Primary Periodic Paralysis

A complex disorder.
A challenging diagnosis.

Primary Periodic Paralysis: A Complex Disorder

A Group of Rare Channelopathies With Varying Subtypes and Triggers

Primary Periodic Paralysis (PPP) causes recurrent, progressive, and debilitating episodes of muscle weakness and temporary paralysis that can negatively impact patients' daily lives[1-4]

- This condition includes a spectrum of rare and chronic genetic neuromuscular disorders with autosomal dominant inheritance[1,5]
- Primary Periodic Paralysis is very rare, with only **~4,000 to 5,000** diagnosed individuals in the US[6]
- The most common forms of Primary Periodic Paralysis are Hyperkalemic (also known as potassium sensitive) and Hypokalemic Periodic Paralysis (also known as potassium responsive)[7,8]
- Related variants include Paramyotonia Congenita (PMC), or Eulenburg Disease, and Andersen-Tawil Syndrome (ATS), or Long QT Syndrome 7[5,9,10]

Hyperkalemic Periodic Paralysis

Associated with[5,11,12]:

- Paralytic episodes, lasting from hours to days, associated with increased potassium levels
- Some patients have normal serum potassium levels (normokalemic) during an attack

Triggers may include[1,3,5]:

- Rest after exercise
- Foods or supplements high in potassium
- Alcohol
- Skipping meals
- Becoming chilled
- Periods of inactivity, including sleep
- Pregnancy and menstruation
- Changes in activity level or daily schedule
- Stress, fatigue, or surgery
- Abrupt weather changes
- Illness, such as infections with fever
- Some medications

Hypokalemic Periodic Paralysis

Associated with[5,13]:

- Paralytic episodes usually associated with decreased potassium levels

Triggers may include[3,5,13]:

- Rest after exercise
- Eating foods high in salt, sugar, and starch
- Alcohol
- Becoming chilled
- Periods of inactivity, including sleep
- Pregnancy
- Stress
- Abrupt weather changes

Related PPP Variants: Paramyotonia Congenita and Andersen-Tawil Syndrome

Less common PPP variants include PMC and ATS.[5,9] PMC is characterized by muscle stiffness that gets worse with exercise.[10] ATS has similar triggers to Hyperkalemic and Hypokalemic PPP and includes concomitant cardiac and some physical abnormalities.[14]

Paramyotonia Congenita

Associated with[9]:

- Muscle stiffness after exercise or muscle cooling

Triggers may include[1,15,16]:

- Prolonged exercise
- Skipping meals
- Becoming chilled
- Eating/drinking cold foods
- Pregnancy
- Hypothyroidism
- Stress
- Food or supplements high in potassium

Andersen-Tawil Syndrome

Associated with[10,14]:

- Paralytic episodes, sometimes involving an irregular heartbeat

Triggers may include[5,14]:

- Periods of inactivity
- Rest after exercise
- Foods high in carbohydrates

Primary Periodic Paralysis: Chronic, Lingering, Debilitating

A Significant Impact on Patients' Everyday Lives

PPP is a rare, physically disabling condition with unpredictable attacks that vary in severity and duration and can take a toll on a patient's ability to confidently engage in everyday activities.[1]

Anxiety

Patients may suffer social anxiety for fear of an attack[1]

Lingering Symptoms

Symptoms of attacks may linger after a paralytic episode[1,13]

- May include:

Clumsiness

Palpitations

Weakness

Extreme fatigue

Pain

- Can cause patients to fear oncoming attacks and miss out on daily activities[1]

Permanent Muscle Weakness (PMW)

PPP may lead to progressive Permanent Muscle Weakness[1,5]

- Up to 60% of patients with a history of PPP experience PMW[4]

After years of paralytic attacks, PMW may be irreversible as muscle atrophies[4]

- PMW can be incapacitating and may result in decreased mobility, loss of function, and reduced participation in social activities
  - The less common edematous form of PMW may be reversible with treatment

In a survey of 66 patients with PPP, 68% experienced PMW[4]*

- Weakness was more prominent and reported more often in proximal than in distal muscles
- The prevalence of permanent weakness increased over time

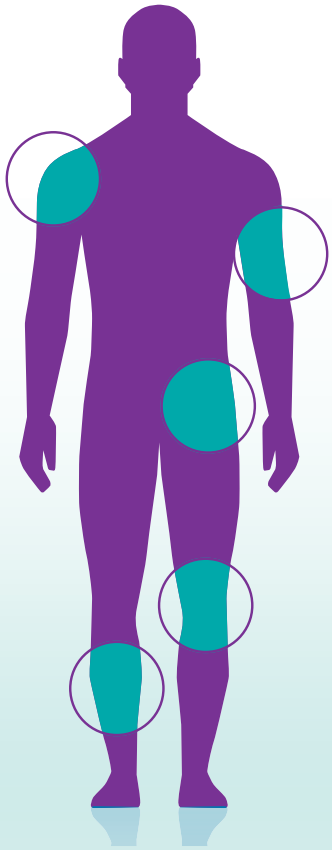
*Based on a survey of 66 self-selected patients over the age of 41 years with a clinical diagnosis of Primary Periodic Paralysis who sought support via the Internet.[4]

