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 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[1,5-7]
- Primary periodic paralysis is very rare, affecting ~5,000 to 6,000 individuals in the US, or ~3 in every 200,000 people[8-12]
- Although there are related variants, the most common forms are hyperkalemic and hypokalemic periodic paralysis[8-12]

Hyperkalemic Primary Periodic Paralysis

Associated with[13]:

- Paralytic episodes with a serum potassium increase of at least 1.5 mmol/L during an attack

Triggers may include[13]:

- Cold environment
- Rest after exercise
- Stress or fatigue
- Alcohol and certain foods/beverages
- Potassium in food
- Hunger
- Changes in activity level
- Changes in humidity
- Extra sleep
- Pregnancy and menstruation
- Illness of any type
- Some medications
- Potassium supplements

Hypokalemic Primary Periodic Paralysis

Associated with[14]:

- Paralytic episodes with concomitant hypokalemia (<2.5 mmol/L)

Triggers may include[14]:

- Rest after exercise
- Carbohydrate-rich evening meals
- Periods of inactivity, including nocturnal rest
- Heavy meals
- Sweets
- Salt
- Cold
- Stress

A Significant Impact on Patients' Lives

Primary periodic paralysis 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

➤ Weakness

➤ Extreme fatigue

➤ Pain

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

Persistent muscle weakness

As they age, patients may experience permanent weakness, further impacting their quality of life[1]

*These symptoms need to be considered within the overall treatment plan. No treatment for primary periodic paralysis is indicated to address all of these symptoms.

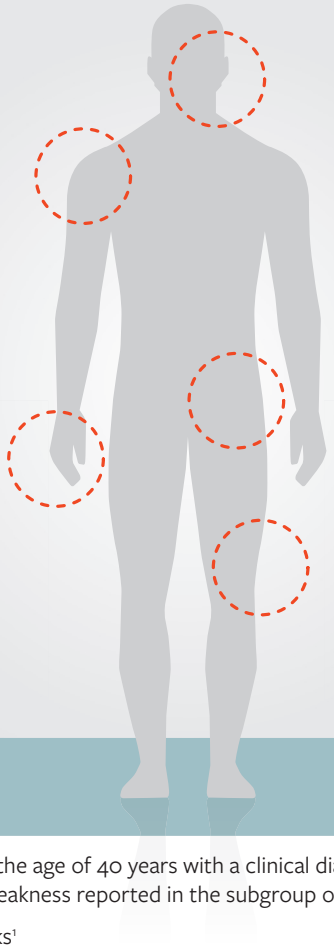
Primary Periodic Paralysis: A Challenging Diagnosis

Signs and Symptoms Vary Among Patients

Symptoms are Often Nonspecific With Varying Clinical Presentations[1,4]*

Symptoms of weakness most commonly affect[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†

* Based on a survey of 66 self-selected patients over the age of 40 years with a clinical diagnosis of primary periodic paralysis who sought support via the Internet. Symptoms of permanent muscle weakness reported in the subgroup of patients with permanent weakness (n=45)[4]

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

Not Easily Diagnosed and May Go Untreated for Many Years[1,4]

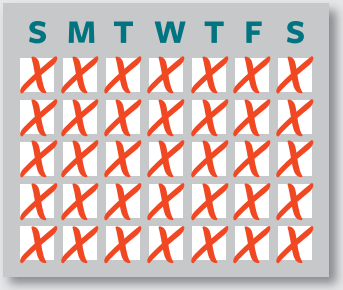
Primary periodic paralysis can be difficult to diagnose. While usually inherited, it sometimes presents as a *de novo* mutation.[1,5-7]

- Misdiagnosis and delays in diagnosis are common because symptoms:
  - Are often nonspecific and patients have varying clinical presentations[1,2,4]
  - Can mimic a variety of more common diseases, from psychiatric conditions to stroke[1,2,4]
- 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 age 18 diagnosed with hyperkalemic periodic paralysis, patients reported seeing an average of 4 healthcare professionals; however, some saw as many as 10 before they were finally diagnosed[1]
- In the same survey, patients also reported undergoing a range of diagnostic studies, including blood tests, electromyographies (EMGs), electrocardiograms (EKGs), compound muscle action potentials (CMAP), and genetic testing before their diagnosis was confirmed[1,13]

The Frequency of Attacks May Vary Considerably[4‡]

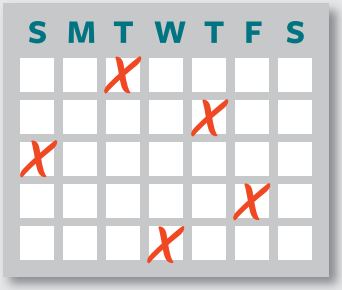
Daily Attacks

28%
of patients



Weekly Attacks

59%
of patients



‡Based on a 68-question online survey of 66 patients over 41 years (mean age, 60 ± 14 years). Not all patients answered all questions.

