cases.[2] Ictal changes in serum potassium usually occur. In addition to episodic weakness, fixed weakness, and muscle atrophy may develop in some patients over a longer time frame.[3,4] Except in secondary forms of periodic paralysis (such as thyrotoxic periodic paralysis), onset typically occurs before 20 years of age. Attacks typically occur in response to specific triggers (rest after vigorous exercise, diet, stress) or may occur spontaneously.[3,5] While earlier in the disease, muscle strength returns to normal between attacks, as patients age into their fifth and sixth decades, up to 60% may experience permanent muscle weakness, impacting their daily functioning and quality of life.[3,6,7]

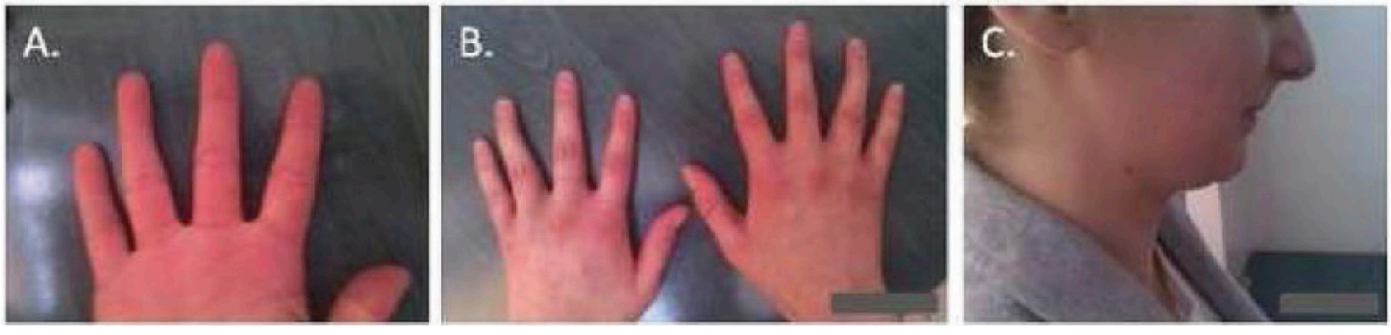
The frequency of attacks of muscle weakness varies widely in patients with PPP.[7] In a 2012 survey of 66 patients over 41 years of age, 59% reported weekly attacks and 28% reported daily attacks.[7] Attacks may be precipitated by environmental triggers, such as cold temperatures or changes in barometric pressure or humidity.[8] The acute attacks of weakness are usually generalized but also may be localized to a particular muscle/region depending on the form of PPP.

> When patients say they don't have attacks, it may not be true. We need astute history taking and we need to ask specific questions, like "How are you doing in the morning?"
>
> **-Emma Ciafaloni, MD**

CLASSIFICATION

The most common types of PPP include hypokalemic periodic paralysis (hypoPP), hyperkalemic periodic paralysis (hyperPP), paramyotonia congenita (PMC), and Andersen-Tawil syndrome (ATS). These are autosomal dominant disorders which have distinguishing genetic mutations and clinical presentations.[2-4,9] HypoPP is the most common form of PPP, with a prevalence of 1/100,000.[2,9] In hypoPP, patients usually have low serum potassium levels (2.0–3.0 mEq/L) during paralytic attacks, and weakness is improved with potassium ingestion (potassium responsiveness).[3] Conversely, in hyperPP, patients may have increased serum potassium levels (>5.5 mEq/L) or they may be normokalemic (3.5–5.5 mEq/L) during an attack, and weakness can occur with potassium ingestion (potassium sensitivity).[3] HyperPP may be accompanied by myotonia or paramyotonia and has a prevalence of 1/200,000.[2,9] A related form of periodic paralysis, PMC, has some symptom overlap with hyperPP.[2] In addition to hyperPP symptoms, patients with PMC may experience aggravation of myotonia with exercise ("paradoxical myotonia"), differentiating it from myotonia congenita, in which the myotonia lessens with sustained muscle contractions and weakness is aggravated by cold temperature (i.e., severe cold intolerance).[9] In ATS, with a prevalence of 1/500,000, patients experience periodic limb paralysis, cardiac arrhythmias with prolonged QT, and have distinctive facial and skeletal features (Figure 1), including low-set ears, increased width between the eyes, small mandible, unusual curvature of the digits or toes, fused digits, short stature, scoliosis, and a broad forehead.[9] Electrocardiographic criteria, including a prominent U-wave pattern, is also helpful in diagnosing ATS.[10]

