Diagnosis and new treatment in muscle channelopathies

G Meola, M G Hanna and B Fontaine

*J. Neurol. Neurosurg. Psychiatry* 2009;80;360-365
doi:10.1136/jnnp.2008.164046

Updated information and services can be found at:
http://jnnp.bmj.com/cgi/content/full/80/4/360

**These include:**

**References**
This article cites 49 articles, 18 of which can be accessed free at:
http://jnnp.bmj.com/cgi/content/full/80/4/360#BIBL

**Rapid responses**
You can respond to this article at:
http://jnnp.bmj.com/cgi/eletter-submit/80/4/360

**Email alerting service**
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

**Notes**

To order reprints of this article go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to *Journal of Neurology, Neurosurgery, and Psychiatry* go to:
http://journals.bmj.com/subscriptions/
Diagnosis and new treatment in muscle channelopathies

G Meola,1 M G Hanna,2 B Fontaine3,4

ABSTRACT

The skeletal muscle fibre membrane plays a major role in muscle contraction by generating and propagating action potentials, and linking the latter to the release of intracellular calcium stores which triggers mechanical contraction. This function relies on the proper functioning of ion channels. In the last two decades, diseases caused by mutations in muscle ion channel genes have been identified, the so-called muscle channelopathies. Even though the pathophysiology of muscle channelopathies is not completely elucidated, major advances have been made in their understanding, thus linking patient symptoms and neurophysiology with abnormal functioning of the muscle membrane. This has facilitated significant progress both in the diagnosis of these disorders and in the rationale for therapeutic intervention. In this review, we will focus on diagnosis and treatments of muscle channelopathies of relevance to the clinical neurologist.

Muscle channelopathies include disorders in which structural changes within the channel protein are caused by mutations which alter the amino acid sequence of the channel protein itself. The voltage-gated ion channels form a large family of proteins that share key structural features. The ion-conducting pore or voltage-gate of the channel is remarkably selective for a specific ion.

The general subunit of a voltage-gated ion channel is a tetrameric association of a series of transmembrane alpha-helical segments, numbered S1–S6 connected both by intracellular and extracellular loops (interlinkers). These six segments comprise one domain which is repeated several times within the α1 subunit (four times within the α subunit of the sodium and calcium channels and only once within that of the potassium channel). The fourth segment S4, containing basic residues, is considered the “voltage-sensor” of voltage-gated ion channels. Genetic mutations in muscle channel genes result in a change of channel function that shares key structural features. The ion-conducting pore or voltage-gate of the channel is remarkably selective for a specific ion.

The general subunit of a voltage-gated ion channel is a tetrameric association of a series of transmembrane alpha-helical segments, numbered S1–S6 connected both by intracellular and extracellular loops (interlinkers). These six segments comprise one domain which is repeated several times within the α1 subunit (four times within the α subunit of the sodium and calcium channels and only once within that of the potassium channel). The fourth segment S4, containing basic residues, is considered the “voltage-sensor” of voltage-gated ion channels. Genetic mutations in muscle channel genes result in a change of channel function that alters membrane excitability and causes the neuromuscular symptoms. The overall incidence of muscle channelopathies is estimated to be around 1:100 000.

The present review gives an overview of current knowledge and recent advances in molecular genetics, diagnosis and treatment of calcium, sodium, chloride and potassium channelopathies (muscle channelopathies) (table 1).

MUSCLE CHANNELOPATHIES

Calcium channelopathies

Hypokalaemic periodic paralysis (hypoPP) is characterised by episodic attacks of muscle weakness associated with decreased blood potassium levels.1 2 HypoPP is a monogenic disorder with an autosomal dominant mode of inheritance. The age at onset is within the second decade. The frequency of attacks is higher from the second to the fourth decades of life, and then tends to decrease. Attack frequency is very variable, ranging from once in a lifetime to several per week. Affected women tend to have fewer attacks than affected men. Attacks of muscle weakness usually affect all four limbs. Respiration, deglutition and ocular motility are usually spared but may be affected in the most severe attacks. Typically, patients wake in the night paralysed several hours after strenuous exercise or a meal rich in carbohydrates. Attacks then last several hours and resolve spontaneously. Recovery may be hastened by the ingestion of potassium chloride. If blood potassium levels are measured at the beginning of an attack, they are found to be below the normal range.

