Skeletal Muscle Channelopathies – a guide to diagnosis and management

Emma Matthews[1, 2], Sarah Holmes[3], Doreen Fialho[2,3]

[1]Atkinson-Morley Neuromuscular Centre, St George's University Hospitals NHS Foundation Trust, London, UK

[2]Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, UK

[3]Queen Square Centre for Neuromuscular Diseases, London, UK

London, UK

Correspondence to: Dr Emma Matthews, emma.matthews@ucl.ac.uk

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Abstract

Skeletal muscle channelopathies are a group of rare episodic genetic disorders comprised of the periodic paralyses and the non-dystrophic myotonias. They are a source of significant morbidity for patients, can limit their vocational opportunities, be socially embarrassing and in some cases are associated with sudden cardiac death. Diagnosis is often hampered by symptoms that may be difficult for patients to describe, a normal exam in the absence of symptoms and the need to interpret numerous tests that may be normal or abnormal. Symptoms are extremely responsive to holistic management and pharmacological treatment however, with great benefit to a patient's quality of life. Here we review when to suspect a muscle channelopathy, how to investigate if you do, and the options for therapy once a diagnosis is made.

Introduction

Skeletal muscle channelopathies (SMCs) are a group of rare genetic neuromuscular disorders caused by dysfunction of sarcolemmal ion channels that are critical for muscle membrane excitability[1]. In simple terms they affect the ability of skeletal muscles to either contract, causing muscle weakness, or to relax, causing myotonia. This group of conditions is divided into the periodic paralyses and the non-dystrophic myotonias based on the predominant clinical symptom of either muscle weakness or myotonia. The hallmark of a skeletal muscle channelopathy is that symptoms occur in an episodic or paroxysmal fashion causing acute disability[2]. As a group they affect approximately 1 in 100 000 people in the U.K[3].

Myotonia (delayed muscle relaxation after contraction) is often described by patients as muscles "locking", "sticking" or "cramping". Episodic weakness can vary significantly from one limb "not working or feeling right" to quadriparesis. Symptoms commonly affect the leg muscles and in the case of myotonia may be precipitated by sudden or initial movement leading to falls and injury. Symptoms are also exacerbated by prolonged rest, especially after preceding physical activity, and changes in environmental temperature[4]. Leg muscle myotonia can be particularly problematic on public transport which may stop abruptly causing falls or the patient may not be able to rise and exit quickly enough missing their destination. These difficulties can limit independence, social activity, choice of employment (based on ability to both travel to the location and to perform certain tasks) and are often socially embarrassing. The symptomatic relationship with activity often leads to sedentary behavior which in turn may be a risk factor for additional co-morbidities e.g. heart disease or stroke. Muscle channelopathies are also frequently painful with pain and impaired physical ability having a significant impact on quality of life[5 6].

The burden of morbidity in muscle channelopathies can usually be successfully ameliorated by readily available symptomatic treatments[7] and the biggest barrier to improving a patient's quality of life is more often a lack of diagnosis. Diagnosis is not always easy however, the conditions are rare and patients may be completely asymptomatic with a normal examination in the out-patient clinic. The diagnosis hinges on careful history taking arousing clinical suspicion supported by an accumulation of examination findings (or lack of abnormality) and investigative clues. There is no single test that will provide an answer in isolation.
Here we review when to suspect a skeletal muscle channelopathy, how to investigate for one when you do and how to manage symptoms and disability after diagnosis.

Clinical history

Skeletal muscle channelopathies include the periodic paralyses and the non-dystrophic myotonias. The periodic paralyses are hypokalaemic periodic paralysis (hypoPP), hyperkalaemic periodic paralysis (hyperPP) and Andersen-Tawil Syndrome (ATS). The non-dystrophic myotonias are paramyotonia congenita (PMC), sodium channel myotonia and myotonia congenita (MC) (see Fig 1 for causative genes and the resultant dysfunctional ion channels). These are genetic disorders and in the majority of cases symptoms can be traced back to the first or second decade highlighting the importance of taking an early life history. In some cases symptom onset can be delayed into the 30s or 40s and/or may only appear during certain life events e.g. pregnancy.