Figure 1. Facial and Skeletal Features Indicative of ATS[11]



Reprinted from Krych M, Biernacka EK, Ponińska J, et al. Andersen-Tawil syndrome: Clinical presentation and predictors of symptomatic arrhythmias - Possible role of polymorphisms K897T in KCNH2 and H558R in SCN5A gene. *J Cardiol*. 2017 Nov;70(5):504-510, with permission from Elsevier.

NEUROPHYSIOLOGY AND GENETICS OF PPP

PPP results from mutations in ion channels of the sarcolemma,[2] including sodium, calcium, and potassium channels.[5, 9, 12–15] Abnormality in a specific channel does not necessarily define the type of PPP disorder, as dysfunction of the same channel can be found in the different PPP types.[5, 9, 12–15] Specific ion channel amino acid substitutions are associated with the specific PPP types, though, and can give rise to more than one type of PPP disorder.[5, 9, 12–16] PPP-related mutant ion channels all result in depolarization of the sarcolemma,[1, 13, 16] leading to loss of muscle excitability resulting in weakness and paralysis.[1, 17–19]

DIAGNOSIS OF PPP: A CHALLENGING JOURNEY

Unfortunately, patients with PPP often experience delay in diagnosis after the onset of symptoms.[7] Symptoms are nonspecific, episodic, and vary between patients, in addition to mimicking more common diseases, from psychiatric to cardiovascular disorders, which contribute to diagnostic delays.[7, 20,21] There is an average of 26 years between onset and diagnosis for patients living with PPP, indicating that diagnostic schemes can be improved.[7] Though the diagnostic journey can be challenging, there are many clinical features that may help to distinguish the diagnosis of PPP and its subtype[2,11,23] (both clinically and on EMG): ictal potassium level, presence of cardiac arrhythmias and EKG abnormalities, developmental skeletal anomalies, sensitivity to cold, and localization of weakness (i.e., calves and arms [most common], and trunk[21]).[2,9,22] A positive family history is very important to help confirm the diagnosis but in some instances patients and family members may minimize or ignore symptoms (especially if mild), given their episodic nature and frequent spontaneous recovery. For example, affected parents may consider their own attacks of weakness as "normal," so when they observe similar symptoms in their children, they may not seek medical attention. Therefore, the process of obtaining a family history should be detailed and probing in order to avoid overlooking other affected individuals in the family. A systematic and comprehensive algorithm that incorporates patient and family history, symptomology, laboratory workup, genetic testing, and electrodiagnostic studies is important to facilitate and expedite the diagnosis of PPP. To meet this need, the authors propose a diagnostic algorithm (Figure 2), developed at the consensus conference based on three existing ones (Supplemental Figure 1, Supplemental Table 2, and Supplemental Table 3).[6,12,23,24] The new proposed approach to diagnosing PPP includes patients who exhibit clinical symptoms yet have a negative genetic test.

