The inherited muscle ion channel diseases (muscle channelopathies) are a group of disorders of skeletal muscle membrane excitability characterised by variable muscle stiffness and/or intermittent weakness. Myotonia is a common but not universal feature of these disorders which are nevertheless distinct from the myotonic dystrophies (Table 1). External and environmental factors can be important triggers to attacks or lead to worsening of symptoms and may include alterations in serum potassium levels, reduction in ambient temperature and muscle activity, particularly when followed abruptly by rest.

Common muscle channelopathies are the result of chloride, sodium and calcium channel dysfunction and are therefore amenable to therapeutic interventions.

**ABBREVIATIONS USED IN THIS ARTICLE**

- MC: myotonia congenita
- PMC: paramyotonia congenita
- PAM: potassium-aggravated myotonia
- HyperPP: hyperkalaemic periodic paralysis
- HypoPP: hypokalaemic periodic paralysis

**Presentations**

**MYOTONIA AND PARAMYOTONIA**

Myotonia is the phenomenon of delayed relaxation of skeletal muscle following voluntary contraction (see Box below). Affected individuals may report muscle stiffness following voluntary contraction (myotonia) or spontaneous muscle contraction after prolonged periods of rest but diminishes with repeated muscle contractions, the so-called warm-up phenomenon.

The classic clinical findings are an inability to relax after prolonged contraction (eg handgrip) and percussion myotonia, spontaneous muscle contraction after direct percussion (eg abductor pollicis brevis). Lid-lag may be seen on suddenly looking downwards after prolonged upwards gaze. These findings become less marked with repetition but reappear after rest.

In contrast to myotonia, muscle stiffness in paramyotonia is precipitated rather than ameliorated by exercise. This is the opposite of the warm-up phenomenon in myotonia (hence paradoxical myotonia or paramyotonia). Paramyotonia is also particularly temperature-sensitive. Marked exacerbation by cold and exercise is useful clinically in distinguishing paramyotonia from myotonia.

**WEAKNESS**

Episodic weakness is seen in many of the muscle channelopathies and is a hallmark feature of the periodic paralyses. Individuals may experience not only generalised limb weakness but also single limb, hemibody or very focal muscle weakness. Bulbar and respiratory muscle weakness are either spared or insufficiently affected to be clinically significant.

Attacks of weakness most commonly occur in the morning after waking from sleep but can be triggered by stress, fasting (sodium channelopathies) or a carbohydrate meal (hypokalaemic periodic paralysis). Exercise followed by rest is a potent trigger for attacks of weakness in all forms of periodic paralysis. Cold exposure can trigger an episode of weakness in the periodic paralyses and, particularly dramatically, in paramyotonia congenita.

Depressed tendon reflexes during an attack are an important clinical pointer to the organicity of ‘generalised limb weakness’ caused by periodic paralysis. Some patients with periodic paralysis develop a fixed myopathy which can be significantly disabling. A mild fixed weakness can develop in patients with myotonia congenita and paramyotonia congenita.

**MUSCLE HYPERTROPHY**

Muscle hypertrophy is a characteristic feature of myotonic disorders and is a direct result of muscle overactivity. This is very different from the muscle 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).

**Chloride channelopathies**

The primary membrane defect in myotonia congenita (MC) is reduced chloride conductance. Mutations in the CLCN1 gene encoding the ClC-1 muscle voltage-gated chloride channel can give rise to allelic disorders with autosomal dominant or recessive modes of inheritance. It is interesting to note that recent evidence suggests the myotonia in myotonic dystrophy is caused by altered expression of the same chloride channel secondary to abnormal RNA aggregation.

**MYOTONIA CONGENITA**

Becker-type myotonia (recessive MC) is more common and is usually more severe. Muscle stiffness may be worse in the cold, although never to the extent seen in paramyotonia, and improves with exercise. Onset is usually in the morning after waking from sleep and improves with exercise.

The morphology of myotonic discharges can be of fibrillation potentials (spikes) or positive sharp waves (see waveform). This allows the source generator to be identified as muscle as distinct from spontaneous activity arising in the motor nerve which has the morphology of a motor unit potential. Neuromyotonia, caused by abnormal firing of the motor nerve, bears some clinical resemblance to myotonia (stiffness, delayed muscle relaxation, ‘true’ muscle hypertrophy). However, the shape and frequency of discharges in neuromyotonia are easily differentiated from myotonic potentials in the EMG laboratory.

Normal muscle at rest is electrically silent outside the end-plate zone. Electrophysiological myotonia is caused by spontaneous repetitive discharges of a single muscle fibre. Myotonic discharges have a waxing and waning quality that gives rise to the characteristic “dive-bomber” or “chain-saw” sound heard in the EMG laboratory. They are a defining feature of both the dystrophic and non-dystrophic myotonic myopathies (Table 1) but they may also be found in acid maltase deficiency, polymyositis and centronuclear myopathy.
second decade and the condition progresses slowly over
years. The lower extremities are affected first, giving rise
to a disproportionate figure with calf and gluteal muscle
hypertrophy but relatively poorly developed neck and
shoulder girdle muscles. Grip and percussion myotonia
may appear during adolescence. Characteristics presenta-
tions include blepharospasm after prolonged crying and tongue stiffness after eating an ice
cream. Symptoms of paramyotonia are usually static
through life but attacks of weakness and hyperkalaemia
may appear during adolescence.

