In the name of God

Hypokalemic Periodic Paralysis

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Case presentation

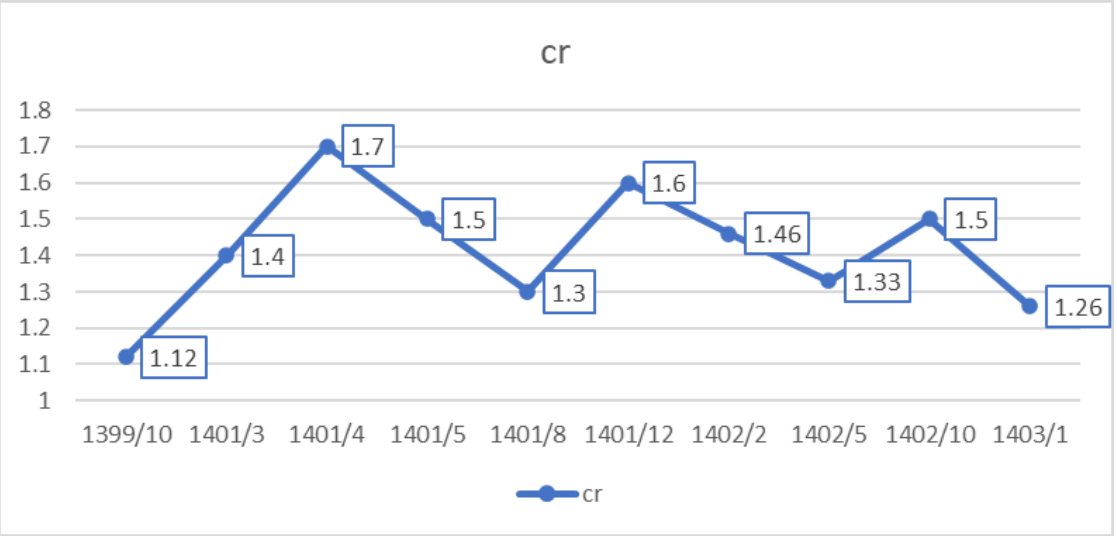
- A 50 years old woman came to the clinic with fatigue, dizziness & muscle weakness accompanied with pain of both lower & upper extremities & cold intolerance from 3 years ago. The patient has had **hypokalemia** in lab data since that time.

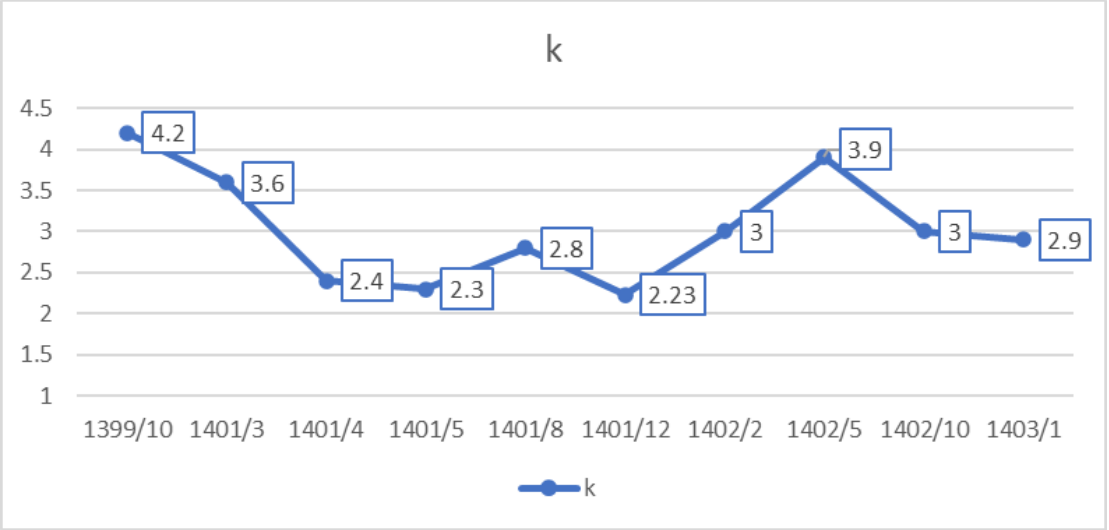
- **Past history**: Chronic kidney disease (stage3a)
- Depression from 3 years ago
- Hysterectomy 1402/10

