Abstract
The inherited muscle ion channel diseases (muscle channelopathies) are rare disorders of the skeletal muscle cell membrane whose manifestations range from muscle stiffness to flaccid weakness. Primary periodic paralyses are autosomal dominant disorders characterized primarily by attacks of weakness, while non-dystrophic myotonias are primarily characterized by muscle stiffness. Triggers to attacks or worsening of symptoms are frequently identifiable. Treatment consists of a combination of avoidance of triggers and medications.

Introduction
The inherited muscle ion channel diseases (muscle channelopathies) are rare disorders of the skeletal muscle cell membrane whose manifestations range from muscle stiffness (sarcolemmal hyperexcitability) to flaccid weakness (sarcolemmal inexcitability). Primary periodic paralyses are autosomal dominant disorders whose major feature is attacks of weakness, although some patients additionally experience muscle stiffness. Non-dystrophic myotonias (which are distinct from the myotonic dystrophies) may be recessive or dominant and are characterized by muscle stiffness, although some patients also experience attacks of weakness. Triggers to attacks or worsening of symptoms are frequently identifiable and include alterations in serum potassium, cooling, rest after strenuous exercise, carbohydrate loading or emotional stress.

Presentations and diagnostic tests
Myotonia and Paramyotonia
Myotonia is the phenomenon of delayed muscle relaxation after contraction. It is experienced by patients as stiffness, cramp or locking of muscles. Stiffness may be mildly worse in the cold or after periods of rest but diminishes with repeated muscle contractions (the warm-up phenomenon). The clinical findings are an inability to immediately relax muscles after forceful contraction and contraction induced by direct percussion (percussion myotonia). Lid-lag may be seen on rapid down-gaze. These findings become less marked with repetition (the warm up phenomenon) but reappear after rest. In paramyotonia muscle stiffness is precipitated by exercise. This is the opposite of the warm-up phenomenon in myotonia (hence paradoxical myotonia or paramyotonia). Paramyotonia is much more temperature-sensitive than classical myotonia. Exposure to cold not only produces muscle stiffness in paramyotonia, but may also trigger muscle weakness.
Weakness
The hallmark of the periodic paralyses is episodic weakness, which may affect all the limbs, one side or be very focal. Bulbar and respiratory muscles are rarely affected. Attacks of weakness most commonly occur in the morning after waking from sleep. Triggers include stress, cold, fasting (Hyperkalemic periodic paralysis or HyperPP), carbohydrate-rich meal (Hypokalemic periodic paralysis or HypoPP), and exercise followed by rest. Tendon reflexes are depressed during an attack of periodic paralysis. Some patients with periodic paralysis develop a fixed myopathy, which can be disabling. Mild fixed weakness may develop in patients with myotonia congenita and paramyotonia congenita.

Muscle hypertrophy
Muscle hypertrophy is characteristic of the non-dystrophic myotonias and is a direct result of muscle overactivity. This is different from the pseudohypertrophy seen in some of the dystrophinopathies: the ‘true’ hypertrophy of myotonic disorders results in increased muscle strength. Some individuals are able to participate in sports requiring strength rather than speed or endurance (eg Thomsen-type myotonia).

Clinical-genetic correlation
Skeletal muscle channelopathies produce a spectrum of clinical phenomena from pure muscle stiffness (myotonia) to pure muscle weakness (periodic paralysis) with overlap syndromes in between. Chloride channel mutations cause Myotonia Congenita, characterized by classical myotonia, warm up phenomenon and never any periodic paralysis. At the other end of the spectrum calcium channel and potassium channel mutations both produce pure periodic paralysis without myotonia. Sodium channel disease sits in the central overlapping part of the spectrum and causes 4 syndromes - pure myotonia, paramyotonia, hyperPP, and hypoPP.

Genetic testing
The gold standard for the diagnosis of a skeletal muscle channelopathy is identification of the causative mutation from a blood sample. Sequencing ion channel genes is labor-intensive and the clinician should suggest which gene to test first based on the clinical manifestations. The genetic laboratory will usually sequence regions of that gene where mutations are commonly found. If a mutation has been identified in another member of the patient’s family, clearly indicating this to the genetics laboratory will enable a more focused search.

