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NLM Citation: Weber F. Hyperkalemic Periodic Paralysis. 2003 Jul 18 [Updated 2021 Jul 1]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Hyperkalemic Periodic Paralysis

Synonyms: HyperKPP, HyperPP, HYPP

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Created: July 18, 2003; Updated: July 1, 2021.

Summary

Clinical characteristics

Hyperkalemic periodic paralysis (hyperPP) is characterized by attacks of flaccid limb weakness (which may also include weakness of the muscles of the eyes, throat, breathing muscles, and trunk), hyperkalemia (serum potassium concentration >5 mmol/L) or an increase of serum potassium concentration of at least 1.5 mmol/L during an attack of weakness and/or provoking/worsening of an attack by oral potassium intake, normal serum potassium between attacks, and onset before age 20 years. In approximately half of affected individuals, attacks of flaccid muscle weakness begin in the first decade of life, with 25% reporting their first attack at age ten years or older. Initially infrequent, the attacks then increase in frequency and severity over time until approximately age 50 years, after which the frequency of attacks declines considerably. The major attack trigger is eating potassium-rich foods; other triggers include: cold environment; rest after exercise, stress, or fatigue; alcohol; hunger; and changes in activity level. A spontaneous attack commonly starts in the morning before breakfast, lasts for 15 minutes to one hour, and then passes. Individuals with hyperPP frequently have myotonia (muscle stiffness), especially around the time of an episode of weakness. Paramyotonia (muscle stiffness aggravated by cold and exercise) is present in about 45% of affected individuals. More than 80% of individuals with hyperPP older than age 40 years report permanent muscle weakness and about one third develop a chronic progressive myopathy.

Diagnosis/testing

The diagnosis of hyperPP is established in a proband with suggestive findings and a heterozygous pathogenic variant in *SCN4A* identified by molecular genetic testing. In case of diagnostic uncertainty, a provocative test can be employed, although the availability of genetic testing and electrophysiologic studies largely obviates the need for such dangerous tests.

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Management

Treatment of manifestations: At the onset of weakness, attacks may be prevented or aborted with mild exercise and/or oral ingestion of carbohydrates, intravenously injected glucocorticoids, inhalation of salbutamol, or intravenous calcium gluconate.

Prevention of primary manifestations: Hyperkalemic attacks of weakness can be prevented by frequent meals rich in carbohydrates; continuous use of a thiazide diuretic or a carbonic anhydrase inhibitor; and avoidance of potassium-rich medications and foods, fasting, strenuous work, and exposure to cold.

Surveillance: Yearly neurologic examination with focus on muscle strength in the legs in order to detect permanent weakness; in those with permanent muscle weakness, MRI of leg muscles every one to three years; during prophylactic treatment, determination of serum potassium concentration twice per year to avoid severe diuretic-induced hypokalemia; annual monitoring of thyroid function.

Agents/circumstances to avoid: Potassium-rich medications and foods, fasting, strenuous work, exposure to cold, and use of depolarizing anesthetic agents during general anesthesia or ACE-inhibitor medications.

Evaluation of relatives at risk: It is appropriate to test asymptomatic at-risk family members for the pathogenic variant identified in an affected relative in order to institute preventive measures, particularly those that would decrease the risk of unexpected acute paralysis or anesthetic events.

Genetic counseling

HyperPP is inherited in an autosomal dominant manner. Most individuals with hyperPP have an affected parent; the proportion of individuals with hyperPP caused by a *de novo* pathogenic variant is unknown. Each child of an individual with hyperPP has a 50% chance of inheriting the pathogenic variant. Once the *SCN4A* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for hyperPP are possible.

Diagnosis

Suggestive Findings

Hyperkalemic periodic paralysis (hyperPP) **should be suspected** in individuals with the following family history and clinical, electromyogram, and suggestive laboratory findings:

Clinical findings

- History of at least two attacks of flaccid limb weakness (which may also include weakness of the muscles of the eyes, throat, breathing muscles, and trunk)
- Onset or worsening of an attack as a result of oral potassium intake
- Disease manifestations before age 20 years
- Absence of cardiac arrhythmia between attacks
- Normal psychomotor development

Family history

- Typically, at least one affected first-degree relative
- Note: Absence of a family history suggestive of hyperPP does not preclude the diagnosis.

Electromyogram (EMG)

- During the attack, EMG demonstrates a reduced number of motor units or may be silent (no insertional or voluntary activity).
- In the intervals between attacks, EMG may reveal myotonic activity (bursts of muscle fiber action potentials with amplitude and frequency modulation, firing rate generally between 20 and 150 Hz), even though myotonic stiffness may not be clinically present.
- In some individuals, especially in those with permanent weakness, a myopathic pattern may be visible.
- Note: Approximately 50% of affected individuals have no detectable electric myotonia.