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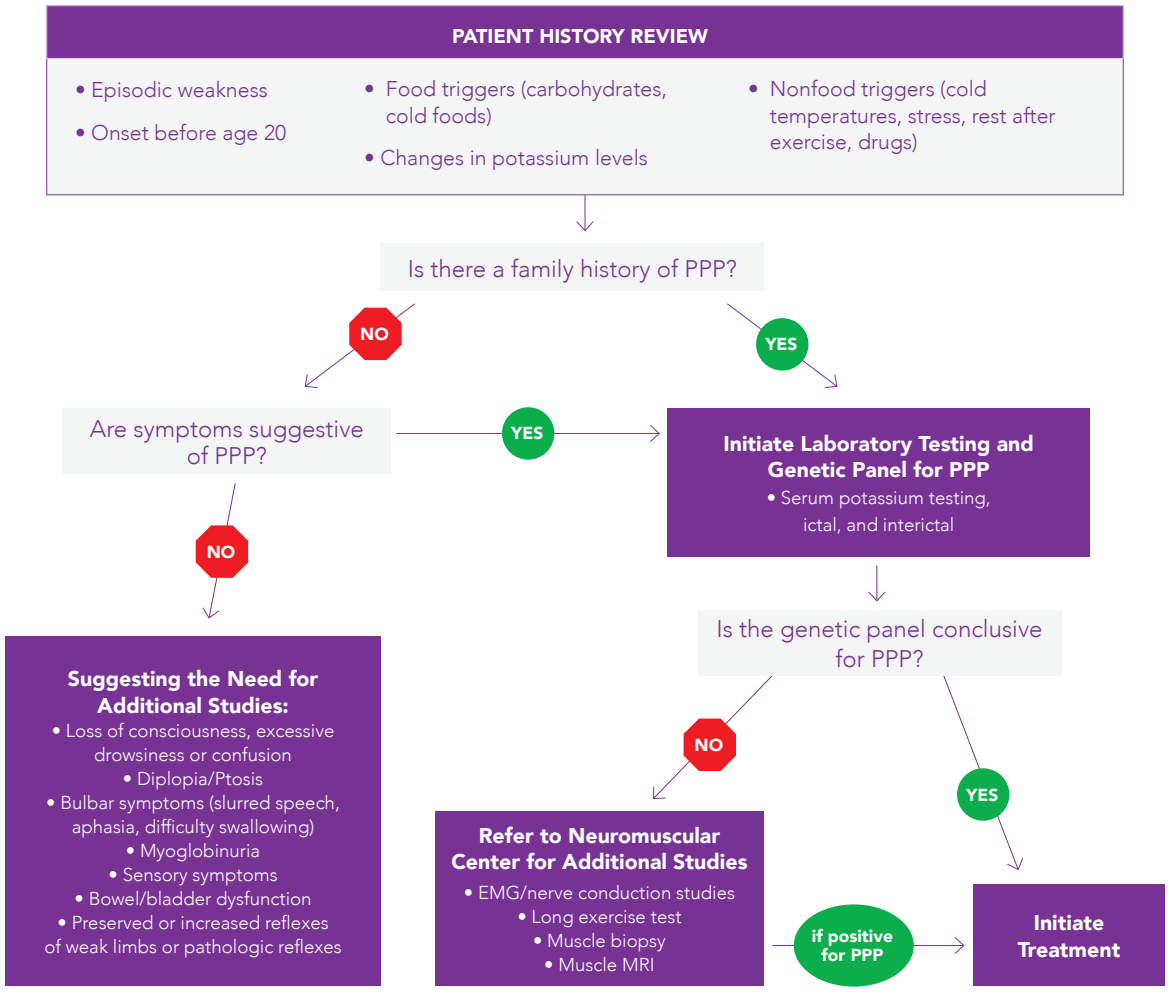
Figure 2. Diagnostic Algorithm for PPP



DISCUSSION

Several researchers have developed diagnostic algorithms, including Supplemental Figure 1, Supplemental Table 1, Supplemental Table 2, and Supplemental Table 3.[6,12,23,24] Notably, the existing algorithms were developed when genetic testing was cost-prohibitive or not easily available; technological development and improved access to genetic testing necessitate an up-to-date algorithm. With a deeper understanding of the long-term complications of frequent attacks, there is a greater need to educate clinicians on how to diagnose and treat PPP earlier—this is especially important in patients with an unknown family history and negative genetic testing. As our understanding of PPP grows, additional expert perspectives, new platforms to discuss and report clinical experiences in diagnosis, and opportunities to enhance this proposed algorithm are warranted.