In the late 1980s, it was shown that when decreasing the potassium concentration in the extracellular medium, muscle cells from patients with hypoPP could be depolarised, which correlated with paralysis.3 This observation suggested that abnormal ion fluxes might be implicated. Multigeneration families were collected to enable linkage analysis. Genetic markers which co-segregated with the disease were in close vicinity to a voltage-gated calcium channel. Soon after, mutations were found in the voltage-gated calcium channel CACNA1S, establishing it as the first hypoPP-causing gene.3 6 CACNA1S accounts for approximately 55–70% of hypoPP.7 Voltage-gated calcium channels are made of four homologous domains, each composed of six trans-membrane segments. Remarkably, all mutations change positively charged amino acids arginines in the voltage sensor segment 4 (R528H or G in domain II, as well as R1239H of G in domain IV). Voltage-gated calcium channels lie within T-tubules, which are intracellular invaginations of muscle membrane. Their known role is to couple the action potential with the intracellular release of calcium from the sarcoplasmic reticulum. Expression studies of mutated calcium channels have shown minor abnormalities pointing to a loss-of-function effect (decreased current density and slowed activation). However, this mild loss of function of the calcium channel does not adequately explain the sustained membrane depolarisation that characterises an attack of paralysis.3 More recently it has been proposed that the loss of positive charge mutations in the S4 segment which associate with HypoPP may result in an alternative pathway for protons to enter the muscle fibre. This so-called “gating pore hypothesis” predicts a reduced pH within the...
Sodium-channelopathies

Genetic linkage studies established that hypoPP was a heterogeneous disease. The study of multigeneration families by linkage analysis and mutation search showed that mutations in the voltage-gated sodium channel also caused hypoPP.\(^5\)\(^6\) SCN4A accounts for approximately 8–10% of HypoPP.\(^7\)

The voltage-gated sodium channel belongs to the same channel family as the calcium channel and shares a similar organisation. It is the key player in the action potential, being responsible for the firing and propagation of action potentials. Mutations causing hypoPP affect similar amino acids to those mutated in the calcium channel. Differences have been noted in the phenotype displayed by patients bearing calcium or sodium-channel mutations. In patients with sodium-channel mutations, hypoPP tends to begin later, is accompanied by muscle aches, shows a predominance of tubular aggregates compared with vacuoles in the muscle biopsy and is aggravated by acetazolamide.\(^12\)

Hyperkalaemic periodic paralysis (hyperPP) is defined by the occurrence of episodic attacks of generalised weakness (sometimes focal), accompanied by an increase in serum potassium blood levels. In hyperPP, hyperkalaemia is far from constant, since it may be lacking in 50% of patients as shown by studies in well-characterised hyperPP families. A more consistent finding which relates potassium blood levels to paralysis is weakness provocation by ingestion of potassium salts (potassium challenge). Attacks begin during the first decade of life. The episodes vary in frequency from several in a day to once a while. They last minutes to several hours and then remit spontaneously. In comparison with hypoPP, hyperPP tends to have an earlier onset and more frequent attacks but much shorter and milder. Attacks are environmentally triggered. The most frequent triggering factors are rest after exercise, fasting and cold exposure. Other provocation factors depend on individuals and may include ethanol ingestion, stress, ingestion of food with high K-content and pregnancy. Patients quickly learn that keeping exercising after the onset of an attack alleviates muscle weakness or even aborts it. In contrast to hypoPP, myotonia may be associated with paralytic attacks in HyperPP. Myotonia is a prolonged failure of muscle decontraction. When present, it is a permanent manifestation (and not episodic) which is usually mild (compared with truly myotonic syndromes). The role of voltage-gated sodium channels in hyperPP was suggested by the observation of a non-inactivating sodium current in muscle fibres from hyperPP patients, when the extracellular potassium concentrations were raised above normal values.\(^13\) This observation led to the hypothesis that the sodium channel might be the site of the primary defect in hyperPP. The answer to this question came in two steps: (1) linkage studies established a link between the voltage-gated sodium-channel gene, SCN4A, and hyperPP;\(^14\) (2) mutations were found in the coding sequence of SCN4A gene establishing it definitively as the hyperPP gene.\(^15\)\(^16\) Two mutations causing hyperPP, Thr704Met and Met1592Val, account for approximately 20–30% of HyperPP.\(^17\) In order to gain insight into disease pathophysiology, sodium-channel mutations causing hyperPP were expressed in an in vitro system and studied by patch-clamp analysis. Disruption of slow inactivation is probably one of the mechanisms that cause paralysis because it is found in a majority if not all sodium-channel mutations that cause FP.\(^18\)