Suggestive laboratory findings during attacks

- Hyperkalemia (serum potassium concentration >5 mmol/L) or an increase of serum potassium concentration of at least 1.5 mmol/L.
- Note: Serum potassium concentration seldom reaches cardiotoxic levels, but changes in the EKG (increased amplitude of T waves) may occur.
- Elevated serum creatine kinase (CK) concentration (sometimes 5-10x the normal range)

Suggestive laboratory findings between attacks

- Normal serum potassium concentration and muscle strength between attacks

  Note: At the end of an attack of weakness, elimination of potassium via the kidney and reuptake of potassium by the muscle can cause transient hypokalemia that may lead to the misdiagnosis of hypokalemic periodic paralysis.

- Elevated serum CK concentration with normal serum sodium concentration

Establishing the Diagnosis

The diagnosis of hyperkalemic periodic paralysis (hyperPP) **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *SCN4A* identified by molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *SCN4A* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from other inherited disorders with periodic paralysis are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SCN4A* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected.

Typically, if no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date such variants have not been identified as a cause of this disorder.

A periodic paralysis multigene panel that includes *SCN4A* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Hyperkalemic Periodic Paralysis (hyperPP)

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SCN4A	Sequence analysis [3]	~66% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]
Unknown [6]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. In a clinical setting in about one third of individuals with a typical phenotype of hyperPP, no pathogenic variant in SCN4A or in any other gene is identified on molecular genetic testing.

Provocative Testing

In case of diagnostic uncertainty (i.e., in the absence of a measurement of ictal (during an attack) serum potassium concentration and normal molecular genetic studies), a provocative test may be employed to ensure the diagnosis. The availability of genetic testing and electrophysiologic studies largely obviates the need for such dangerous tests. Systemic provocative testing carries the risk of inducing a severe attack; therefore, such testing must be performed by an experienced physician and a stand-by anesthetist, with close monitoring of the EKG and serum concentration of potassium.

The classic provocative test consists of the administration of 2-10 g potassium under clinical surveillance with serum potassium concentration and strength measured at 20-minute intervals. Usually, an attack is induced within an hour and lasts approximately 30 to 60 minutes, accompanied by an increase in serum potassium concentration, similar to spontaneously occurring attacks of weakness. Note: The test is contraindicated in

individuals who already have hyperkalemia and in those individuals who do not have adequate renal or adrenal function.

Clinical Characteristics

Clinical Description

The attacks of flaccid muscle weakness associated with hyperkalemic periodic paralysis (hyperPP) usually begin in the first decade of life and increase in frequency and severity over time, with 25% experiencing their sentinel attack in the second decade of life. Initially infrequent, the attacks increase in frequency and severity over time until approximately age 50 years, after which the frequency declines considerably.

Triggers include cold environment; rest after exercise, stress, or fatigue; alcohol; hunger; changes in activity level; potassium in food; specific foods or beverages; changes in humidity; extra sleep; pregnancy; illness of any type; menstruation; medication; and potassium supplements [Charles et al 2013]. The major attack trigger is eating potassium-rich foods.

Of note, attacks occur more frequently on holidays and weekends when people rest in bed longer than usual.

Pattern of attacks. A spontaneous attack commonly starts in the morning before breakfast, lasts for 15 minutes to an hour, and then passes. In about 20% of affected individuals the attacks last considerably longer, from more than two days to more than a week.

In some individuals, paresthesias (probably induced by the hyperkalemia) herald the weakness. During an attack of weakness, the muscle stretch reflexes are abnormally diminished or absent. Dysphagia during an attack of weakness has also been described [Benhammou et al 2017]. The strength of the attacks is not always consistent; sometimes the patient only feels fatigued, but can still move around slowly. Other times the patients are completely paralyzed. Sometimes attacks may come very suddenly.

Individuals most commonly describe their attacks as stiffness followed by weakness, although many have described their attacks as some other permutation of weakness and/or stiffness. The arms and hands are just as frequently affected as the thighs and calves [Charles et al 2013].

Frequency of attacks can vary greatly among individuals. Some have attacks every day, others several times a month; others have them every few months or less often.

Usually, cardiac arrhythmia or respiratory insufficiency does not occur during the attacks. When present, respiratory insufficiency manifests as shortness of breath. In a study by Charles et al [2013], 26% of subjects reported that their breathing musculature was affected and 62% reported that their face was affected during attacks. The mouse model has demonstrated a resistance to weakness triggered by hyperkalemia in diaphragmatic muscle as compared to skeletal muscle [Ammar et al 2015].

Interictal period (i.e., between paralytic attacks) findings. After an attack, affected individuals report clumsiness, weakness, and irritability, and in 62% muscle pain secondary to the attack. One observational study identified fibromyalgia in half of the individuals surveyed who had hyperPP [Giacobbe et al 2021]. Between attacks, the majority report no or mild symptoms. However, 12% report severe symptoms between attacks that impair activities of daily living.