- **Ph.E**: BP: 105/65 HR: 72 RR:22 T: 36.8
- neurologic examination was normal

- **Drug history:**
- spironolactone 100 mg daily
- Kcl 600mg q8hr
- Sertraline 100mg daily
- Buspirone 5 mg daily
- Atorvastatin 20 mg daily
- Omeprazole 20 mg daily

Laboratory data





Na: 137
Ca: 8.9
Ph: 3.5
Alb: 4.5
Mg: 2.5

24 hr urine:
volume: 2750
Cr : 1252
K: 43
Na : 326
Ca: 119
Pr: 105

24 hr Mg urine: 50
Serum Mg: 2.5

U/A: SG:1008
Pr: neg
RBC: 0-1
WBC: 0-1

Renin: 206
Aldosterone: 66.5
TSH: 2.56

pH: 7.40
pCO2: 44
HCO3: 27

Objectives

- **Identify** the key clinical features & diagnostic criteria of HPP to facilitate accurate diagnosis.
- **Screen** patients presenting with episodes of muscle weakness for hypokalemia & perform necessary diagnostic tests for HPP.
- Select & prescribe pharmacological **therapies** for HPP based on patient needs for acute attacks & long-term prophylaxis.
- Collaborate with interprofessional healthcare teams to optimize patient **outcomes**, minimize disease-related complications, & provide comprehensive care for patients with HPP.

History

- **Dr. Mary Broadfoot Walker** (1888 – 1974) was a Scottish physician who first demonstrated the effectiveness of **physostigmine** in the treatment of Myasthenia gravis.
- She was also the **first** to recognize the association between familial periodic paralysis & low blood K levels.

StatPearls [Internet].
Show details
Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

Hypokalemic Periodic Paralysis

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Author Information and Affiliations

Last Update: March 19, 2024.

Continuing Education Activity

Go to:

Hypokalemic periodic paralysis (hypoPP) is a rare channelopathy caused by skeletal muscle ion channel mutations, mainly affecting calcium or sodium channels. Patients with hypoPP experience a sudden onset of generalized or focal flaccid paralysis associated with low blood potassium levels (or hypokalemia), which can last for several hours before

Introduction

- HPP is a **rare** disorder caused by skeletal muscle ion channel mutations, mainly affecting **Ca** or **Na** channels.
- HPP is characterized by **episodic** severe muscle weakness, usually triggered by strenuous exercise or a high-carbohydrate diet.
- Patients experience a sudden onset of generalized or focal flaccid paralysis associated with hypo K, which can last for several hours before resolving spontaneously.