Paramyotonia congenita (PC) is present at birth or is noted by the parents in the first years of life. The distinction with myotonia congenita (see below) relates to the effect of exercise.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>HypoPP</th>
<th>HyperPP</th>
<th>Myotonia congenita</th>
<th>ATS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of inheritance</strong></td>
<td>AD</td>
<td>AD</td>
<td>AR/AD</td>
<td>AD</td>
</tr>
<tr>
<td><strong>Gene</strong></td>
<td>CACNA1S–SCN4A</td>
<td>SCN4A</td>
<td>CLCN1</td>
<td>KCNJ2</td>
</tr>
<tr>
<td><strong>Chromosome</strong></td>
<td>1q32</td>
<td>17q33.1–q25.3</td>
<td>7q35</td>
<td>17q23.1–q24.2</td>
</tr>
<tr>
<td><strong>Mutations</strong></td>
<td>CACNA1S (60%–SCN4A (10%)</td>
<td>SCN4A (55%)</td>
<td>CLCN1 (95%)</td>
<td>KCNJ2 (70%)</td>
</tr>
<tr>
<td><strong>Penetrance</strong></td>
<td>↓ Females</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>Reduced</td>
</tr>
<tr>
<td><strong>Functional defect</strong></td>
<td>↓ Fast inactivation</td>
<td>↑ Fast+slow inactivation</td>
<td>↓ K conduction</td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>1:100 000</td>
<td>1:200 000</td>
<td>1:100 000</td>
<td>1:500 000</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>1–2 decades</td>
<td>1 decade</td>
<td>1–2 decades</td>
<td>1–2 decades</td>
</tr>
<tr>
<td><strong>Duration of attacks</strong></td>
<td>Hours to days</td>
<td>Hours</td>
<td>Hours to days</td>
<td></td>
</tr>
<tr>
<td><strong>Usual triggers</strong></td>
<td>Rest after exercise</td>
<td>Rest after exercise</td>
<td>K-rich foods</td>
<td>Prolonged rest after exercise</td>
</tr>
<tr>
<td><strong>Ictal K</strong></td>
<td>↓</td>
<td>↑, normal</td>
<td>Normal</td>
<td>↓, normal, ↑</td>
</tr>
<tr>
<td><strong>EMG myotonia</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>EMG functional</strong></td>
<td>Pattern IV–V</td>
<td>Pattern IV</td>
<td>Pattern II</td>
<td>Pattern V</td>
</tr>
<tr>
<td><strong>Fixed proximal weakness</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td><strong>Cardiac arrhythmias</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Skeletal developmental anomalies</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Response to potassium</strong></td>
<td>Improves weakness</td>
<td>Triggers weakness</td>
<td>No effect</td>
<td>Depends on ictal K improves</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>ACZ Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>DCP Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Thiazides No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Mexiletine No/yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