The periodic paralyses

HypoPP and hyperPP are named in relation to episodes of muscle weakness occurring in the presence of either high or low serum potassium levels[8]. They can be further distinguished by the typical pattern and duration of attacks and symptomatic triggers that drive serum potassium up (foods high in potassium) or down (carbohydrate meals) – see Fig 2. Myotonia can also be present in hyperPP but episodic weakness is usually the presenting complaint.

When taking a history of someone with possible periodic paralysis several caveats are important to bear in mind. Despite being called periodic paralysis not all episodes of weakness are this dramatic. The most profound episodes do include quadriparesis and these

cases are most likely to present to the emergency department with deranged (often low) potassium. Many patients however will describe more modest weakness e.g. they can stand but only furniture walk, or they are able to walk on the flat but feel weak and can't run or climb stairs. Weakness will often present with a period of rest following physical activity. A common early event or recollection of symptoms is having played with friends during school lunch break, returning to sit at a desk for lessons and then being unable to stand or walk. Sometimes weakness may seem task specific or only affect one limb e.g. the dominant hand is weak after a prolonged period of writing. In these cases there is usually a history of more generalised weakness but these may be the only symptoms initially volunteered as they are the most troubling.

HypoPP characteristically presents in the early teens with episodes of weakness experienced on waking and lasting several hours. If this results in being unable to attend school in the morning but appearing "normal" by the afternoon it may be mis-interpreted as school avoidance[9]. Similar scenarios can lead to disciplinary procedures for working adults.

The recurring episodes of weakness in periodic paralysis although similar are not usually stereotyped. Stereotyped episodes are more indicative of a paroxysmal movement disorder or episodic ataxia and the term "weakness" may be used erroneously by a patient struggling to quantify a difficult to describe symptom e.g. dyskinesia.

Andersen-Tawil Syndrome

ATS is the only skeletal muscle channelopathy to affect any system other than skeletal muscle – namely cardiac muscle and bony development. The classical syndrome is described as a triad of periodic paralysis (usually mirroring the hypoPP variety), cardiac conduction defects and dysmorphic features[10]. In many cases however, the dysmorphic features can be subtle and overlooked and the skeletal or cardiac muscle symptoms may dominate the clinical picture obscuring the true breadth of systematic involvement. Patients predominantly affected by periodic paralysis may be mis-diagnosed as hypoPP. This has important implications as a lack of awareness of cardiac risk and subsequent monitoring can be detrimental. Sudden cardiac death is described in ATS but generally considered a rare event. Emerging evidence indicates however that cardiac arrhythmias requiring medical intervention are relatively common with an ICD required in 20% of patients in one series[11], and may occur without prominent cardiac symptoms. We recommend yearly cardiac review by an experienced cardiologist with ECG and prolonged Holter monitor in all patients with ATS (regardless of symptoms).

The non-dystrophic myotonias

Myotonia is usually the presenting complaint in both myotonia congenita and paramyotonia congenita. It can be difficult for patients to describe (especially before a diagnosis is made) and terms such as muscles cramping, being stiff, stuck, aching, or "not working" may be used. Myotonia can affect any skeletal muscle so although typical patterns of involvement occur (legs more than hand and face in MC, hands and face more than legs in PMC), symptoms affecting the trunk, back (back pain) and chest muscles (unable to catch

breath/take a deep breath) can all be problematic. Myotonia affecting the face can include the jaw and tongue making chewing or swallowing difficult especially if a cold item or drink is consumed. Cardiac and smooth muscle (bowel or bladder) are not affected in the non-dystrophic myotonias.