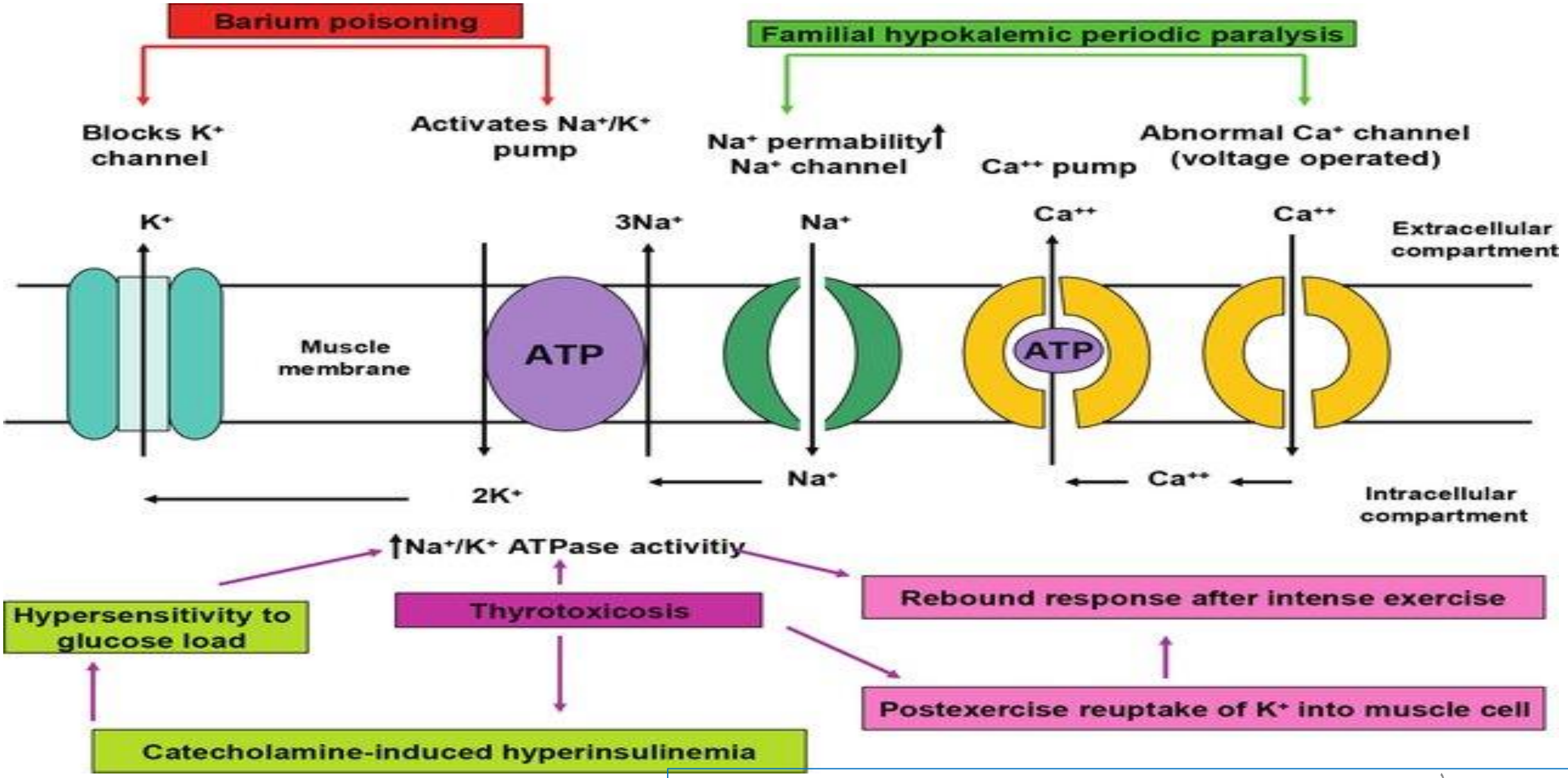
Etiology

- Hereditary or familial & acquired
- **Familial** HPP is caused by mutations in either of the 2 genes:
  - The most common familial form, **type 1** hypoPP, mutation in the dihydropyridine-sensitive skeletal muscle Ca channel gene, *CACNA1S*.
  - The **type 2** familial form: mutations in the voltage-sensitive skeletal muscle Na channel gene, *SCN4A*.
  - Disease-causing mutations in the genes *KCNJ2* & *KCNJ18*, which code for the inward rectifier potassium (Kir) channel, have also been identified as contributors to HPP.
- **Acquired** HPP has been associated with thyrotoxicosis, whereas the familial form & thyrotoxic hypoPP constitute the **primary** hypoPP.
- Periodic muscle weakness can also result from hypoK due to K loss **secondary** to renal & GI issues such as RTA, GE, or endocrine-related causes.