Caution
A negative genetics test does not necessarily rule out a channelopathy because mutations may occur in regions of channel genes that have not been tested.

Electrodiagnosis
The roles of electrodiagnostic medicine are i) to indicate the presence of myotonia that is not detectable clinically, ii) to indicate the presence of myopathy (eg. where myotonic dystrophy is a possibility, or in
Science Revisited

Ion channels:
An ion channel is a transmembrane protein that controls the flow of a particular type of ion across a plasma membrane. The channels considered in this chapter are in surface and t-tubule membranes of skeletal muscle cells. An ion channel is formed by the association of several proteins. Each protein is identified by a protein name and a gene name. For example the SCN4A gene encodes the NaV1.4 subunit of the voltage-gated skeletal muscle sodium channel. Four Nav1.4 proteins associate to form a sodium channel. A single gene can cause different syndromes depending on the mutation (e.g. paramyotonia congenita and periodic paralysis are caused by different mutations of SCN4A). Conversely a syndrome can be caused by mutation of different genes (e.g myotonia can be caused by CLCN1 or SCN4A mutations. The channels discussed in this chapter are as follows:

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<th>Ion</th>
<th>Gene</th>
<th>Protein</th>
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<td>Sodium</td>
<td>SCN4A</td>
<td>NaV 1.4</td>
<td>Sodium channel myotonia, Potassium aggravated myotonia, Paramyotonia congenita, Hyperkalemic periodic paralysis, Hypokalemic periodic paralysis (type 2)</td>
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<tr>
<td>Calcium</td>
<td>CACNA1S</td>
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variant (Thomsen's disease). Muscle stiffness may be slightly worse in the cold, although never to the extent seen in paramyotonia, and improves with exercise. Onset is usually in the second decade and the condition progresses slowly over years. The legs are affected first, giving rise to a disproportionate figure and improved with exercise. Onset is usually in the second decade. Myotonia congenita, which is not a primary channelopathy, causes myotonia by reducing expression of CLC1.

Mutations occur throughout the CLCN1 gene; some produce dominant disease while others give rise to recessive inheritance. A few mutations are reported to cause dominant disease in one family but recessive disease in another. Interestingly the abnormal RNA splicing underlying myotonic dystrophy, which is not a primary channelopathy, causes myotonia by reducing expression of CLC1.

Tip and Tricks
- Transient weakness can be tested by asking the patient to repeatedly abduct the shoulder strongly against the examiner’s hand.
- The first abduction is usually strong but the second is weak, and with continued repetitions strength improves again (warm up phenomenon)

Paramyotonia Congenita (PMC) – sodium channel
PMC is caused by mutation of the skeletal muscle voltage gated sodium channel NaV1.4, encoded by the SCN4A gene. The hallmarks of PMC are autosomal dominant inheritance, myotonia that is exacerbated by exercise, and marked cold sensitivity. Symptoms of PMC start in infancy and, in contrast to Myotonia
Congenital myotonia affects bulbar, facial, neck and hand muscles more than lower limb muscles. Stiffness can be precipitated by exercise and is usually accompanied by weakness. Unlike the transient weakness of recessive myotonia congenita, weakness in PMC may persist for hours. Cold-sensitivity is typically much more extreme than in myotonia and can cause profound muscle weakness. Cold water presents a serious risk to children with PMC. Characteristic presentations include blepharospasm after prolonged crying and tongue stiffness after eating ice cream. Symptoms of paramyotonia are usually static through life but attacks of weakness and hyperkalemia may appear during adolescence.

The diagnosis is often clear from the history and clinical examination, but needle EMG and the short exercise test before and after cooling of the muscle may be helpful where there is uncertainty.

**Potassium aggravated myotonia (PAM) – sodium channel**
Some individuals with mutation in the SCN4A sodium channel gene present with symptoms of myotonia which, unlike MC, are potassium-sensitive. Several variants of PAM (also known as sodium channel myotonia) have been described. The myotonia can be painful, can fluctuate and may be induced by exercise but the variants share the characteristic of being worse after potassium ingestion (eg fruit juices). Unlike other sodium channelopathies, however, there is no weakness and symptoms are not usually worse in the cold. Distinguishing PAM from autosomal dominant MC is sometimes difficult.