Other characteristic pointers towards either a diagnosis of MC or PMC include the presence of the warm up phenomena in MC (myotonia improving with repetitive activity) or paradoxical myotonia in PMC (worsens with repetition) as well as different forms of episodic weakness (see Table 1). Sodium channel myotonia can have overlapping features of both MC and PMC but refers essentially to a pure myotonic disorder without any episodic weakness due to mutations in the SCN4A (sodium channel) gene.

Myotonia itself is a symptom and/or sign, not a diagnosis. Myotonia can be seen or detected during EMG in other conditions including myotonic dystrophy type 1 and 2, Pompes disease[12] and other myopathies[13] (where it may be detected on EMG only without overt clinical signs) or be drug induced[14]. Of all possible differentials for a patient with myotonia, myotonic dystrophy type 1 is by far the most common and should always be considered especially in younger patients who may not yet manifest the multi-system involvement of this disorder. In addition, although less common than DM1, the systemic features of DM2 are often more mild (even at older ages) causing confusion with non-dystrophic myotonia.

Pain and fatigue

Episodic weakness or myotonia are the dominant clinical symptoms in the SMCs but pain (myalgia) and fatigue are often prominent and in some cases may be the symptom causing the most concern to the patient[5 6 15]. It is important to enquire about these and to attempt to treat them as well as addressing weakness and myotonia.

Examination findings

Typical examination findings in the periodic paralyses are normal although a proportion of patients do develop a proximal myopathy. If examined during an episode of weakness, in addition to reduced power, reflexes are reduced or absent. Myotonia may be detectable in someone with hyperPP. Patients with Andersen-Tawil syndrome can have dysmorphic features including short stature, low set ears, micrognathia, clinodactyly, dental abnormalities[16] (these may have been corrected in childhood so important to enquire in the history about dental work, especially extraction for overcrowding).

Those with myotonia often have generalised muscle hypertrophy, or well defined muscles[9]. They are also often young adults when they present and it is easy to assume they look this way because they are young and fit. Muscle hypertrophy must always be considered in context and a specific enquiry made as to how active or how many times a week your patient actually attends the gym.

Patients with a myotonic disorder will (nearly always) have evidence of myotonia on examination but it can be easily overlooked in a general neurological exam. Patients with MC are best diagnosed from the waiting room. It is likely they will have sat for some time waiting

to be called. When they first rise leg muscle myotonia will cause them to be slow and to have a stiff gait. By the time they have walked with you to the clinic room this is often normal. Examination for eyelid closure or hand grip myotonia should be repeated. If the patient has PMC the first movement may appear unrestricted and it is only with repetition that myotonia becomes evident (paradoxical myotonia). Conversely for MC myotonia may be immediately evident with the first test but improves or disappears with repetition i.e. the warm up phenomenon may be demonstrated. We usually ask the patient to grip their hands tightly or close their eyes "as if they have soap in them" for 5 secs, then to open the hand/eyes as fast as possible. This should be repeated 3 to 5 times. Other findings can include contractures e.g. at the elbow and scoliosis although this is most commonly seen in children and young adults.

Investigations

Investigations performed when considering the possibility of a muscle channelopathy need to be interpreted in light of the overall presentation as a negative test in isolation does not exclude a channelopathy.

Bloods tests/CK

The role of blood tests in investigating a SMC is largely in excluding other differential diagnoses. A standard "battery" includes renal function (is there any evidence of renal disease causing deranged potassium levels), thyroid function tests (does your patient have thyrotoxic periodic paralysis), white cell enzymes (Pompe's disease) and creatine kinase (CK). Creatine kinase typically ranges from within normal limits to up to 1000IU/L[6]. It is a non-specific test but an abnormal result always helps to lend support to the suspicion of a neuromuscular disorder. However, a normal result does not exclude a SMC. Values above 1000IU/L can occur and are consistent with a SMC diagnosis but they are less common[17] and with values this high it is always worth considering the whole presentation and asking if this could reflect an alternative neuromuscular diagnosis (see table 2). Rare cases of CKs above 10 000IU/L and presentation with rhabdomyolysis have been reported in the SMCs[18].