Etiology

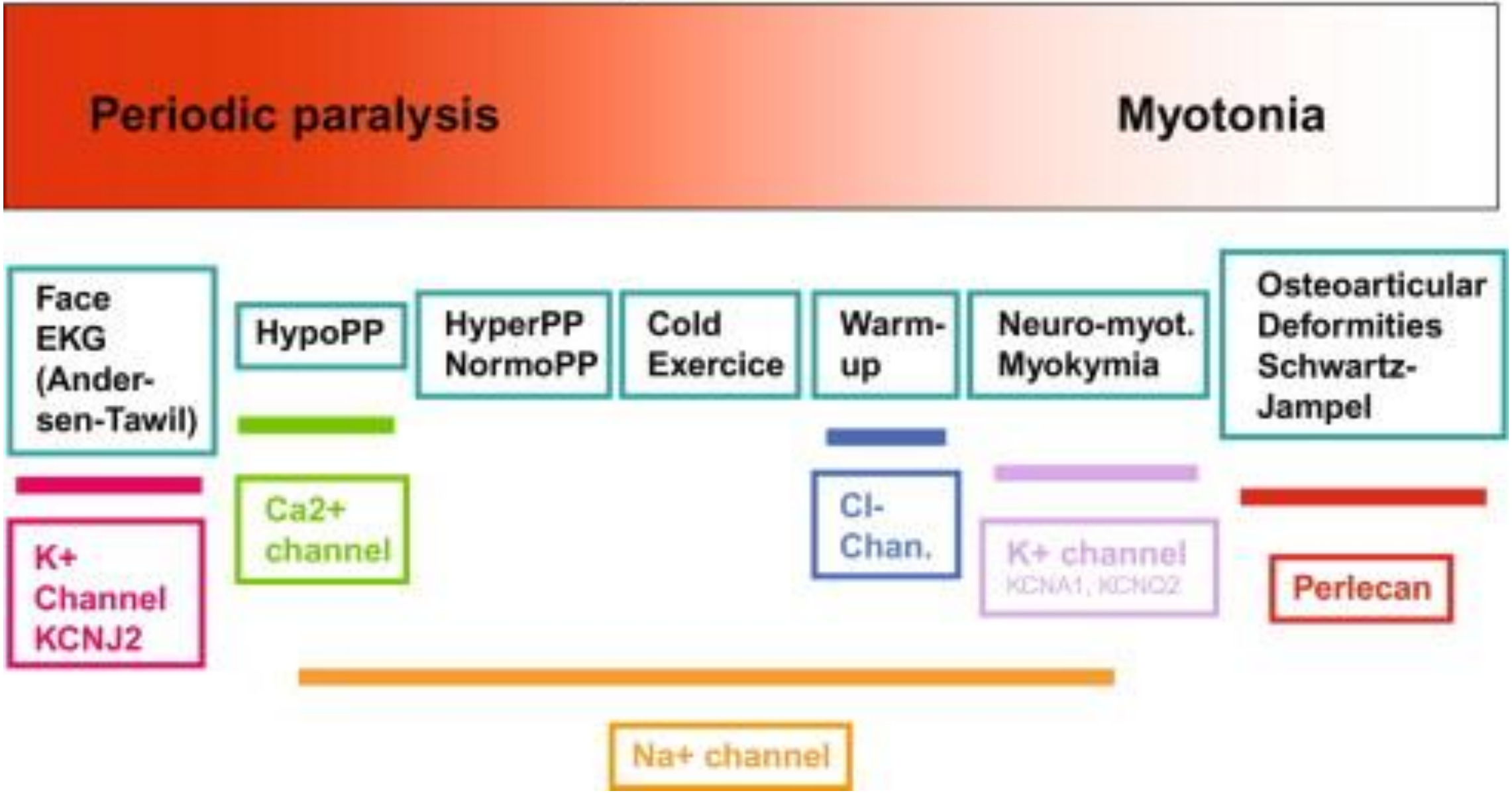
- Primary:
  - Familial or Hereditary
    - Type 1: Mutation in the dihydropyridine-sensitive skeletal muscle Ca channel gene, *CACNA1S*.
    - Type 2: Mutation in the voltage-sensitive skeletal muscle Na channel gene, *SCN4A*.
  - Acquired:
    - Thyrotoxicosis
- Secondary
  - Renal loss
  - GI loss

Pathogenesis of hypok Paralysis in transcellular distribution of K without depletion



Cesur M. Thyrotoxic Hypokalemic Periodic Paralysis. IntechOpen. 2022

Muscle channelopathies and related disorders



Bertrand Fontaine, Handbook of clinical Neurology, 2013

Epidemiology

- HPP is a **rare** disorder with an estimated prevalence of **1 in 100,000**.
- Most familial cases exhibit an **AD** inheritance pattern with incomplete penetrance, particularly noticeable in women.
- The genetic disorder may also be acquired in patients with thyrotoxicosis or familial with AD inheritance.
- This disorder typically manifests with lower clinical expression in women due to lower penetrance & attack rates compared to men.
- Many cases are sporadic, representing new mutations.
- Most cases of thyrotoxic hypoPP are **sporadic** & more prevalent among individuals of Asian descent, with a male predominance of **9 to 1**.