| Notes | AD, autosomal dominant; AR, autosomal recessive; ATS, Andersen–Tawil Syndrome; DCP, dichlorophenamide; HyperPP, hyperkalaemic periodic paralysis; HypoPP, hypokalaemic periodic paralysis. |
which aggravates myotonia (so-called paradoxical myotonia or paramyotonia). Muscle stiffness is exacerbated not only by exercise but also by cold. It is usually predominant in the face and the upper extremities. A careful examination of the face is important to diagnose myotonia in PC, since myotonic features are almost constantly present in the face, even if they may be mild in the limbs. When the patient is asked to close and open their eyes, they cannot open their eyes anymore after a few movements (paradoxical myotonia). Pharyngeal muscles might also be affected, and the patient may have difficulties in eating ice or swallowing cold beverages. In addition to myotonia, patients with PC also present attacks of muscle weakness which typically follow attacks of stiffness in case of prolonged exercise in a cold environment. PC has been associated with several missense mutations in the gene encoding the voltage-gated sodium-channel SCN4A. Mutations affecting codons 1313 and 1448 are the most frequent. In vitro expression of sodium channels with mutations causing PC changes the biophysical properties of the mutated channel: a slowed inactivation and an incomplete closure of the channel following depolarisation compared with the control are observed. Leaking channels shift the membrane towards depolarisation. The increased number of action potentials due to increased numbers of sodium-channel openings correlates with myotonia.

In contrast with the definitions of myotonia congenita and PC, which are only clinical, the term sodium-channel myotonia has been introduced, implying a molecular diagnosis. Included in this category are a group of different myotonic syndromes of autosomal dominant inheritance. Some of the phenotypes did not attract enough attention to be specifically termed, whereas others bear specific names.13 Myotonia fluctuans begins in adolescence. The myotonia is induced by exercise but usually occurs with a delayed onset, during immediate rest after exercise. Stiffness severity tends to fluctuate from day to day. While ingestion of potassium aggravates markedly myotonic symptoms (potassium-aggravated myotonia), cold has generally no effect. Mutations in the voltage-gated sodium-channel SCN4A associated with myotonia fluctuans are S804F and G1306A. In myotonia permanens, myotonia is permanent and severe. Myotonia is so severe that patients may be suspected of having Schwartz–Jampel disease. Ventilation impairment may arise from severe stiffness of respiratory muscles or of the diaphragm. This phenotype has been associated with a de novo mutation of the voltage-gated sodium-channel SCN4A (G1306E). Acetazolamide-responsive myotonia begins in childhood. Patients complain from intermittent painful muscle movements (paradoxical myotonia). Pharyngeal muscles might also be affected. Percussing the belly of a muscle with a hammer provokes a contraction with delayed relaxation. Percussion of the tongue is classical but may be inconvenient for the patient. The cause of myotonia congenita is the presence of mutations in the chloride channel gene CLCN1. Two modes of inheritance are recognised: autosomal dominant and recessive. A transient muscle weakness is usually associated with the most severe recessive forms of myotonia congenita. It occurs after rest or after the initiation of the first contraction, only lasts a few seconds and rapidly improves with repetition of muscle contraction. It can be evidenced by asking the patient to raise and sit several times from his chair without using their arms.

The understanding of the pathophysiology of myotonia congenita has benefited from the study of animal models. These animal studies identified reduce membrane chloride conductance. Mutations in the skeletal muscle chloride channel gene CLCN1 were subsequently shown to be the cause of both dominant and recessive forms of the human disease.21,22 Mutations in the CLCN1 gene account for more than 95% patients with myotonia congenita. A large number of missense, splice-site and non-sense mutations have now been identified in the muscle chloride channel gene. In vitro co-expression in Xenopus oocytes of mutant and wild-type chloride channels suggests that the muscle chloride channel functions as a homomultimer. Accordingly, nonsense mutations or mutations affecting a splice site result in non-functional gene products, suggesting that a loss of function underlies the recessive form of myotonia congenita. Missense (or dominant) mutations dramatically alter the functioning of the chloride channel by exerting a dominant negative effect on an oligomer composed of wild-type and mutant subunits.24

It is well established that chloride channels play a role in the repolarisation of the muscle membrane and thus participate in the maintenance of the resting potential. Their inactivation by mutations modifies the cycle of excitability of the muscle membrane shifting it towards hyper-excitability by slowing the return of the membrane to the rest potential after depolarisation. Myotonia is directly correlated with the repetitive firing of sodium channels caused by this state of hyper-excitability.