**Management of the non-dystrophic myotonias**
Management of non-dystrophic myotonia comprises avoidance of precipitating factors such as cold or strenuous exercise, and drugs that reduce muscle excitability. However, in many cases myotonia is mild and no specific treatment is required. In others drug treatment can be ceased in the summer months.

Most muscle specialists consider mexiletine (a class Ib antiarrhythmic that acts on sodium channels) to be the most effective drug for myotonia but evidence is anecdotal. A randomized controlled trial is underway. Mexiletine is generally well tolerated but can prolong the QT interval and thereby predispose to arrhythmia. It should be avoided in patients who already have a long QT interval, and the QT interval should be checked regularly in those taking the drug. Other drugs that act on sodium channels are often effective, including phenytoin, carbamazepine, procainamide, propafenone and flecainide. Acetazolamide, a carbonic anhydrase inhibitor, and quinine are generally considered to be second line treatments.

**Caution**
Mexiletine can prolong the QT interval and predispose to arrhythmia.

**The Periodic Paralyses**

**Tips & Tricks**
The presence of clinical or electromyographic myotonia in a patient with periodic paralysis suggests a sodium channel disorder.
Hyperkalemic periodic paralysis (HyperPP) – sodium channel
HyperPP is characterized by recurrent attacks of limb weakness (sometimes focal) lasting minutes up to a few hours with onset in the first decade of life. The term ‘hyperkalemic’ is somewhat misleading since the potassium may be normal during an attack. The characteristic feature is precipitation of attacks by potassium-rich foods, for example fruit juice, but the serum potassium need not exceed normal. Attacks can occur on waking and can be precipitated by the cold, fasting, rest after exercise, and emotional stress. Tendon reflexes are depressed during an attack, but bulbar and respiratory muscles are usually spared. A large proportion of subjects with HyperPP develop progressive proximal myopathy, similar to HypoPP, which is seen with increasing age.

HyperPP is distinguished from HypoPP by shorter, more focal attacks, potassium-sensitivity and the presence of myotonia. The presence of myotonia, however subtle, in a patient with periodic paralysis strongly suggests hyperPP. Intercritically, lid lag and eyelid myotonia may be the only clinical signs. Electrical myotonia is found in fifty to seventy five percent of affected individuals yet is clinically apparent in less than twenty percent.

Like PMC and PAM, HyperPP is caused by mutations in the skeletal muscle voltage-gated sodium channel gene, SCN4A. Sodium channel disorders span the middle of the spectrum between episodic weakness and muscle stiffness and overlap syndromes exist with characteristics of both hyperPP and PMC or hyperPP and PAM.

Hypokalemic periodic paralysis (HypoPP) – calcium channel or sodium channel
HypoPP is the most common form of primary periodic paralysis but is still a rare disorder with a prevalence of about 1 per 100,000. Paralytic attacks usually begin in the first or second decade, usually occurring early in the morning. Weakness may be focal or generalized, and tends to be more severe and prolonged than in HyperPP, lasting for hours (occasionally days) with gradual resolution. Tendon reflexes are depressed during an attack. Respiratory and facial muscles are usually spared. Attacks occur spontaneously or are provoked by prolonged rest after vigorous exercise or a carbohydrate-rich meal on the previous day, and serum potassium is invariably low during an attack.

Other triggers include emotional stress, intercurrent viral illness, lack of sleep, menstruation and specific medications (e.g. beta agonists, corticosteroids and insulin). Attack frequency varies widely from patient to patient. Some experience daily episodes of weakness, others have a few episodes in a lifetime. After the age of 40 attacks become less frequent and less distinct. With time, fixed proximal muscle weakness may develop.

Myotonia never occurs in HypoPP; the presence of myotonia in a patient with periodic paralysis strongly suggests HyperPP.

Patients without a family history or presenting after age 20 should be assessed for Thyrotoxic Periodic Paralysis by checking for suppressed TSH and elevated free T4 (fT4) or fT3 levels. The serum potassium
is often profoundly low. Thyrotoxic periodic paralysis, which is otherwise indistinguishable from HypoPP, can be inherited and is more common in men and in particular East-Asians.