Pathophysiology

- When serum K level drops **< 3.0 mEq/L**, the affected fibers paradoxically undergo sustained depolarization, making muscle electrically inexcitable, whereas normal fibers undergo hyperpolarization at this drop in serum K.
- Normally, the inward rectifying K (Kir) channel & membrane Na-K-ATPase maintain the normal negative resting membrane potential.
- In the presence of *CACNA1S* & *SCN4A* mutations, the depolarization induced by the gating pore currents, at the modest drop in serum K levels to around 3.0 mEq/L, counterbalances the Kir current, resulting in sustained depolarization.

History & Physical

- Although the genetic abnormality remains throughout the life span of an affected individual, the mean age of presentation of attacks is the **first or second decade** of life, commonly during late childhood or teenage years.
- The frequency of these attacks tends to decrease as individuals age.
- However, in cases of thyrotoxic hypoPP, onset usually occurs after the age of 20.
- HPP is characterized by sporadic attacks rather than regular occurrences, with episodes occurring suddenly & episodically.

History & Physical: Triggers

- The **most consistent** triggers are rest following strenuous exercise & consumption of carbohydrate-rich diets.
- Other triggers:
  - Excitement, stress, fear, cold temperatures, high salt intake, glucocorticoid use, alcohol consumption, or undergoing anesthesia procedures.
- Patients typically experience sudden & severe attacks of generalized muscle weakness, with more pronounced involvement of proximal muscles than distal muscles & a significant decrease in serum K levels **(< 2.5 mmol/L**).

History & Physical

- Many patients also report experiencing prodromal symptoms such as fatigue, paresthesia, & behavioral changes a day before a muscle weakness attack.
- However, when attacks are incomplete, they typically affect the lower limbs more than the upper limbs.
- Bulbar, ocular, & respiratory muscles are usually unaffected, although respiratory muscle involvement can be life-threatening in severe cases.
- The **frequency of attacks varies** widely, with some patients experiencing attacks only once in their lifetime, while others may have them several times a week.

History & Physical

- Women tend to have fewer attacks than men. The duration of each attack varies as well, ranging from **minutes to days**, with some attacks lasting several hours before resolving spontaneously.
- During a muscle weakness attack, neurological examination typically reveals generalized muscle weakness, with proximal muscles more affected than distal ones.
- In incomplete attacks, the legs are often more involved than the arms.
- Hyporeflexia or areflexia is a common finding.
- **Myotonia is uncommon** in HPP, unlike hyperk PP, where myotonia is a common feature.

History & Physical

- People with HPP are often misdiagnosed as having a **conversion disorder or hysterical paralysis** since the weakness is muscle-based & doesn't correspond to nerve or spinal root distributions.
- The tendency of people with HPP to get paralyzed when epinephrine is released in "**fight or flight**" situations further adds to the temptation to misdiagnose the disorder as psychiatric.

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Correlating phenotype and genotype in the periodic paralyses

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Abstract—*Background:* Periodic paralyses and paramyotonia congenita are rare disorders causing disabling weakness and myotonia. Mutations in sodium, calcium, and potassium channels have been recognized as causing disease. *Objective*: To analyze the clinical phenotype of patients with and without discernible genotype and to identify other mutations in ion channel genes associated with disease. *Methods*: The authors have reviewed clinical data in patients with a diagnosis of hypokalemic periodic paralysis (56 kindreds, 71 patients), hyperkalemic periodic paralysis (47 kindreds, 99 patients), and paramyotonia congenita (24 kindreds, 56 patients). For those patients without one of the classically known mutations, the authors analyzed the entire coding region of the *SCN4A*, *KCNE3*, and *KCNJ2* genes and portions of the coding region of the *CACNA1S* gene in order to identify new mutations. *Results*: Mutations were identified in approximately two thirds of kindreds with periodic paralysis or paramyotonia congenita. The authors found differences between the disorders and

Miller TM. Neurology. 2004

Correlating phenotype & genotype in the PP

- The authors have reviewed clinical data in patients with a diagnosis of hypok PP (71 patients), hyperk PP (99 patients), & paramyotonia congenita (56 patients).
- Mutations were identified in approximately **two thirds** of kindreds with PP.
- Patients without mutations had a less typical clinical presentation including an **older age** at onset, no changes in diet as a precipitant, & absence of vacuolar myopathy on muscle biopsy.