Primary Periodic Paralysis: Evaluation & Testing

A Multidimensional Assessment is Required

Because primary periodic paralysis is so often difficult to diagnose, evaluation and testing can include multiple levels of evaluation and testing.[13,14]

Findings that suggest hyperkalemic periodic paralysis include[13]:

- 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; however, absence does not preclude diagnosis
- 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 with serum potassium >5 mmol/L or an increase of at least 1.5 mmol/L during attacks; normal between attacks
- Elevated serum creatine kinase (CK) concentration during attacks

Findings that suggest hypokalemic periodic paralysis include[14]:

- A history of episodes of flaccid paralysis with spontaneous recovery
- A family history consistent with autosomal dominant inheritance
- Low serum concentration of potassium (K <3.5 mEq/L) during attacks, but not between
- Precipitating factors such as rest after strenuous exertion or prolonged immobility
- Approximately 60% of patients have genetic mutations in *CACNA1S*, ~20% in *SCN4A*, and ~3.5% in *KCNJ18*

Although genetic testing can help confirm a suspected diagnosis, the absence of a genetic alteration does not preclude diagnosis[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; all encode subunits of ion channels that are primarily expressed in skeletal muscle cells
  - *CACNA1S* (60% of patients)
  - *SCN4A* (20% of patients)
  - *KCNJ18* (3.5% of patients)

Primary Periodic Paralysis: Management Strategies

Management of Hyperkalemic Periodic Paralysis[13]

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 such as dichlorphenamide ➤ 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[14]

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 electrocardiogram ECG monitoring)
Managing attacks (medical and non-medical approaches)	**Attacks may be managed by:** ➤ Prescription medications such as dichlorphenamide ➤ 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)

Primary Periodic Paralysis: Summary

Primary Periodic Paralysis

- The condition includes a spectrum of rare and chronic neuromuscular disorders, the most common forms of which are hypokalemic and hyperkalemic periodic paralysis[8-12]

Impact on Everyday Life

- Primary periodic paralysis 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]

Diagnosis

- The diagnosis of primary periodic paralysis can be challenging. While usually inherited, it sometimes presents as a *de novo* mutation[1,5-7]
- Diagnosis requires a multidimensional assessment including the clinical presentation, family history, response to potassium, physiological tests, exclusion of secondary causes, and may include genetic confirmation (although the absence of a genetic mutation does not preclude diagnosis)[13,14]

Signs and Symptoms

- Symptoms of weakness most commonly affect the quadriceps, hip girdle, upper arms, calves, and shoulder girdle, but may also affect the lower back, hands, neck and throat, eyelids, and other parts of the body[1,4]

Disease Management

- Treatment for primary periodic paralysis typically includes both lifestyle management and medical treatment[13,14]

References:

1. Charles G, Zheng C, Lehmann-Horn F, Jurkatt-Rott K, Levitt J. Characterization of hyperkalemic periodic paralysis: a survey of genetically diagnosed individuals. *J Neurol*. 2013;260:2606-2613. **2.** Arya SN. Periodic paralysis. *Journal, Indian Academy of Clinical Medicine*. 2002;3:374-382. **3.** Cannon SC. Channelopathies of skeletal muscle excitability. *Compr Physiol*. 2015;5:761–790. **4.** Cavel-Greant D, Lehmann-Horn F, Jurkat-Rott K. The impact of permanent muscle weakness on quality of life in periodic paralysis: a survey of 66 patients. *Acta Myol*. 2012;31:126–133. **5.** Grieg SL. Dichlorphenamide: a review in primary periodic paralyses. *Drugs*. 2016;76:501-507. **6.** Fontaine B, Phillips LH. A newly approved drug for a rare group of diseases: dichlorphenamide for periodic paralysis. *Neurology*. 2016;86:1366-1367. **7.** Sansone VA, Burge J, Smith PC, et al. Randomized, placebo-controlled trials of dichlorphenamide in periodic paralysis. *Neurology*. 2016;86:1408-1416. **8.** National Institutes of Health. Hyperkalemic periodic paralysis. Available at: https://ghr.nlm.nih.gov/condition/hyperkalemic-periodic-paralysis. Accessed December 5, 2016. **9.** National Institutes of Health. Hypokalemic periodic paralysis. Available at: https://ghr.nlm.nih.gov/condition/hypokalemic-periodic-paralysis. Accessed December 5, 2016. **10.** National Institutes of Health. Anderson-Tawil syndrome. Available at: https://ghr.nlm.nih.gov/condition/andersen-tawil-syndrome. Accessed December 5, 2016. **11.** National Institutes of Health. Potassium-aggravated myotonia. Available at: https://ghr.nlm.nih.gov/condition/potassium-aggravated-myotonia. Accessed December 5, 2016. **12.** National Institutes of Health. Paramyotonia congenita. Available at: https://ghr.nlm.nih.gov/condition/paramyotonia-congenita. Accessed December 5, 2016. **13.** Weber F, Jurkat-Rott K, Lehmann-Horn F. Hyperkalemic Periodic Paralysis. NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health. 2016. **14.** Vicart S, Sternberg D, Arzel-Hezode M, et al. Hypokalemic Periodic Paralysis. NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health. 2014.

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KEV011-01 v2 06/2017

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