Muscle Weakness Can Occur Throughout the Body

The Most Common Sites of Muscle Weakness in PPP[1,4]*

Symptoms of weakness most commonly affect[1,4]:

- Quadriceps
- Hip girdle
- Upper arms
- Calves
- Shoulder girdle



May also affect[1,4]:

- Lower back
- Hands
- Neck & throat
- Forearms
- Glutes
- Chest
- Face & jaw

May be associated with[1]:

- Eyelid myotonia†
  - Interictal lid lag†

†May be the only clinical sign present between attacks.[1]

Primary Periodic Paralysis: Challenges in Diagnosis

Symptoms Are Broad and Inconsistent

PPP can be difficult to diagnose. While usually inherited, it sometimes presents as a de novo mutation.[1,5]

- Misdiagnosis and delays in diagnosis are common because symptoms:
  - **Can mimic a variety of more common diseases, from psychiatric conditions to cardiovascular disorders**[1,2,4]
  - **Do not present themselves consistently throughout the patient population**[1,2,4]

A Long and Frustrating Journey for Patients

The diagnostic journey from the first symptom until a confirmed diagnosis can take more than 20 years.[1,4]

- In a survey of 94 patients over 18 years of age diagnosed with Hyperkalemic Periodic Paralysis, patients reported seeing an average of 4 healthcare professionals before they were finally diagnosed; however, some saw as many as 10[1]
- In the same survey, patients also reported undergoing a range of different diagnostic tests including blood tests, electromyography (EMG), and electrocardiography (ECG), before a diagnostic confirmation[1]
  - **Other common studies used to help diagnose PPP include compound muscle-action potential (CMAP) testing (long-exercise test) and genetic testing**[5]

Attack Frequency Can Vary Considerably

There is a range of how often patients experience episodes of PPP.[4‡]

- Some can experience daily attacks (or no attacks at all), while many more experience at least one attack a week
- As patients age, the frequency of attacks may either increase or decrease; however, in about 2/3 of patients there was no change in frequency

Daily Attacks

28%

of patients

Weekly Attacks

59%

of patients

There Is a Range of Severity of Attacks

PPP attacks can occur spontaneously or in response to type-specific triggers.[5]

- Attacks can last for less than 2 hours to as long as days, and patients may experience muscle stiffness between events[17]
- Attacks can be focused in certain muscles or areas, but they can also be more generalized

In a study of patients with Hyperkalemic Periodic Paralysis surveyed about their disease[15§]:

- 43.3% said the majority of their attacks were mild (defined as "some limitations on mobility, others would notice I am in an attack")
- 15.6% said their attacks were either severe (defined as "can speak, cannot move at all, can call for help") or very severe (defined as "cannot speak, cannot call for help")

The effects of the attacks can linger[1]

- 12.4% reported severe symptoms between attacks that impair their activities of daily living

‡Based on a 68-question online survey of 66 patients of at least 41 years of age (mean age, 60 ± 14 years). Not all patients answered all questions.
§Based on a survey of adults (>18 years of age) with a diagnosis of Hyperkalemic Periodic Paralysis and a genetic diagnosis. Percentages are based on the total number of respondents who answered a given question.

Primary Periodic Paralysis: Evaluation & Testing

A Multidimensional Assessment Is Required

Because PPP is so often difficult to diagnose, multiple levels of evaluation and testing are often required.[5,11,13]

Findings that suggest Hyperkalemic Periodic Paralysis include[5,11]:

- A history of at least two attacks of flaccid limb weakness (may include eyes, throat, breathing muscles, trunk)
- Disease manifestations before 20 years of age
- A family history
- Onset or worsening of an attack resulting from oral potassium intake
- Absence of cardiac arrhythmia between attacks
- EMG with reduced motor units or silence during attacks
- CMAP with a greater-than-normal increase during exercise followed by a progressive decline in amplitude
- Hyperkalemia or an increase of at least 1.5 mmol/L during attacks; normal between attacks
- Elevated serum creatine kinase concentration during attacks

Findings that suggest Hypokalemic Periodic Paralysis include[5,13]:

- A history of episodes of flaccid paralysis with spontaneous recovery
- Disease manifestation beginning between age 5 and 35 years
- A family history
- Low serum concentration of potassium during attacks, but not between
- Precipitating factors such as rest after strenuous exertion or prolonged immobility
- Reduction in CMAP amplitude during long-exercise test
- Absence of myotonic discharge during EMG test
- Absence of myotonia, except for eyelids

Findings that suggest PMC[1,9,18]