Muscle issues. Individuals with hyperPP frequently (i.e., >50% of the time) have myotonia, especially around the time of an episode of weakness. Mild myotonia (muscle stiffness) that does not impede voluntary movements is often present between attacks. Myotonia is most readily observed in the facial, lingual, thenar, and finger extensor muscles; eyelid myotonia (lid lag myotonia) has been rarely reported. Paramyotonia (muscle stiffness aggravated by cold and exercise) is present in about 45% of affected individuals. Of individuals with myotonia,

37% have experienced progressive myopathy, while of those reporting absence of myotonia, 33% have experienced progressive myopathy [Charles et al 2013].

Bradley et al [1990] reported more than 80% of the affected individuals older than 40 years to have permanent muscle weakness and approximately one third of older affected individuals developed a chronic progressive myopathy. The myopathy mainly affects the pelvic girdle and proximal and distal lower-limb muscles. A more recent study using MRI reveals an even earlier onset of progressive myopathy: progressive myopathy was observed even in individuals at the second and third decades of life with myopathic findings prominent in the gastrocnemius muscle. Muscle atrophy, edematous change, and fatty change were prominent in the superficial posterior compartment of the lower leg [Jeong et al 2018].

Thyroid dysfunction. As shown by an observational study, individuals with hyperPP appear to be at higher risk for thyroid dysfunction (relative risk of 3.6) than those in the general population [Charles et al 2013].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Usually, the penetrance is high (>90%). A few individuals with rare heterozygous pathogenic variants do not present with clinically detectable symptoms but have signs of myotonia detectable by EMG only [McClatchey et al 1992, Wagner et al 1997].

Nomenclature

Names for hyperPP no longer in use include adynamia episodica hereditaria and Gamstorp disease.

Prevalence

The prevalence of hyperPP is approximately 0.17/100,000 (95% CI 0.13-0.20) [Horga et al 2013]. In the Netherlands, a prevalence of 0.06/100,000 (95% CI 0.03–0.12) has been reported [Stunnenberg et al 2018]. In a large cohort of Italian patients with periodic paralysis and *SCN4A* pathogenic variants, the hyperPP/normo-PP phenotype accounted for seven of 80 (8.7%) individuals [Maggi et al 2020]. In a German observational study of nondystrophic myotonia, 20% of the patients with *SCN4A* pathogenic variants showed periodic paralysis [Vereb et al 2021].

Genetically Related (Allelic) Disorders

Several types of myotonia and periodic paralyses (PP) are caused by pathogenic variants in *SCN4A*. All of the phenotypes in Table 2 occur in association with a heterozygous pathogenic variant in *SCN4A* except for congenital myasthenic syndrome, which is associated with biallelic pathogenic variants (autosomal recessive inheritance).

Some *SCN4A* pathogenic variants may be associated with more than one phenotype. For example, the clinical overlap of paramyotonia congenita (PMC) and hyperkalemic periodic paralysis (hyperPP) is extensive, and family members with the same pathogenic variant may have a syndrome typical of PMC or hyperPP [Cannon 2018].

See Table 3 (pdf) for an author-curated list of associated *SCN4A* pathogenic variants by phenotype.

Table 2. Selected *SCN4A* Allelic Disorders

Phenotype	Main Findings
Hypokalemic periodic paralysis (hypoPP)	See Differential Diagnosis.
Normokalemic periodic paralysis (normoPP)	See Differential Diagnosis.
Paramyotonia congenita (PMC) (OMIM 168300)	Cold-induced muscle stiffness that ↑ w/continued activity; inability to reopen the eyes after several forceful closures in rapid succession; usually not induced or aggravated by potassium. Often stiffness gives way to flaccid weakness or even paralysis on intensive exercise & cooling.
Sodium channel myotonias known as potassium-aggravated myotonia (SCM/PAM)	Development of severe stiffness following vigorous exercise or oral ingestion of potassium. Spectrum ranges from **mild** (myotonia fluctuans in which affected persons either are not aware of muscle stiffness or may experience stiffness that tends to fluctuate from day to day) to **very severe** (myotonia permanens in which continuous myotonic activity is noticeable on EMG & → generalized muscle hypertrophy incl face muscles).
Congenital myasthenic syndrome (CMS)	Fatigable generalized muscle weakness & recurrent attacks of respiratory & bulbar paralysis from birth
Alternating hemiplegia of childhood	One report [1]
Essential tremor	One report [2]

1. Duan et al [2019]
2. Bergareche et al [2015]

Differential Diagnosis

In addition to the allelic disorders described in Genetically Related Disorders, other conditions with periodic paralysis or with hyperkalemia to consider when making the diagnosis of hyperkalemic periodic paralysis (hyperPP) are discussed below.