Miller TM. Neurology. 2004

Table 2 *Clinical data for hypokalemic periodic paralysis (HypoKPP)*

	HypoKPP with mutations				
	Na^+ channel (*SCN4A*)	Calcium channel (*CACNA1S*)			HypoKPP without mutations
Summary findings	All mutations	R1239H	R528H	All calcium channel	
	(n = 7)	(n = 24)	(n = 17)	(n = 42)	(n = 22)
Age at onset, y					
Average ± SD	16 ± 5	7 ± 4	14 ± 5	10 ± 6	22 ± 12
Range	13–27	2–14	8–30	2–26	5–61
	(n = 7)	(n = 21)	(n = 16)	(n = 38)	(n = 18)
Frequency of attacks/mo					
Average ± SD	7 ± 6	10 ± 10	8 ± 10	9 ± 9	1 ± 1
Range	4–14	3.5–30	0.3–10	0.5–30	0.3–2
	(n = 3)	(n = 7)	(n = 7)	(n = 14)	(n = 5)
Duration, h					
Average ± SD	1 ± 0.6	19 ± 12	20 ± 27	20 ± 21	29 ± 23
Range	1–2	2–72	2–72	2–72	1–60
	(n = 3)	(n = 11)	(n = 9)	(n = 21)	(n = 13)
Usual precipitants, %					
Exercise	75	93	50	76	52
Sweets/high carbs	50	43	80	60	18

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Weakness, %					
None	100	40	14	28	80
Mild	0	50	29	39	7
Severe	0	10	57	33	13
	(n = 2)	(n = 10)	(n = 7)	(n = 18)	(n = 15)
Clinical myotonia, %	0	0	0	0	15
	(n = 4)	(n = 11)	(n = 8)	(n = 20)	(n = 13)
EMG/NCS, %					
Normal	100	100	33	56	71
Myopathic	0		67	44	19
	(n = 4)	(n = 2)	(n = 6)	(n = 9)	(n = 7)
Muscle biopsy, %					
Vacuolar myopathy	50	100	71	80	0
Tubular aggregates	50	0	0	7	0
Myopathic changes	0	0	29	13	40
Normal	0	0	0	0	60
	(n = 2)	(n = 7)	(n = 7)	(n = 15)	(n = 5)
Potassium, mEq/L					
Average ± SD	2.2 ± 0.8	1.9 ± 0.4	2.9 ± 0.7	2.4 ± 0.7	2.3 ± 0.5
Range	1.2–3.1	1.6–2.6	1.8–4.2	1.6–4.2	1.4–3.3
	(n = 5)	(n = 8)	(n = 12)	(n = 21)	(n = 15)
Attacks helped by potassium, %	100	100	100	100	100
	(n = 1)	(n = 15)	(n = 9)	(n = 25)	(n = 12)

Miller TM. Neurology. 2004

Evaluation

- TSH, T3, & T4 levels
- ECG
- A low serum K between attacks often indicates a **secondary** cause of hypoK, such as distal RTA.
- Additional diagnostic options include:
  - **Genetic testing**
  - **Provocative testing**
  - **EMG**
  - **Muscle Biopsy**

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Mini Review

IF: 2.1

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Periodic paralysis: what clinician needs to know?

Abstract

Acute flaccid paralysis is a diagnostic challenge in the emergency department. Periodic paralysis syndromes are characterized by recurrent episodes of flaccid hyporeflexic paralysis in association with potassium abnormalities. Periodic paralysis with hypokalaemia may be genetic, secondary to systemic hypokalaemia or associated with thyrotoxicosis. Genetic syndrome result from mutations in sodium (SCN4A) or calcium (CACNA1S) channels, inherited in autosomal dominant pattern. Diagnosis is established by demonstrating recurrent nature, family history and abnormal serum potassium during an episode. Thyrotoxic periodic paralysis is often sporadic but possibly has a genetic predisposition. Presence of thyrotoxicosis and hypokalaemia during an episode confirms the diagnosis. Management of acute episode is by cautiously correction of potassium abnormality. Long term therapy depends on the cause. Pathogenic mechanisms, differential diagnosis and treatment principles are discussed.