**Potassium channelopathies**

Andersen–Tawil Syndrome (ATS) is a rare muscle channelopathy with distinct features and accounts for an incidence of about 1:500 000.25 The distinguishing features of ATS are the coexistence of the abnormalities in two excitable tissues: skeletal and cardiac muscle. Periodic paralysis in ATS occurs in the setting of either hyperkalaemia or hypokalaemia, and cardiac involvement ranges from asymptomatic ventricular arrhythmias to sudden death. The dysmorphic skeletal features are often a diagnostic clue to ATS, although they may be subtle. Clinical heterogeneity is remarkable in this syndrome: ECG abnormalities may be the only manifestation of an affected individual within a family with typical triad of ATS (periodic paralysis, cardiac arrhythmia and multiple dysmorphic features).26–28

A mutation in the KCNJ2 gene on chromosome 17q23.1 has been described. KCNJ2 mutations accounts for approximately 70% of ATS patients.29 KCNJ2 encodes a pore-forming subunit of inward rectifying potassium channels (Kir 2.1), a critical contributor for the Ikr current (which maintains normal resting membrane potentials and regulates the final phase of action potential repolarisation in various types of cells). The channel is a dimer of subunits, each with two transmembrane spanning domains called M1 and M2. The NH2 terminal is on the M1 segment, and the COOH terminal on the M2 segment. To date, more than 30 KCNJ2 mutations have been identified and mostly localise on the intracellular COOH terminal.29–32 Most mutations in KCNJ2 show loss of function and a dominant

---

**Chloride channelopathies**

Myotonia congenita was first defined clinically in the second part of the 19th century. Myotonia is more pronounced after rest and improves with exercise, the so-called “warm-up phenomenon.”11 Myotonia can be evidenced by asking the patient to repeat the opening and closure of his eyes. Slow at the beginning, the movement will become normal after a few trials (warm-up phenomena). Myotonia can be elicited by percussion. Percussing the belly of a muscle with a hammer provokes a contraction with delayed relaxation. Percussion of the tongue is classical but may be inconvenient for the patient. The cause of myotonia congenita is the presence of mutations in the chloride channel gene CLCN1. Two modes of inheritance are recognised: autosomal dominant and recessive. A transient muscle weakness is usually associated with the most severe recessive forms of myotonia congenita. It occurs after rest or after the initiation of the first contraction, only lasts a few seconds and rapidly improves with repetition of muscle contraction. It can be evidenced by asking the patient to raise and sit several times from his chair without using their arms.

The understanding of the pathophysiology of myotonia congenita has benefited from the study of animal models. These animal studies identified reduce membrane chloride conductance. Mutations in the skeletal muscle chloride channel gene CLCN1 were subsequently shown to be the cause of both dominant and recessive forms of the human disease.21,22 Mutations in the CLCN1 gene account for more than 95% patients with myotonia congenita. A large number of missense, splice-site and non-sense mutations have now been identified in the muscle chloride channel gene. In vitro co-expression in Xenopus oocytes of mutant and wild-type chloride channels suggests that the muscle chloride channel functions as a homomultimer. Accordingly, nonsense mutations or mutations affecting a splice site result in non-functional gene products, suggesting that a loss of function underlies the recessive form of myotonia congenita. Missense (or dominant) mutations dramatically alter the functioning of the chloride channel by exerting a dominant negative effect on an oligomer composed of wild-type and mutant subunits.24

It is well established that chloride channels play a role in the repolarisation of the muscle membrane and thus participate in the maintenance of the resting potential. Their inactivation by mutations modifies the cycle of excitability of the muscle membrane shifting it towards hyper-excitability by slowing the return of the membrane to the rest potential after depolarisation. Myotonia is directly correlated with the repetitive firing of sodium channels caused by this state of hyper-excitability.