- A history of muscle stiffness (sometimes with accompanying pain) and weakness, mainly affecting the face, neck, arms, and hands, as well as lid lag or intermittent diplopia
- Rapid decline in CMAP amplitude, followed by a slow increase
- Attacks and paralysis occurring during or after exercise
- Change in potassium levels, though more commonly hyperkalemia or normokalemia
- Pain in affected muscles for up to several days following an attack

Findings that suggest Andersen-Tawil syndrome[5,14]

- A history of episodic paralysis
- Patients with a mutation in the KCNJ2 gene who experience attacks most often have hypokalemia (65%) but could also present with hyperkalemia (15%) or have normal potassium levels (20%)
- Long QT intervals occur in 50% of patients; ventricular arrhythmias, in 84% of patients
- Distinctive skeletal features, including broad forehead, hypoplastic mandible, ocular hypertelorism, low-set ears, digit clinodactyly, and syndactyly of the toes

Several different genes are associated with the various forms of PPP[9,11,13,14]**:**

- In Hyperkalemic Periodic Paralysis, SCN4A is primarily associated
  - If no pathogenic variant is identified, sequencing of KCNJ2 and CACNA1S may be considered
- In Hypokalemic Periodic Paralysis, 3 genes have been associated
  - CACNA1S (60% of patients)
  - SCN4A (20% of patients)
  - KCNJ18 (3.5% of patients)
- Similar to Hyperkalemic Periodic Paralysis, the gene associated with PMC is SCN4A
- Approximately 80%–90% of patients with ATS have a mutation in the KCNJ2 gene

Although genetic testing can help confirm a suspected diagnosis, there may be other gene variants involved in PPP, and the absence of a known genetic alteration does not preclude diagnosis[5,11,13]

Primary Periodic Paralysis: Management Strategies

Management of Hyperkalemic Periodic Paralysis[11]

Treating attacks	**Attacks may be minimized with:** › Mild exercise and/or oral ingestion of carbohydrates, inhalation of salbutamol, or intravenous calcium gluconate
Managing attacks (medical and non-medical approaches)	**Attacks may be managed by:** › Prescription medications › Eating meals rich in carbohydrates › Avoiding potassium-rich medications and foods, fasting, strenuous work, and exposure to cold
Preventing secondary complications	**Depolarizing anesthetic agents should be avoided during surgery:** › Includes potassium, suxamethonium, and anticholinesterases › These may aggravate myotonia and can interfere with intubation and mechanical ventilation

Management of Hypokalemic Periodic Paralysis[13]

Treating attacks	**Attack intensity and duration may be managed by:** › Oral potassium salts, as needed, for mild-to-moderate attacks › Intensive management for severe attacks (intravenous potassium infusion, serial measurement of serum potassium concentration, evaluation of possible respiratory involvement, and continuous ECG monitoring)
Managing attacks (medical and non-medical approaches)	**Attacks may be managed by:** › Prescription medications › Counseling patients to avoid triggers; follow a low-sodium, low-carbohydrate, high-potassium diet; and take oral potassium supplementation
Preventing secondary complications	**Complications can be avoided by:** › Creating a safe home environment to prevent falls and accidents › Taking steps to prevent anesthetic complications (ie, malignant hyperthermia)

Management of Paramyotonia Congenita[16]

Treating attacks	Mild exercise can help mitigate symptoms; treatments include pharmacologic intervention when myotonia limits routine activities.
Managing attacks (medical and non-medical approaches)	**Attacks may be managed by:** › Prescription medications › Avoiding strenuous exercise and cold environments

Management of Andersen-Tawil Syndrome[14]

Treating attacks	Treatment of ATS symptoms requires intervention for both periodic paralysis attacks as well as cardiac arrhythmias.
Managing attacks (medical and non-medical approaches)	**Attacks may be managed by:** › Prescription medications › Potassium supplements Management of cardiac abnormalities associated with ATS.

Primary Periodic Paralysis: Summary

Primary Periodic Paralysis

- The condition includes a spectrum of rare and chronic neuromuscular disorders, including Hyperkalemic and Hypokalemic Periodic Paralysis, Paramyotonia Congenita, and Andersen-Tawil Syndrome[5]

Impact on Everyday Life

- The unpredictable attacks vary in severity and length and may take a toll on a patient's ability to engage in everyday activities[1]
- Permanent Muscle Weakness occurs in a majority of patients with PPP and is often irreversible[4]*

Diagnosis

- The diagnosis of Primary Periodic Paralysis can be challenging[1,2,4]
- Diagnosis requires a multidimensional assessment including clinical presentation, family history, response to potassium, and long-exercise testing, and may include genetic confirmation[5,11,13]
- Primary Periodic Paralysis is predominantly an inherited autosomal dominant disease, though up to 30% of patients lack an identified genetic mutation[1,5,13,14]

Disease Management

- Treatment for Primary Periodic Paralysis typically includes both lifestyle management and medical treatment[5]

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*Based on a survey of 66 self-selected patients over the age of 41 years with a clinical diagnosis of Primary Periodic Paralysis who sought support via the Internet.[4]

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