Adult onset of clinical manifestations points to other diagnoses such as the Andersen-Tawil syndrome or secondary acquired forms of hyperPP.

The following signs and symptoms suggest a diagnosis **other than hyperPP**:

- Associated sensory symptoms, including pain or tenderness
  - Sensory loss could suggest polyneuropathy such as Guillain-Barré syndrome.
  - Pain could suggest myositis; however, some individuals with hyperPP report paralytic episodes as painful and show symptoms of fibromyalgia (see Clinical Description).
- Urinary retention or constipation, which may be observed in other causes of acute or subacute paralysis, but can occur rarely in hyperPP. (Bowel incontinence and bladder incontinence during attacks are reported in hyperPP.)
- Associated symptoms that suggest myasthenia or involvement of the neuromuscular junction, including:
  - Ptosis (Lid lag myotonia, which may mimic ptosis, may rarely be reported in hyperPP; see Clinical Description.)
  - Diplopia
  - Dysphagia (may rarely be reported in hyperPP; see Clinical Description.)
  - Dysarthria
- Alteration or loss of consciousness
- Abnormal movement
- History of fever days before an attack, which could suggest poliomyelitis or other virus-caused paralysis

- History of back pain days before an attack, which could suggest acute transverse myelitis or Guillain-Barré syndrome
- History of tick bite, which could suggest tick paralysis

The four major differential diagnoses of hyperPP are hypokalemic periodic paralysis (hypoPP), normokalemic potassium-sensitive periodic paralysis (normoPP), thyrotoxic periodic paralysis (TPP), and Andersen-Tawil syndrome (ATS) (see Table 4). HypoPP is the most common cause of periodic paralysis.

Table 4. The Different Categories of Periodic Paralyses (PP) with Membrane Excitability Disorder and Associated Findings

	HypoPP	NormoPP	HyperPP	TPP [1]	ATS
Main clinical features	Weakness episodes lasting hrs to days w/ concomitant hypokalemia	Weakness episodes lasting hrs to days w/ concomitant normokalemia	Weakness episodes lasting mins to hrs w/concomitant normo- or hyperkalemia	Identical to that of the paralytic episodes of hypoPP	Episodic PP, ventricular arrhythmias, prolonged QT interval, characteristic anomalies [2]
Age at first attacks	Late in 1st decade or in 2nd decade	Late in 1st decade or in 2nd decade	1st years of life	Variable, dependent on onset of thyrotoxicosis	Late in 1st decade or in 2nd decade (usually after cardiac events)
Main triggers	Rest after exercise, carbohydrate-rich meal, salt intake, stress, cold	Rest after exercise, carbohydrate-rich meal, salt intake, stress, cold	Cold; rest after exercise, stress, & fatigue; alcohol; hunger; changes in activity level; potassium in food; specific foods	Thyrotoxicosis	Prolonged rest, rest after exertion
EMG: myotonic discharges	No	Some	Some	No	No
EMG tests	Late decrement w/LET (pattern IV, V)	Late decrement w/LET (pattern IV, V)	Pattern IV, V	Initial CMAP ↑ + ↓	Variable (CMAP ↑ + ↓, normal CMAP + ↓, etc)
Extramuscular expression	None	None	None	Possible manifestations of thyrotoxicosis	Cardiac arrhythmia, dysmorphy
Prevention of paralysis attacks	ACZ, DCP	ACZ, DCP	ACZ, DCP	Normal thyroid function	ACZ, DCP
Curative treatment	None	None	None	Treatment of thyroid disorder	None
Known causative or susceptibility gene(s) [3]	*CACNA1S*; *SCN4A*	*SCN4A*	*SCN4A*	*KCNJ18*	*KCNJ2*
Defective ion channel(s)	Cav 1.1; Nav 1.4; Kir 6.2	Nav 1.4	Nav 1.4	Kir 6.2	Kir 2.1

ACZ = acetazolamide; CMAP = compound muscle action potential; DCP = dichlorphenamide; LET = long exercise test

1. OMIM 613239

2. ATS anomalies include low-set ears, widely spaced eyes, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis.

3. In a cohort of 60 Chinese individuals with primary periodic paralysis, 92.5% of those with a genetic diagnosis had pathogenic variants in *CACNA1S*, *KCNJ2,* or *SCN4A* [Luo et al 2019].