**Potassium channelopathies**

Andersen–Tawil Syndrome (ATS) is a rare muscle channelopathy with distinct features and accounts for an incidence of about 1:500 000.25 The distinguishing features of ATS are the coexistence of the abnormalities in two excitable tissues: skeletal and cardiac muscle. Periodic paralysis in ATS occurs in the setting of either hyperkalaemia or hypokalaemia, and cardiac involvement ranges from asymptomatic ventricular arrhythmias to sudden death. The dysmorphic skeletal features are often a diagnostic clue to ATS, although they may be subtle. Clinical heterogeneity is remarkable in this syndrome: ECG abnormalities may be the only manifestation of an affected individual within a family with typical triad of ATS (periodic paralysis, cardiac arrhythmia and multiple dysmorphic features).26–28

A mutation in the KCNJ2 gene on chromosome 17q23.1 has been described. KCNJ2 mutations accounts for approximately 70% of ATS patients.29 KCNJ2 encodes a pore-forming subunit of inward rectifying potassium channels (Kir 2.1), a critical contributor for the Ikr current (which maintains normal resting membrane potentials and regulates the final phase of action potential repolarisation in various types of cells). The channel is a dimer of subunits, each with two transmembrane spanning domains called M1 and M2. The NH2 terminal is on the M1 segment, and the COOH terminal on the M2 segment. To date, more than 30 KCNJ2 mutations have been identified and mostly localise on the intracellular COOH terminal.29–32 Most mutations in KCNJ2 show loss of function and a dominant
negative suppression effect, and a mutation, pS136F, has been shown to suppress the native I\(\text{k}\), in neonatal rat cardiomyocytes. Less clear is the way these mutations account for facial and skeletal abnormalities and whether there are other clinical manifestations of ATS given the ubiquitous distribution of Kir 2.1 channels.

The mutation with the most potent dominant negative is the T75R missense mutation. Other mutations act by a mechanism of haploinsufficiency probably affecting trafficking and assembly of second messengers via the interaction of abnormal amino acid positioning along the muscle membrane where the Kir 2.1 channels are localised.

ATS patients display a wide range of penetrance and severity of clinical phenotype, and may provide a diagnostic challenge. ATS is clinically characterised by the triad of periodic paralysis with a duration of 1 h to few days, cardiac arrhythmias (such as bigeminy, long QT syndrome, prolonged QUc interval, ventricular arrhythmias, resulting in syncope, cardiac arrest or sudden cardiac death) and multiple dysmorphic features (such as short stature, broad-base nose, broad forehead, hypertelorism, low-set ears, micrognathia, cleft palate, clinodactyly, syndactyly or scoliosis). Only 60% of the affected individual manifest the complete triad of cardinal features and 80% express two of the cardinal features.

Recently it has been reported that Japanese ATS patients are exclusively associated with KCNJ2 mutations (100%) and present a high percentage penetrance of cardiac manifestations.

Mild learning difficulties and deficit in executive functions have also been described.

Proximal muscle is usually more severely affected than distal, and occasional slight weakness may persist after the attacks. Onset of the clinical manifestation is between 2 and 18 years of age.

Determination of ictal serum potassium is critical in the diagnostic workup. Serum potassium levels may be normal, elevated or decreased during the attacks. Previously, when ictal potassium levels could not be obtained, patients were subjected to hypokalaemic and hyperkalaemic challenges. Such challenges should be not used for diagnostic purposes in ATS because of the risk of precipitating or worsening cardiac arrhythmias. So far, no ATS patient has been reported to have myotonia on EMG.

The diagnosis of ATS is suspected if, in addition to periodic paralysis, the patient manifests at least one of the two other characteristic features of ATS. Ultimately, confirmation of the diagnosis requests genetic testing for the presence of KCNJ2 mutations.

**Functional Electromyography is a Useful Tool to Diagnose Muscle Channelopathies**

The classification of muscle channelopathies is shown in fig 1. In this figure, the reasoning for diagnosing these disorders is also presented. After considering symptoms and signs, functional electromyography is a useful tool to suggest which gene and mutation type is implicated.

The functional consequences of ion-channel mutations on muscle membrane excitability in patients can be studied by the non-invasive technique of electromyography (EMG). During attacks of PP, the muscle membrane has been shown to be depolarised and unable to respond to electrical stimulation. Since muscle weakness may be triggered by exercise, it has been proposed to use strong and sustained voluntary contraction as a provocative test for diagnosis. Surface-recorded muscle responses to supra-maximal nerve stimulation are used to monitor muscle membrane activity and are considered to reflect muscle membrane activity. Analysis of the compound motor action potential (CMAP) amplitude before and at various times following long (5 min) exercise provides information on changes in the number of active fibres, and on their ability to depolarise and repolarise.