Ictal potassium levels are helpful but not absolute in a patient with possible periodic paralysis. If weakness is severe enough to cause quadriparesis potassium levels usually lie outside a normal range. The key element associated with weakness however is a rise or fall in potassium levels and the absolute value is not always outside normal limits. This can be especially true if an attack is beginning to subside, or has subsided by the time any blood tests are taken.

Neurophysiology

Standard EMG and NCS assessments are usually normal in the periodic paralyses (with the exception of the presence of myotonia in some cases of hyperPP). If considering a diagnosis of periodic paralysis the most informative test is a long exercise test (LET)[19]. This involves stimulating the ulnar nerve and recording a series of CMAPS from abductor digiti minimi before and after "exercise" of the muscle (abduction against resistance over a 5 minute period). The post-exercise CMPAPs are recorded for a 50minute period looking for a greater

than or equal to 40% decline in CMAP amplitude compared to the post-exercise peak. If positive this indicates periodic paralysis but not the sub-type. In a significant minority of cases, especially in those with ATS as well as patients who have rare attacks of weakness, the LET can also be within normal limits[20]. So a positive test is helpful but a negative test does not exclude a diagnosis of periodic paralysis.

EMG will determine the presence of myotonia. This is non-specific and once myotonia is identified the differential diagnoses (see Table 2) all need to be considered. Electrical myotonia without clinical myotonia is more commonly seen in the presence of a myopathic disorder but usually there are other indicators of this e.g. myopathic EMG, fixed weakness on exam and persistent functional disability. A repeat short exercise test can illustrate certain patterns of response that help to indicate the different sub-types of non-dystrophic myotonia[21] but there is overlap with the patterns seen in myotonic dystrophy and it is not specific. With the advent of next generation sequencing allowing genes to be sequenced in parallel, rather than having to choose a "first choice" this test has less practical value in everyday clinical practice.

Genetic testing

Next generation sequencing (NGS) means that in the UK parallel testing of all genes indicated in SMC is now available. This has particular benefit for ATS which may present as a hypoPP picture clinically but an accurate diagnosis will be detected by NGS which includes analysis of all three periodic paralysis genes, *SCN4A*, *CACNA1S* and *KCNJ2*. Due to the cardiac risks of ATS we recommend all relatives of a proband are offered genetic testing regardless of symptoms.

For a possible myotonic disorder, *CLCN1* and *SCN4A* are also analysed in parallel. DM1 and DM2 genetic testing needs to be requested separately and should not be forgotten even if the patient appears to "only" have a myotonic disorder.

In terms of inheritance pattern all of the SMCs are autosomal dominant or de novo with the exception of myotonia congenita which can be dominant or recessive. Recessive CLCN1 variants can co-segregate with an SCN4A variant or an expansion in the *DMPK* and *CNBP* genes associated with DM1 and DM2. This can cause diagnostic confusion e.g. if a proband is diagnosed clinically with MC and genetic analysis reveals one variant in a family with dominant inheritance of a myotonic disorder, it may be assumed that this reflects a positive diagnosis when in fact the proband may be a carrier for a recessive *CLCN1* variant and have myotonic dystrophy. This has clinical implications as monitoring for cardiac and other systemic complications will be omitted if diagnosed with myotonia congenita.

The characteristic phenotypes of SMC have been described for over 100 years and the genetic basis of these disorders known since the early 1990s. A significant minority of patients do present with a channelopathy like clinical presentation but have a negative genetic result for these established disease causing genes.

In the last few years a number of alternative genetic causes of episodic neuromuscular weakness with expanding phenotypes have been identified[22 23]. Other neuromuscular diagnoses can also have episodic or fluctuant presentations e.g. metabolic disorders (see Table 2) and do need to be considered if genetic testing for a SMC is negative. In addition other paroxysmal disorders, especially GLUT 1 deficiency and Paroxysmal Kinesigenic Dyskinesia (PKD), can erroneously be referred to a neuromuscular clinic[24].