HYPERKALAEMIC PERIODIC PARALYSIS

Patients with HyperPP have episodes of generalised weak-
ness lasting minutes up to 1 hour beginning in the first
decade of life. Attacks can occur on waking and can be
precipitated by the cold, fasting, rest after exercise, emo-
tional stress and potassium ingestion (eg fruit juices).
Symptoms improve with an oral carbohydrate load, mild
exercise and inhaled \beta-agonists. Bulbar and respiratory
musculature is characteristically spared. Depressed deep
tendon reflexes during an attack are a key clinical finding
and the serum potassium is usually raised (4.5-8.0 mM) if
it is measured early in an attack. Coexisting paramyotonia
may be present.

POTASSIUM-AGGRAVATED MYOTONIA

Some individuals with sodium channel mutations present
with symptoms of myotonia which, unlike MC, are potas-
sium-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 characteris-
tic of being worse after potassium ingestion (eg fruit juices). Unlike other sodium channelopathies, however,
there is no true weakness and symptoms are not usually
worse in the cold.

Calcium channelopathies

Pathological mutations are recognised in two different
muscle calcium channels. Mutations in the non-voltage-
sensitive ryanodine receptor gene (RYR1) encoding a sar-
coplasmic reticulum calcium channel involved in excita-
tion-contraction coupling cause malignant hyperthermia
which can be associated with central core disease (cf. Rakowicz (2003): ACNR 2(6):11-13). Pathogenic mutations in the dihydropyridine receptor gene (CACNA1S) encoding the muscle voltage-gated calcium channel give rise to HypoPP. The disease is inherited with autosomal dominant inheritance but with reduced penetrance in women. Recently HypoPP has also been reported in association with mutations in exon 12 of the SCN4A gene encoding the muscle voltage-gated sodium channel.

HYPOKALAEMIC PERIODIC PARALYSIS

HypoPP is the commonest inherited periodic paralysis. As in HyperPP, episodes of weakness can be triggered by the cold, prolonged rest, rest after exercise and emotional stress but are usually of longer duration (hours to days). Unlike HyperPP heavy meals rather than fasting predispose the individual with HypoPP to an attack and there may be a characteristic history of weakness occurring on waking on the day after a large meal. Depressed deep tendon reflexes during an attack are a key clinical finding and the serum potassium is usually depressed (2-3 mM). Although attacks may be very mild and kindreds frequently include asymptomatic individuals, compromised respiratory function has occasionally been reported. The presence of even asymptomatic myotonia excludes the diagnosis of HypoPP.

An important differential diagnosis of HypoPP is symptomatic hypokalaemia. 'Secondary' HypoPP is seen most frequently in the context of treatment with potassium-wasting diuretics but can be the result of primary hyperaldosteronism, inadequate dietary intake, excessive potassium loss (sweat, gastrointestinal and renal) and chronic liquorice ingestion. Usually in symptomatic hypokalaemia the patient is persistently weak rather than experiencing attacks of weakness. In some Far-Eastern populations hyperthyroidism can lead to attacks of weakness with a depressed serum potassium concentration which are very similar to HypoPP but the cause is unknown.

Potassium channelopathies

Two muscle potassium channelopathies are now recognised. A rare form of HyperPP is described in association with mutations in the MinK gene. A more common potassium channelopathy is Andersen’s syndrome caused by mutations in the KCNJ2 gene encoding the muscle voltage-independent potassium channel Kir2.1.

ANDERSEN’S SYNDROME

The diagnosis of Andersen’s syndrome is based on a triad of (1) periodic paralysis; (2) prolonged QT interval or ventricular arrhythmias; (3) dysmorphic features. The attacks of paralysis may be accompanied by a reduced, normal or raised serum potassium level. Cardiac involvement varies from the asymptomatic to cardiac arrest in childhood and requires close cardiological supervision. Dysmorphic features include short stature, low-set ears, hypertelorism, micrognathia, a short index finger and syndactyly of the toes. It is important to note that dysmorphic features may be subtle and that cardiac complications can present at any age. Therefore in any patient with periodic paralysis a careful search for dysmorphic features should be undertaken as well as a 12-lead ECG.

Treatments

Acute and prophylactic treatments can be used in the muscle channelopathies. Patients with mild MC may not require treatment. However, most MC and PMC patients will benefit significantly from antymotonic treatment and in our experience the antiarrhythmic drug mexiletine is easily the most effective. Pretreatment ECG is important.

Mild attacks of HyperPP can be treated at onset with continued slight exercise or ingesting carbohydrates. Lifestyle preventive measures in HyperPP may be helpful. Prevention of attacks can usually be achieved with carbonic anhydrase inhibitors, either acetazolamide or dichlorphenamide. Thiadize diuretics may also be useful preventive agents. J-agonists such as salbutamol have a useful role to play in preventing HyperPP attacks in certain patients.

Mild attacks of HypoPP need no treatment but potassium chloride may be given orally (but not in a carbohydrate-containing drink) in more severe attacks. Intravenous potassium replacement is not usually required and may be hazardous. Attacks of HypoPP are best prevented by avoiding carbohydrate-rich meals and heavy exercise but carbonic anhydrase inhibitors are often effective.

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REFERENCE


FOOTNOTE

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