Keywords: periodic paralysis, hypokalaemia, hyperkalaemia, channelopathies, acute flaccid paralysis

Volume 6 Issue 4 - 2018

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Received: June 30, 2018 | **Published:** July 18, 2018

Evaluation: Provocative tests

- Induce precipitating factors in controlled environment.
- This can be achieved by administration of a **glucose load** (increasing endogenous insulin), **insulin**, **ACTH** (permissive effect on beta adrenoceptors) or by **exercise.**
- Evidence for these methods is limited to observations from case series, but they may be useful when diagnosis is in doubt.
- Exercise provocation test is probably the **safest** out of provocation methods.
- However, no studies have compared sensitivity, specificity & relative safety of any of the diagnostic methods.

Dissanayake HA. Endocrinol Metab Int J. 2018

Evaluation: EMG

- During episodes of muscle weakness, EMG may reveal a reduced amplitude of compound muscle action potential (**CMAP**) & electrical silence, the extent of which depends on the severity of muscle weakness observed during the attack.
- Between attacks, EMG techniques such as the "exercise test" can be employed to assess the change in muscle fiber excitability due to channelopathy.
- During the long exercise test, a focal muscle weakness attack is induced by vigorous exercise of a single muscle for 2 to 5 minutes, & EMG measurements track the post-exercise CMAP in muscle fibers.
- A **reduction of ≥ 40%** in CMAP is considered abnormal & typical for PP.
- This change was present in **> 70%** of patients.

Evaluation: Muscle Biopsy

- Interattack muscle biopsy is usually not performed to confirm the diagnosis.
- Biopsy findings may include **vacuolar changes** or **tubular aggregates**, but these are nonspecific & not diagnostic of PP.
- Tubular aggregates are more commonly associated with Andersen syndrome & the sodium channel mutation variant of hypoPP.

Treatment / Management: Acute Treatment

- Incremental doses of oral KCL, starting at **0.5 to 1 mEq/kg** .
- If there is no response, a repeat dose of 30% (0.3 mEq/kg) can be administered every 30 minutes. Some clinicians suggest administration at a slower rate (10 mEq/h) to minimize rebound hyperK.
- If a patient requires > 100 mEq, close monitoring of serum K levels is essential, & the total oral K dose should **not** exceed 200 mEq within 24 hs of initiating treatment.
- Patients should be monitored with **ECG, & muscle strength** should be assessed regularly.
- Serum K levels should be monitored for **24 hours** after treatment, as the post-treatment rise in serum K levels can have adverse effects on patients.

Treatment / Management: Acute Treatment

- IV potassium is not typically the first choice of treatment & is reserved for specific situations such as:
  - Arrhythmias due to hypoK
  - Swallowing difficulties
  - Respiratory muscle paralysis.
- When IV potassium is necessary, it is preferably administered with **mannitol** rather than dextrose or saline.
- A common protocol involves infusing 40 mEq/L of IV potassium in a 5% mannitol solution at a rate not exceeding 20 mEq/h, with a total dosage not exceeding 200 mEq in 24 hours.

Preventive Treatment : Nonpharmacologic

- Educating patients about **trigger factors**
- Implementing lifestyle modifications to avoid these triggers

Preventive Treatment : Pharmacologic

- Chronic K supplementation
- Carbonic anhydrase inhibitors
- K-sparing diuretics

- The preferred approach involves combining one diuretic with chronic K supplementation, with the initial choice of diuretic being the CAI acetazolamide.

Preventive Treatment : Pharmacologic

- Chronic K supplementation
- Carbonic anhydrase inhibitors:
  - Acetazolamide 250 mg twice daily
  - Dichlorphenamide 50 mg twice daily
- K-sparing diuretics: (either in combination with CAIs or as monotherapy)
  - Spironolactone 25=100 mg daily
  - Triamterene 150 mg daily
- The preferred approach involves combining one diuretic with chronic K supplementation, with the initial choice of diuretic being the CAI acetazolamide.