Other investigations – MRI and muscle biopsy

MRI scanning of the muscles, usually lower limb muscles in SMC can demonstrate fatty infiltration of the muscles in keeping with the clinical development of fixed myopathy[25] or T1 STIR hyperintensity. In the case of periodic paralysis the STIR hyperintensity is thought to be reflective of disease activity i.e. ongoing recurrent episodes of weakness. This can be useful in terms of guiding symptomatic treatment and response. Early pattern recognition including a gastrocnemius "central stripe" in myotonia congenita[26] are proposed as diagnostic pointers (Fig 3) but a definitive MRI pattern of muscle involvement is not yet established for SMCs.

A muscle biopsy is not necessary or generally informative for the diagnosis of typical SMC. Those that have been performed historically have illustrated non-specific myopathic findings including the presence of a vacuolar myopathy in periodic paralysis[27]. Exceptions to this include the newer and atypical phenotypes of channelopathy e.g. RYR1 related periodic paralysis where a muscle biopsy can be supportive of the diagnosis[22].

Management

SMCs are genetic disorders which currently are not curable but there are numerous symptomatic treatments and management approaches that can have a significant impact on morbidity.

Lifestyle and activity

There are clear symptomatic triggers for many patients with SMCs e.g. foods high in carbohydrate or potassium. Keeping a food diary can be a useful way to identify these and help to avoid them or make alternative food choices.

The relationship between symptoms and exercise means that many people with SMCs describe exercise and activity avoidance, low levels of physical activity, and difficulties maintaining an active lifestyle. However, people who have been able to develop ways of keeping active do describe this as beneficial.

The benefits of keeping active, in terms of extending health-span, are well established for the general population and for people with long term conditions. Correlations between extended periods of inactivity (sedentary behaviour), health outcomes including obesity, cardiovascular and metabolic diseases, and increased risk of mortality have also been reported for the general population[28 29].

Little is published about activity in SMCs specifically, although our personal experience suggests a trend for high levels of sedentary behaviour in this population, indicating that interventions addressing this may help improve health outcomes.

Advice on extended periods of warm up and cool down, and stretches before and after exercise, can support an individual to transition in and out of, and prepare for exercise, without precipitating symptoms and/or in some cases associated muscle pain. Low intensity and low resistance exercises, focusing on gradually increasing repetitions and resistance as muscles adjust can also help to avoid an increase in myotonia, or precipitation of weakness. The use of activity monitors or apps can be helpful tools to measure activity, and to establish a baseline from which individuals can set goals to gradually increase activity and/or interrupt extended periods of sedentary behaviour. Walking and moving around is often more accessible than formally working out at the gym**.**

Fatigue may also benefit from these approaches or may require additional referral to a formal fatigue management programme.

Pharmacological therapies

Some patients will choose to manage symptoms by adjustment of triggers as much as possible[7]. When medication is indicated there are numerous choices. In the periodic paralyses prophylactic treatment is aimed at controlling potassium levels with either daily potassium sparing (aldosterone antagonists e.g. spironolactone, or amiloride) or potassium wasting (thiazides) diuretics. For those with hypoPP potassium supplements taken at the onset of an attack can also help to abort or minimise symptoms[7]. Other options shown to be effective in both forms of periodic paralysis include carbonic anhydrase inhibitors acetazolamide, or dichlorphenamide (not currently available in England). Long-term acetazolamide requires a yearly renal ultrasound scan to monitor for the development of renal calculi. Treatment of non-dystrophic myotonia of any sub-type is with sodium channel blockers. Mexiletine is most widely used and has the greatest available evidence of efficacy and safety[30-32] but lamotrigine is increasingly popular following a recent clinical trial[33]. Other options with more limited or anecdotal data include ranolazine, carbamazepine, flecainide, propafenone and phenytoin. All options are primarily aimed at treating either episodic weakness or myotonia. There are no studies to indicate the best treatment of pain or myalgia in SMCs. Our personal experience is that acetazolamide, often combined with an anti-myotonic agent e.g. mexiletine can be beneficial in the NDMs but that analgesics, including neuropathic agents, often have limited benefit.