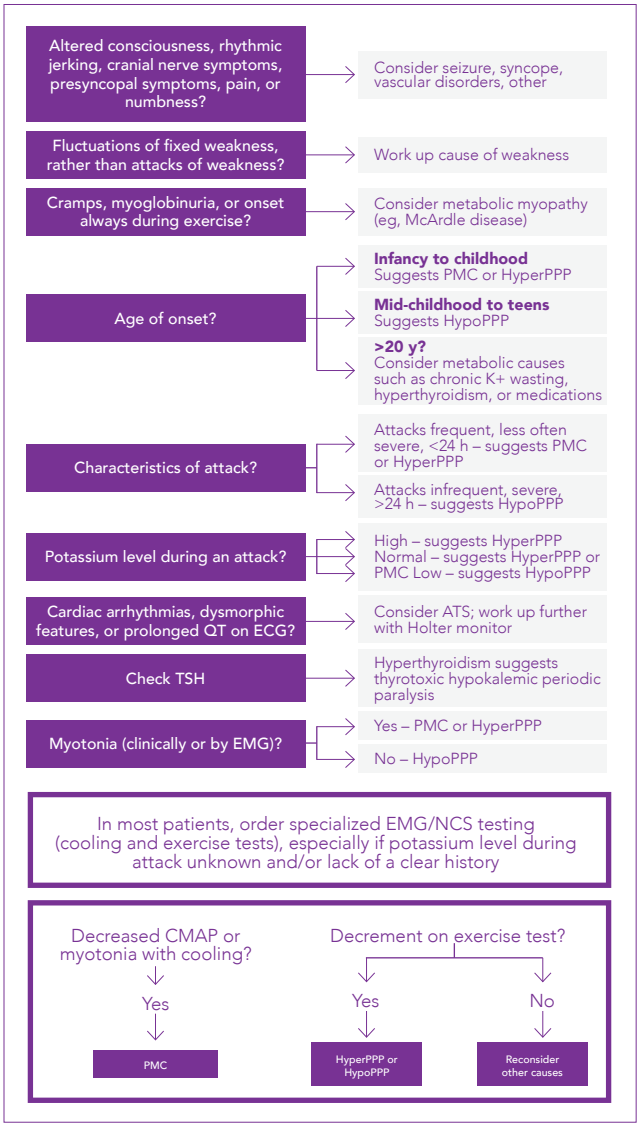
A clinical exam and history are requisite criteria for genetic testing... Also, it is important to note that if you have a negative result (on a genetic test), you may still have the disease.

- Mario Saporta, MD, PhD, MBA, FAAN

CONCLUSION

This paper provides an overview of the clinical features, classification, neurophysiology, and genetics of PPP, and how these factors contribute to a challenging path to diagnosis. While reviewing previously developed diagnostic algorithms, the authors recognized a need for an updated algorithm that takes into account access to newer diagnostic technologies for guiding the diagnosis of PPP. The dissemination and implementation of this new algorithm has the potential to shorten the time to diagnosis and improve outcomes for patients impacted by PPP.

Supplemental Table Figure 1[12]



Adapted from Miller TM, Dias da Silva MR, Miller HA, et al. Correlating phenotype and genotype in the periodic paralyses. Neurology. 2004;63(9):1647-1655, with permission from Wolters Kluwer Health, Inc.

Supplemental Table Figure 1[23]

HypoPPP

- ≥2 attacks of muscle weakness with documented serum K+ <3.5 mEq/L
- 1 attack in proband and 1 attack in 1 relative with documented serum K+<3.5 mEq/L in ≥1 attack
- ≥3 of the following:
  - Onset in the 1st or 2nd decade
  - Attack duration >2 hours
  - Presence of known triggers
  - Improvement with K intake
  - Family history of PPP or positive genetic test
  - Positive short exercise test
- Exclusion of other causes of hypokalemia

HyperPPP

- ≥2 attacks of muscle weakness with documented serum K+ >4.5 mEq/L
- 1 attack in proband and 1 attack in 1 relative with documented serum K+>4.5 mEq/L in ≥1 attack
- ≥3 of the following:
  - Onset prior to 3rd decade
  - Attack duration <2 hours
  - Presence of known triggers
  - Myotonia
  - Family history of PPP or positive genetic test
  - Positive short exercise test
- Exclusion of other causes of hypokalemia

Adapted from Sansone V, Meola G, Links TP, Panzeri M, Rose MR. Treatment for periodic paralysis. *Cochrane Database Syst Rev.* 2008;23(1):CD005045.