Normo- and hyperkalemic paralysis (normo/hyperPP) differ in several ways from hypoPP:

- Serum concentration of potassium during the paralytic attacks is normal or elevated.
- Some triggering factors for hypoPP attacks (e.g., carbohydrate-rich meals) are not found.
- Age of onset of paralytic attacks is lower.
- Duration of attacks is assumed to be shorter. However, this is questionable, according to surveys of affected individuals.
- Electromyography shows myotonic discharges in most individuals between attacks; however, the response patterns for short exercise test (SET) and long exercise test (LET) may be indiscernible; i.e., pattern IV or V defined by Fournier et al [2004] may be caused by both hypokalemic and normo/hyperkalemic periodic paralysis.
- In normokalemic PP, the reaction to oral potassium administration may be different from that in hypoPP – anything from amelioration to worsening of the weakness [Jurkat-Rott et al 2012].

Usually, the distinction between hypoPP and normo/hyperPP can be made on the basis of clinical, laboratory (i.e., kalemia during an attack), and EMG findings, and confirmed by molecular genetic testing [Miller et al 2004, Vicart et al 2004, Fan et al 2013].

Thyrotoxic periodic paralysis (TPP) (OMIM 613239) typically mimics hypoPP. Individuals with paralytic attacks associated with hypokalemia and hyperthyroidism should be evaluated for TPP.

Andersen-Tawil syndrome (ATS) is characterized by a triad of episodic flaccid muscle weakness (i.e., periodic paralysis), ventricular arrhythmias and prolonged QT interval, and anomalies including low-set ears, widely spaced eyes, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis. The periodic paralysis may be accompanied by hypokalemia, normokalemia, or hyperkalemia. Affected individuals 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. Long-lasting interictal weakness is common. Mild learning difficulties and a distinct neurocognitive phenotype (i.e., deficits in executive function and abstract reasoning) have been described. Incomplete clinical presentations are possible. An electrocardiogram or a Holter-EKG recording between attacks of weakness is necessary to evaluate for the possibility of ATS. EKG should be performed in an interictal period in order to evaluate for a U wave, which is observed in ATS. Pathogenic variants in *KCNJ2* are causative [Plaster et al 2001]. Inheritance is autosomal dominant with reduced penetrance and variable expressivity.

Hereditary disorders characterized by hyperkalemia

- Adrenal insufficiency is characterized by hyperkalemia, hyponatremia, and hypoglycemia. Adrenal insufficiency in infancy may be caused by congenital adrenal hyperplasia (most commonly caused by 21-hydroxylase deficiency, associated with biallelic pathogenic variants in *CYP21A2*) and congenital adrenal hypoplasia including X-linked adrenal hypoplasia congenita, associated with pathogenic variants in *NR0B1*).
- Adrenal cortical hypofunction (Addison disease) can be an autoimmune disorder with familial aggregation or combined with other endocrinopathies, particularly hypoparathyroidism. Addison disease also occurs in X-linked adrenoleukodystrophy.
- Recessive infantile hypoaldosteronism (corticosterone methyloxidase type II deficiency; OMIM 610600), another hyperkalemic disorder, leads to a rare form of salt wasting that may be life threatening during the first years of life. Recurrent dehydration and severe failure to thrive, associated with mild hyponatremia and hyperkalemia, are typical features. Laboratory tests reveal elevated plasma renin-to-serum aldosterone ratios and serum 18-hydroxycorticosterone to aldosterone ratios.
- Pseudohypoaldosteronism type I is characterized by neonatal salt-wasting resistant to mineralocorticoids. The autosomal recessive form (OMIM 264350) with symptoms persisting into adulthood is caused by

pathogenic loss-of-function variants in *SCNN1A*, *SCNN1B*, and *SCNN1G*. The autosomal dominant form (OMIM 177735), associated with pathogenic variants in *NR3C2,* shows milder symptoms that remit with age.

- Pseudohypoaldosteronism type II (PHAII), also known as Gordon's syndrome or familial hyperkalemia and hypertension, is characterized by hypertension, increased renal salt reabsorption, and impaired potassium and hydrogen excretion resulting in hyperkalemia that may be improved by thiazide diuretics. PHAII is caused by pathogenic variants in *CUL3*, *KLHL3*, *WNK1*, or *WNK4.* PHAII is frequently inherited in an autosomal dominant manner; PHAIID (caused by pathogenic variants in *KLHL3*) may also be inherited in an autosomal recessive manner.

Periodic paralysis secondary to acquired sustained hyperkalemia. This type of periodic paralysis can occur in any individual when the serum potassium concentration exceeds 7 mmol/L. Weakness can be accompanied by glove-and-stocking paresthesias. Hyperkalemia can cause cardiac arrhythmia, usually tachycardia, and typical EKG abnormalities (i.e., T-wave elevation, disappearance of P waves). Rest after exercise provokes weakness as in hyperPP. The diagnosis is suggested by very high serum potassium concentration during the attack, persistent hyperkalemia between attacks, and the underlying disorder. Serum potassium concentrations are far higher than those in hyperPP. The usual cause is chronic use of medications such as spironolactone, ACE inhibitors, trimethoprim, nonsteroidal anti-inflammatory drugs, heparin, and nonselective beta blockers. Myopathies associated with paroxysmal myoglobinuria (e.g., glycogen storage disease type V [McArdle disease], carnitine palmitoyltransferase II deficiency) can damage the kidneys and thus also lead to potassium retention. Therapy of acquired sustained hyperkalemia involves restricting dietary potassium intake and treating the underlying cause of the hyperkalemia.