It is unknown if aggressive control of episodic symptoms has any influence on the longer-term development of a proximal myopathy that can occur in NDMs but there is some limited evidence that it may.

Cardiac management

Yearly follow up with a cardiologist is recommended for all patients with ATS. Extended ECG recording e.g. 24 or 72 hour Holter monitors may have benefit in detecting arrhythmias

requiring treatment even when symptoms are not reported. There is no RCT evidence for the most effective anti-arrhythmic regime but beta-blockers or flecainide are commonly used. The requirement for interventional devices such as an ICD appears to be more common than previously appreciated emphasising the importance of expert cardiac involvement[11].

Emergency treatment of periodic paralysis

Due to the extended nature of attacks those with hypokalaemic periodic paralysis tend to be the patients with SMCs who most commonly present to the emergency department. All patients presenting with a first episode of hypokalaemic periodic paralysis should be investigated for secondary causes of hypokalaemia especially thyrotoxicosis (Fig 2). In the event of low potassium, ECG monitoring is required. If ECG changes occur this is an indication to use IV rather than oral potassium replacement. ECG and potassium monitoring must continue during replacement and for several hours post-correction to normal range. This is because during an attack, potassium is held intracellulary but total body potassium is not actually low. As the attack subsides, potassium returns to the serum. If this is combined with exogenous replacement it can result in a rebound hyperkalaemia and iatrogenic death[34].

Pregnancy and labour

The majority of pregnant women do report symptoms of SMCs are exacerbated when they are pregnant[35 36]. This may be due to both hormonal changes and the current recommendation that medication is discontinued prior to and during pregnancy due to evidence of teratogenicity or a lack of safety data. There are some reports of mexiletine having been used without major adverse event during pregnancy[37 38] and more recently the evidence of efficacy for lamotrigine in myotonic disorders[33] offers a potential new option for pregnant women. Worsening symptoms can be particularly detrimental if they provoke increased falls or they may necessitate taking maternity leave early which has a knock on effect of limiting time available to spend with baby post-partum.

Many women with SMCs have spontaneous unassisted vaginal deliveries, and this option should not be routinely denied when birth planning. We usually recommend labour is considered relatively high risk however in the sense that labour takes place in a facility where senior paediatric, obstetric and anaesthetic staff and facilities are available if required. Symptoms of weakness or myotonia may prolong a labour and delivery with all the inherent complications of this, but in addition, a subgroup of infants can have life-threatening respiratory complications if they have inherited the disorder[39] (predominantly those at risk of inheriting an SCN4A gene mutation).

Anaesthetic considerations

For any patient requiring an anaesthetic (including during labour) it is essential the anaesthetist be informed of the diagnosis of SMC beforehand, where feasible. Local or regional anaesthetics are preferred to a general anaesthetic if possible. If general anaesthesia is used propofol and non-depolarising anaesthetic agents appear to be effective and safe[40]. Depolarising anaesthetics or suxamethonium can precipitate a myotonic crisis with profound

muscle rigidity which can mimic a malignant hyperthermia type reaction. If the rigidity includes the jaw muscles intubation may be impossible[41]. Suxamethonium can also induce hyperkalaemia and ventricular arrhythmia which can be fatal[42]. Emergency treatment for a myotonic crisis is with intravenous sodium channel blockers e.g. lidocaine[40].

It should be noted that other peri-operative factors can also exacerbate symptoms of a SMC e.g. prolonged immobility, or a cold operating theatre/recovery room.

In summary skeletal muscle channelopathies are rare. They can evade diagnosis because they are sometimes hard for a patient to describe, often have no positive examination findings and investigations may be normal or negative unless conducted during symptoms. Yet they are extremely treatable and the benefits of appropriate diagnosis and management while rewarding for clinicians, are profound for patients.