Ninety percent of cases of HypoPP are caused by mutation of the CACNA1S gene which encodes the voltage gated calcium channel, CaV1.1 (Type I HypoPP). Mutations in SCN4A, encoding the voltage gated sodium channel NaV1.4, account for only ten percent of HypoPP families (Type II HypoPP).

**Andersen-Tawil syndrome – potassium channel**

Andersen-Tawil syndrome (ATS) is caused by mutation of the inward rectifier potassium channel, Kir2.1, encoded by the KCNJ2 gene. The prevalence is estimated at one-tenth that of HypoPP. Symptomatic onset typically is with episodic weakness in the first or second decade. This type of familial periodic paralysis is characterized by extra-muscular features. The full clinical presentation in ATS is periodic paralysis (usually hypokalemic, although normo- or hyperkalemic attacks are reported), cardiac arrhythmia, and distinctive skeletal features. Intermittent weakness occurs spontaneously or may be triggered by prolonged rest or rest following exertion; permanent proximal weakness often develops. Attack frequency, duration and severity are variable between and within affected individuals.

The cardiac manifestations are variable and may include prolongation of the QT interval (long-QT syndrome), prominent U waves, premature ventricular contractions, ventricular bigeminy and polymorphic ventricular tachycardia. A subset of patients manifests bidirectional ventricular tachycardia, a unique form of ventricular tachycardia in which the QRS axis polarity alternates from one beat to the next. While many patients with ventricular ectopy are asymptomatic, others present with palpitations, syncope or rarely cardiac arrest.

ATS patients may remain asymptomatic despite frequent runs of tachycardia, and there appears to be a lower incidence of syncope and sudden death in ATS compared with other long QT (LQT) syndromes. Distinctive physical findings include a small mandible, ocular hypertelorism, low set ears, clinodactyly, syndactyly and broad nasal root. Short stature, unilateral hypoplastic kidney, vaginal atresia and brachydactyly. Learning difficulties and a neurocognitive phenotype are also described. The penetrance of symptoms is highly variable in ATS and some affected members of the same family may have only cardiac arrhythmia or only periodic paralysis, whereas others may have all three features.

A diagnosis of ATS can be made when at least two of the following are present: (i) periodic paralysis; (ii) ventricular ectopy and (iii) typical ATS physical features. However, the phenotypic variability in ATS may obscure the diagnosis so ATS should be considered in any individual presenting with isolated PP or polymorphic ventricular ectopy. A prolonged QU interval or large amplitude U wave may be more sensitive than the QTc interval, which overlaps with the upper limit of normal.

**Management of periodic paralysis**

The management of periodic paralysis comprises prevention of attacks and giving patients a contingency plan for the emergency treatment of an attack. Prevention is achieved by avoidance of the precipitants outlined above, and by drug treatment with a carbonic anhydrase inhibitor (either acetazolamide 125mg - 1000mg per day, or dichlorphenamide 50mg – 400mg per day in divided doses). Carbonic anhydrase inhibitors are effective in both HypoPP and HyperPP, and are thought to exert their effect by producing metabolic acidosis. If HypoPP attacks persist on a carbonic anhydrase inhibitor, oral potassium should be
added. In HyperPP, potassium-sensitivity symptoms are helped by lowering serum potassium for example with an oral carbohydrate load, exercise or inhaled beta-agonists.

Attacks of paralysis are rarely acutely life threatening but may render the patient incapable of self-care, sometimes for more than 24 hours, and the associated shifts in serum potassium can lead to cardiac arrhythmia. In an acute HypoPP attack, oral potassium 0.2 – 0.4mmol/kg improves strength. Intravenous potassium is rarely necessary unless the patient cannot swallow. In the rare case that bulbar and respiratory muscles are affected by an attack, respiratory support and measures to prevent aspiration may be necessary. Because the disease is rare emergency physicians are unlikely to be familiar with its management, and giving the patient a letter explaining their condition and its treatment and a telephone contact for their specialist is helpful.

Select Bibliography