Management

No clinical practice guidelines for hyperkalemic periodic paralysis (hyperPP) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hyperkalemic periodic paralysis (hyperPP), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Hyperkalemic Periodic Paralysis (hyperPP)

System/Concern	Evaluation	Comment
Muscle issues	• Neuromuscular eval for myotonia, paramyotonia, & muscle weakness • Perform ^{1}H MRI (STIR) of proximal leg muscles to identify muscular water accumulation & fatty muscle degeneration [Weber et al 2006].	
Genetic counseling	By genetics professionals [1]	To inform patients & their families re nature, MOI, & implications of hyperPP in order to facilitate medical & personal decision making

MOI = mode of inheritance; STIR = short tau inversion recovery

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment for hyperPP is symptomatic and not curative.

Table 6. Treatment of Manifestations in Individuals with Hyperkalemic Periodic Paralysis (hyperPP)

Manifestation/Concern	Treatment	Considerations/Other
Attacks of flaccid muscle weakness	Continuing mild exercise &/or oral ingestion of carbohydrates (2 g glucose per kg body weight) at onset of weakness	May prevent or abort attacks
	IV glucocorticoids or inhalation of 2 puffs of 0.1 mg salbutamol	May abort or attenuate attacks
	Calcium gluconate (0.5-2 g taken intravenously) [1]	May terminate attacks in some persons
Myotonia-assoc issues w/ general anesthesia [2]	An induction sequence incorporating inhalation of oxygen, cricoid pressure, thiopental, & 2x the ED95 dose of an intermediate or short-action non-depolarizing muscle relaxant, followed by intubation, is a reasonable approach to securing the airway in persons w/hyperPP.	• Avoid opioids or depolarizing agents incl potassium, anticholinesterases, & succinylcholine, which can aggravate a myotonic reaction & induce masseter spasms & stiffness of respiratory muscles. • Alterations of serum osmolarity, pH, & hypothermia-induced muscle shivering & mechanical stimuli can exacerbate myotonic reaction.
	Inhalational induction may also be possible for hyperPP & is well tolerated in those undergoing elective surgery.	
Post anesthesia general & respiratory muscle weakness	To prevent this complication the following are recommended: [3] • Glucose infusion • Maintain normal body temperature. • Maintain serum potassium at low level.	
Myotonia	Mexiletine has been used to treat myotonia in this disorder [Modoni et al 2020].	

IV = intravenous

1. One case report suggested that intravenous magnesium is beneficial as well [Mankodi et al 2015].

2. Because the generalized muscle spasms associated with such attacks may lead to an increase in body temperature, individuals with hyperPP have been considered to be susceptible to malignant hyperthermia. Most likely, anesthesia-related complications suggestive of a malignant hyperthermia crisis result from severe myotonic reactions [Lehmann-Horn et al 2004, Klingler et al 2005].

3. Klingler et al [2005], Mackenzie et al [2006], Jurkat-Rott & Lehmann-Horn [2007], Barker [2010]

Prevention of Primary Manifestations

Diet/environment. Preventive measures for individuals with hyperPP consist of frequent meals rich in carbohydrates and **avoidance of the following**:

- Potassium-rich medications and foods (e.g., fruits, fruit juices)
- Fasting
- Strenuous work
- Exposure to cold

Early start to the day. As attacks occur more frequently on holidays and weekends when people rest in bed longer than usual, individuals are advised to rise early and have a full breakfast.

Lifestyle. Individuals should prioritize avoidance or minimization of triggers whenever possible by keeping stress levels low and avoiding exercise that is overly intense (as rest after such exercise is a trigger).

Diuretics. It is often advisable to prevent hyperkalemic attacks of weakness by the continuous use of a thiazide diuretic or a carbonic anhydrase inhibitor, such as acetazolamide or dichlorphenamide. (Note: In a trial of dichlorphenamide, the median attack rate was lower in participants with hyperPP on dichlorphenamide than in participants with hyperPP on placebo (0.9 vs 4.8), but the difference in median attack rate was not significant (p = 0.10) [Sansone et al 2016]). Diuretics are used in modest dosages at intervals from twice daily to twice weekly.