Complications

- **Rhabdomyolysis**
- **Cardiac arrhythmia**
  - ECG changes including U waves, AF, SVT, ventricular ectopics, ventricular tachyarrhythmias & rarely bradycardia. Tachyarrhythmias are more in TPP.
- **Progressive myopathy**
  - Slowly progressive degenerative myopathy is known to affect patients with PP.
  - This is more common with hypoKPP than with hyperKPP, & clinically manifests in the **fifth** decade of life.
  - Lower limb muscles are predominantly affected. With the onset of myopathy, episodes of paralytic attacks become infrequent.
  - Histological characteristics are vacuoles in the center of myofibres & absence of inflammatory cell infiltrates.
  - Degenerating muscles will be replaced by fatty tissue which is detectable in MRI scan. Electron microcopy will demonstrate dilatation and proliferation of T tubules.

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Perioperatively, prevention

- Avoiding neuromuscular blockade, avoid excessive hyperventilation, warm the patient, provide adequate hydration, avoid glucose infusions, do not give diuretics, & closely monitor the ECG for signs of hypoK.
- Normal saline is the preferred IV solution for patients with familial HPP.
- Glucose containing solutions may cause weakness.
- Additionally, the high chloride content can cause a mild acidosis which would be preferred over alkalosis.

Prognosis

- The prognosis of hypoPP varies significantly from one individual to another.
- Generally, attacks of muscle weakness show a **positive response** to oral K administration.
- However, recurrent episodes of muscle weakness can lead to substantial morbidity & increased hospitalizations & consequently impact the patient's social & professional activities.
- Although **deaths** directly related to muscle attacks are rare, several mortality cases have been reported due to complications such as aspiration pneumonia.

Patient Education

- Avoid **triggering factors** through lifestyle & behavioral modifications.
- **Lifestyle changes** such as avoiding strenuous exercise, consuming frequent small meals to prevent carbohydrate overload, reducing salt intake, avoiding stressful events, & maintaining regular movement to prevent prolonged immobilization can be beneficial in preventing attacks.
- Attacks often occur in the **morning** upon waking or at midnight, so creating a safe bedside environment is crucial to prevent falls & mitigate their consequences.

Patient Education

- Importantly, the room floor should not be slippery, & the bed should be positioned away from coolers or windows to avoid hypothermia during episodes of paralysis when patients may be unable to move.
- Patients should have a plan to **alert someone** or call 911 if necessary during such episodes.
- Keeping **K tablets** accessible in multiple locations, such as bedside, office, pockets, or car, is recommended for quick access during attacks.

	hypoKPP
Gene mutation	*SCNA4, CACNA1S*
Inheritance	Autosomal dominant
Age of onset	Before 20-25 years
Precipitating events	High carbohydrate meal Rest after strenuous exercise Alcohol High salt diet Menstruation Stress Cold temperature Steroids
Duration of paralysis	Less than 24-48 hours
EMG	Myopathy during attack, normal in between
Acute treatment	KCl
Long term treatment	Acetazolamide Spironolactone

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	hypoKPP	Thyrotoxic PP	hyperKPP
Gene mutation	*SCNA4, CACNA1S*	Uncertain. ? *KCNJ*	*SCNA4*
Inheritance	Autosomal dominant	Acquired	Autosomal dominant
Age of onset	Before 20-25 years	20 – 40 years	Before 15 years
Precipitating events	High carbohydrate meal Rest after strenuous exercise Alcohol High salt diet Menstruation Stress Cold temperature Steroids	Same as hypoKPP	Fasting Exercise
Duration of paralysis	Less than 24-48 hours	Less than 24-48 hours	Few hours
EMG	Myopathy during attack, normal in between	Myopathy during attack, normal in between	Myopathy during attack, myotonia in between attacks
Acute treatment	KCl	KCl, propranolol	Observe, potassium lowering therapy
Long term treatment	Acetazolamide Spironolactone	Treat thyrotoxicosis	Thiazide, acetazolamide

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با تشکر از توجه شما