Large numbers of patients with known ion-channel mutations associated with different forms of periodic paralysis and myotonias have now been reported. Specific EMG protocols have now established consistent links between the clinical syndromes (and genetic mutations) and the muscle electrical response to different provocative tests (repeated short exercise, long exercise). In addition, statistical analysis of the results obtained from patients carrying the same mutation provided additional evidence that the identified EMG changes are caused by specific ion-channel mutations.

Periodic paralysis patients can be divided into two groups defined as patterns IV and V. The decline in CMAP response, which occurs 15–20 min after completion of a long exercise, is a common feature to both patterns. This loss of muscle excitability correlates well with muscle weakness experienced by patients after strenuous exercise. An early incremental effect of repeated short exercise or long exercise on CMAPs was specific to patients with hyperkalaemic periodic paralysis (pattern IV). Recording of a late CMAP decline after long exercise without preliminary increment (pattern V) is most consistent with mutations in CACNA1S or in SCN4A. A similar pattern has been observed in patients with mutations in KCNJ2.

Needle EMG displays myotonic discharges which confirm the clinical diagnosis in myotonia. In PC, functional EMG showed the existence of postexercise myotonic potentials. Exercise induced a prolonged decrease in compound muscle action potentials (pattern I) which was exacerbated by cooling. Patients with myotonia congenita display a pattern II which is characterised by a transient decrease in muscle action potential after short exercise and no effect of the long exercise test. In autosomal dominant myotonia congenita, muscle cooling potentiates the transient decrease in muscle action potentials. A small number of patients with a clinical and EMG (pattern II) features undistinguishable from myotonia congenita were shown to have a sodium-channel mutation. These patients shifted from the diagnosis of myotonia congenita which was suspected on clinical and EMG grounds to the one of sodium-channel myotonia. In other words, the sodium channel may in rare cases lead to myotonia with a warm-up phenomenon (fig 1).

However, most of the patients with sodium-channel myotonia have no effect or are aggravated by exercise. They do not present weakness and are not always cold-sensitive. Some of them may also complain of muscle pain or cramps. The functional EMG pattern is different from the two distinctive ones described above: no variation of compound muscle action potentials induced by cold or short term exercise (pattern III). The most frequent sodium-channel mutations in these cases affect codon 445, 1293 or 1506.

**Treatment**

The management of skeletal muscle channelopathies is presently largely symptomatic. Affected individuals learn to avoid precipitating triggers through lifestyle and dietary modifications. Patients with hyperPP attacks should eat frequent small meals and should avoid large carbohydrate loads, in contrast to those with hyperPP attacks who need to avoid K-rich foods (eg
Patients with PP (including ATS) should be advised about the possibility of malignant hyperthermia like reactions to volatile anaesthetics and depolarising muscle relaxants. However, we still lack sufficient evidence to provide full guidelines for the treatment of muscle channelopathies, and trials of prophylaxis are therefore warranted in all patients with PP whose attacks are frequent and prolonged.46–55

CONCLUSION
Recent advances in molecular genetics and functional electrophysiological testing has improved diagnosis and treatment of muscle channelopathies. However, large well-conducted randomised trials on PP patients are required. Although current evidence suggests dichlorphenamide and probably acetazolamide reduce attack frequency, it is not known if long-term treatment with such agents can prevent the significant permanent myopathy many patients develop. Although the pathophysiology of the mutated genes in muscle channelopathies is still poorly understood, it is important to direct efforts not only towards the detection of new causative genes and new mutations but also to their pathophysiological consequences. The elucidation of the precise molecular pathophysiology is likely to open new perspectives for future therapeutic approaches.

Funding: The work of BF is financially supported by ANR-maladies rares, AFM and INSERM and of GM by PRIN MIUR (Ministero Istruzione Università di Ricerca Scientifica) 2006. MHG is supported by an MRC Centre grant (G0601943).

Competing interests: Professor Michael Hanna is Deputy Editor of the Journal of Neurology Neurosurgery & Psychiatry but has had no role in the review process.

Patient consent: Obtained.

REFERENCES