- Thiazide diuretics are preferable because they have fewer side effects than either acetazolamide or dichlorphenamide therapy.
- The dosage should be kept as low as possible (e.g., 25 mg hydrochlorothiazide daily or every other day). In severe cases, 50 mg or 75 mg of hydrochlorothiazide should be taken daily very early in the morning.
- Individuals should be monitored so that the serum potassium concentration does not fall below 3.3 mmol/L or the serum sodium concentration below 135 mmol/L [Lehmann-Horn et al 2004]. Thiazides may be helpful even if the serum potassium concentration is in the normal range [Akaba et al 2018].

Four weeks after start of diuretic treatment, effects should be evaluated by muscle strength measurement and MRI of proximal leg muscles.

Surveillance

Table 7. Recommended Surveillance for Individuals with Hyperkalemic Periodic Paralysis (hyperPP)

System/Concern	Evaluation	Frequency
Diuretic-induced hypokalemia [1]	Serum potassium concentration (target: between 3.0 & 3.5 mmol/L)	Every 6 mos
Muscle weakness	Neurologic exam w/focus on muscle strength in the legs in order to detect permanent weakness	Annually
	MRI of the leg muscles [1]	Every 1-3 yrs
Thyroid dysfunction	Thyroid function testing	Annually

1. If on continuous prophylactic diuretic treatment
2. To judge how much normal muscle tissue is preserved and whether edema is present. Na^+ MRI is ideal, but only investigational at this time.

Agents/Circumstances to Avoid

Avoid the following:

- Opioids or depolarizing agents such as potassium, anticholinesterases, and succinylcholine as part of general anesthesia. These can aggravate a myotonic reaction and induce masseter spasms and stiffness of respiratory muscles, which may impair intubation; mechanical ventilation may also be impaired.
- Drugs known as ACE-inhibitors for the treatment of arterial hypertension. These may lead to hyperkalemia as a side effect, especially if they are combined with potassium-sparing diuretics (e.g., spironolactone) and/or renal function is impaired.
- Alterations of serum osmolarity, pH, and hypothermia-induced muscle shivering and mechanical stimuli during general anesthesia. These can exacerbate the myotonic reaction in individuals with hyperPP.

See also Prevention of Primary Manifestations.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from initiation of preventive measures, particularly those that would decrease the risk of unexpected acute paralysis or anesthetic events. Evaluations include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Full neurologic examination to rule out muscular weakness and EMG to rule out myotonia if the pathogenic variant in the family is not known.

At-risk relatives who have not undergone molecular genetic testing or clinical evaluation (i.e., neurologic examination and EMG) must be considered at risk for hyperPP-related complications and precautions are indicated – particularly during anesthesia.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

More than 90% of affected women report an increase in attack frequency during pregnancy. While approximately 80% reported improved muscle weakness during attacks, 75% also reported worse muscle stiffness during attacks [Charles et al 2013, Yong et al 2018]. In contrast, however, are case reports describing improvement during pregnancy [Finsterer et al 2017, Huang et al 2019].

Women who are chronically treated with a diuretic may continue treatment in pregnancy. Human data on prenatal exposure to acetazolamide have not demonstrated an increased risk of fetal malformations. Human data on the use of oral dichlorphenamide therapy during pregnancy – and whether it leads to an increased risk of malformations in exposed fetuses – are limited.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hyperkalemic periodic paralysis (hyperPP) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with hyperPP have an affected parent.
- A proband with hyperPP may have the disorder as the result of a *de novo SCN4A* pathogenic variant. The proportion of individuals with hyperPP caused by a *de novo* pathogenic variant is unknown.
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:

- The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
- The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

- The family history of some individuals diagnosed with hyperPP may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- Substantial intrafamilial clinical variability may be observed among sibs who inherit the same *SCN4A* pathogenic variant: a heterozygous sib may have manifestations of hyperPP identical to those of the proband, subclinical findings only, or very few and minor symptoms during adolescence that may not be recognized as abnormal. (Note: Significant intrafamilial variability can make it difficult to establish a dominant mode of inheritance based on the clinical features of family members.)
- If the proband has a known *SCN4A* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with hyperPP has a 50% chance of inheriting the *SCN4A* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents; if a parent is affected and/or is known to have the *SCN4A* pathogenic variant identified in the proband, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives in order to identify family members who would benefit from initiation of preventive measures (particularly those that would decrease the risk of unexpected acute paralysis or anesthetic events).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *SCN4A* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for hyperPP are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Hyperkalemic periodic paralysis
- **Periodic Paralysis Association (PPA)**
  www.periodicparalysis.org
- **Periodic Paralysis International**
  Canada
  www.hkpp.org
- **Malignant Hyperthermia Association of the United States (MHAUS)**
  11 East State Street
  PO Box 1069
  Sherburne NY 13460
  Phone: 800-644-9737 (Toll-free Emergency Hotline); 607-674-7901; 315-464-7079
  Fax: 607-674-7910
  Email: info@mhaus.org
  www.mhaus.org
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  Email: ResourceCenter@mdausa.org
  mda.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hyperkalemic Periodic Paralysis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

SCN4A	17q23.3	Sodium channel protein type 4 subunit alpha	Sodium channel, voltage-gated, type IV, alpha subunit (SCN4A) @ LOVD	SCN4A	SCN4A

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hyperkalemic Periodic Paralysis (View All in OMIM)

170500	HYPERKALEMIC PERIODIC PARALYSIS; HYPP
603967	SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 4; SCN4A

Molecular Pathogenesis

SCN4A encodes the muscular voltage gated sodium channel $Na_V1.4$. Missense variants that cause gain-of-function defects for $Na_V1.4$ lead to hyperPP symptoms.