Supplemental Table 2[24]

QUESTION	IF POSITIVE, SUGGESTS:
Family history	hyperPP, hypoPP, ATS, PMC, MC, PAM
Carbohydrates	induce attacks TPP, hypoPP +/- PMC, ATS
Stiffness after exercise	PMC, MC
Carbohydrates ameliorate attacks	hyperPP, ATS, PMC, PAM
Tongue stiffens when eating ice cream	PMC
Less stiffness decreases with repeated exercise of a given muscle (warm-up phenomenon)	MC
Myotonia increases with continued exercise	PMC
Serum potassium elevated during attack	PAM, hyperPP, ATS, PMC
Serum potassium normal during attack all diagnoses are possible	all diagnoses are possible
Serum potassium low during attack	hypoPP, TPP, ATS, PMC, diuretic abuse, hyperaldosterone states, RTA
Difficult to open eyes in the cold	PMC
Attacks of muscle stiffness	MC, ATS, PMC, PAM
Attacks of muscle weakness	MC, TPP, hyperPP, hypoPP, ATS, PMC
Duration of attacks are hours	hypoPP, TPP, ATS, PMC
Duration of attacks are minutes to hours	hyperPP, PAM, MC, ATS
EMG with myotonia	hyperPP, PAM, MC
EMG silent during attack of weakness	hypoPP, TPP, ATS, PMC, MC
Palpitations	ATS, hypoPP, hyperPP, TPP, PMC
EKG – tachycardia	TPP
EKG – long QTc and/or ventricular arrhythmia	ATS
EKG – u waves	ATS, hypoPP, TPP
Hyporeflexia during attack of weakness	hypoPP, TPP, ATS, hyperPP Percussion myotonia
Percussion myotonia MC, PMC, PAM	
Physical exam with some of: fifth digit clinodactyly, ocular hypertelorism, low-set ears, webbed fingers/toes, broad nasal root, small mandible, short stature, brachydactyly, microcephaly, short palpebral fissures, thin upper lip, small hands/feet, residual primary dentition, delayed bone age	ATS
McManis nerve conduction protocol (ie, changes in compound muscle action potential after exercise)	ATS, hyperPP, hypoPP, TPP
Muscle biopsy with tubular aggregates	ATS, hyperPP, hypoPP, TPP, PMC, PAM, MC

ATS = Andersen-Tawil syndrome; hyperPP = hyperkalemic periodic paralysis; hypoPP = hypokalemic periodic paralysis; MC = myotonia congenita; PAM = potassium-aggravated myotonia; PMC = paramyotonia congenita; RTA = renal tubular acidosis; TPP = thyrotoxic periodic paralysis.
Graphic adapted from: Levitt JO. Practical aspects in the management of hypokalemic periodic paralysis. J Transl Med. 2008;6:18-24.

Supplemental Table 3[6]

HypoPP[6]	1. ≥2 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 serumK <3.5 mEq/L in at least 1 attack 3. Three of 6 clinical or laboratory features: a. Onset in 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 pathologic skeletal calcium or sodium channel mutation f. Positive long exercise electrodiagnostic test, lasting 5 minutes with 3-4 second resting periods every 30-45 seconds to prevent ischemia17 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
HyperPP[6]	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 first or second 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 long exercise electrodiagnostic test17 4. ,Exclusion of other causes of hyperkalemia (renal, adrenal, thyroid dysfunction; potassium-sparing diuretics use) * Serum potassium may be normal in normokalemic PPP
ATS[6]	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 prolongedQTc or QUc interval25 – 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 or the presence of a genetically confirmed pathologic skeletal muscle potassium channel mutation

Graphic adapted from: Statland JM, Fontaine B, Hanna MG, et al. Review of the diagnosis and treatment of periodic paralysis. Muscle Nerve. 2018;57(4):522-530.

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