All forms of periodic paralysis, regardless of pathogenic variant, share a common final mechanism, a long-lasting partial depolarization of the sarcolemma leading to inactivation of $Na_V1.4$ channels, thereby inhibiting action potentials and rendering the muscle fibers inexcitable. This phenomenon of partial depolarization – which was initially only shown in physiologic studies of biopsies of intact muscle fibers [Lehmann-Horn et al 1987] and in cellular physiologic experiments – has recently been shown in vivo via muscle velocity recovery cycles [Tan et al 2020].

Normal $Na_V1.4$ channels have only a very small persistent current, about 0.2% of the transient peak elicited by a step depolarization. Pathogenic variants associated with hyperPP lead to incomplete fast inactivation, which results in persistent Na^+ currents of 1% to 4% of the transient peak. Although the absolute amplitude of the anomalous persistent current is small, the relative increase of five- to 20-fold has a large effect on the membrane voltage. Normally, the resting membrane potential is -85 mV, and all channels are closed. In response to a stimulus, the inactivation defect is revealed and the fiber may respond with a myotonic burst. The repetitive firing produces a cumulative increase of T-tubular K^+ within the muscle fiber, which together with the inactivation defect results in a steady inward Na^+ current that keeps the fiber depolarized at about -45 mV. From this depolarized potential the normal $Na_V1.4$ channels and most of the abnormal ones are inactivated, rendering the fiber inexcitable, as occurs in periodic paralysis. The requirement for elevated extracellular K^+, either interstitial or T-tubular, to mildly depolarize the fiber and reveal the inactivation defect explains why attacks may be triggered or aggravated by potassium ingestion in hyperPP [Cannon 2018].

Data from mouse models suggest that the lag in onset of clinical features of hyperPP during the first decade and the progression of symptoms during adolescence are a function of $Na_V1.4$ channel content [Khogali et al 2015]. The clinical phenotype can also be affected by polymorphisms, as described for the $Na_V1.4$. pathogenic variant p.Ile692Met, where a concomitant p.Ser906Thr polymorphism results in longer weakness episodes, more affected muscles, CK elevation, and presence of permanent weakness [Fan et al 2017].

Mechanism of disease causation. The pathogenic variants associated with hyperPP all produce gain-of-function changes for Nav1.4. Most often, this gain of function is produced by defects of channel inactivation [Cannon 2018].

Notable *SCN4A* variants. See Table 3 (pdf) for an author-curated list of associated *SCN4A* pathogenic variants.

Chapter Notes

Author Notes

Frank Weber is a clinical neurologist and, as a military physician, is a certified flight surgeon. After many years in hospital-based neurology, he is currently head of the department of research of the German Air Force Center of Aerospace Medicine. He was trained in clinical neurology at the University of Ulm and at the Technical University in Munich, where he met Frank Lehmann-Horn. He has a special interest in neuromuscular disorders and in clinical neurophysiology. His scientific interests include disorders of nerve and muscle and channelopathies of the peripheral nervous system and the muscle system, particularly sodium channels.

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Voltage-Gated Ion Channels and Hereditary Disease

Acknowledgments

Thanks to the many patients who gave their consent to the publication of their data and to the Periodic Paralysis Association. This work was supported by the German Research Foundation (DFG) (JU470/1), the network on Excitation-contraction coupling and calcium signaling in health and disease of the IHP Program funded by the European Community, the non-profit Hertie Foundation, the IonNeurONet of German Ministry of Research (BMBF), The German Muscle Society (DGM), and the Else-Kröner-Fresenius Foundation.

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Revision History

- 1 July 2021 (ha) Comprehensive update posted live
- 28 January 2016 (me) Comprehensive update posted live
- 31 May 2011 (me) Comprehensive update posted live
- 11 August 2009 (cd) Revision: sequence analysis available clinically
- 25 April 2008 (me) Comprehensive update posted live
- 23 September 2005 (me) Comprehensive update posted live
- 2 March 2005 (cd) Revision: sequencing of select exons clinically available
- 18 July 2003 (me) Review posted live
- 27 January 2003 (kjr) Original submission

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