Key Messages

When assessing a myotonic disorder without obvious systemic involvement don't forget myotonic dystrophy

Symptoms of a muscle channelopathy are more than weakness and myotonia, pain and fatigue can be prominent

Andersen-Tawil Syndrome requires cardiac monitoring regardless of symptoms

Episodic movement disorders can be confused with a muscle channelopathy and vice versa

Skeletal muscle channelopathies are treatable disorders

Case Example: A weak patient in A and E with a low potassium – is it periodic paralysis?

History

Hypokalaemia from any systemic, drug induced or genetic cause can induce muscle weakness. Ask the patient if they have diarrhoea and vomiting, tachycardia and palpitations (thyrotoxicosis), is there a known history of renal disease, take a drug history and family history (is there a known family history of PP or other relatives with the same symptoms)? Has this happened before or have they had milder symptoms of weakness that resolved spontaneously without the need to attend A and E? The age of the patient can be indicative. Drug history may be more pertinent in older patients. Genetic disorders are more likely to present for the first time in younger patients, the typical age of onset of hypoPP being in the teens. These are of course pointers only and age is not an absolute criteria for genetic causes of periodic paralysis.

Examination

Weakness typically affects the limbs and trunk with reduced or absent reflexes. Muscles of the neck and face are less commonly affected but can be. This may cause speech to sound slurred if the lower face and tongue are weak or for there to be eye closure weakness. Extraocular muscles are not usually weak and an inability to speak or open eyes at all is not typical and more indicative of functional weakness. In young children with hypoPP respiratory muscle weakness can cause respiratory distress and hypoxia. This is much less common in teenagers and adults but can occur in severe episodes with quadraparesis. Does the patient look dysmorphic? Do they have short stature? Short stature and dysmorphic features vary widely in ATS but among the most common are micrognathia (small chin), clinodactyly (curved digit, usually the little fingers) and low set ears. Are there any other systemic abnormalities? Hypertension may accompany secondary causes of hypokalaemia. Tachycardia may indicate thyrotoxicosis but can occur with hypokalaemia itself or may just indicate the patient is anxious about being unable to walk.

Initial Investigations and Management

Hypokalaemia with normal acid-base balance is expected in genetic forms of hypoPP, acid-base disturbance should prompt more extensive renal, and endocrine investigations for e.g. renal tubular acidosis, Gitelman's syndrome, hyperaldosteronism. Given that the hypokalaemic weakness may be the only indicator of thyroid disease we recommend routinely testing all first presentations. Creatine kinase can be normal or raised and is non-specific to diagnosis but a positive test can be useful in a general setting to triaging an onward referral after the acute episode.

Monitor the ECG and serum potassium levels. There is no absolute value for when to choose oral versus IV replacement but a potassium <2.5mmol/l, severe muscle paralysis especially if breathing is impaired or ECG changes of hypokalaemia (flat T waves, u waves, ST segment depression) are indicators for IV potassium. A typical dose of 40mmol/l KCl in 1L of 0.9% NaCl given at a rate of 10mmol/hour is usually sufficient but local guidelines should be consulted. If potassium replacement is given it is mandatory to monitor the ECG throughout and for several hours after normokalaemia as there is a risk of rebound hyperkalamia.

	Gene	Inheritance pattern	Muscles most commonly affected	Symptomatic triggers	Relieving factors	Warm up phenomena (myotonia improves with repetition)	Paradoxical myotonia (myotonia worsens with repetition)	Episodic weakness	Muscle hypertrophy
Myotonia Congenita	CLCN1	Autosomal dominant or recessive	Legs > hands or face. Falls are common.	Prolonged rest or sitting(especially after activity) Temperature extremes hot or cold	Warm environments (although extremes can provoke myotonia) Gentle movement before engaging in activity	Characteristic finding	No	Transient weakness improving with repetition of task	Yes Characteristically calf muscle hypertrophy but can be generalised
Paramyotonia Congenita	SCN4A	Autosomal dominant	Face and hands > legs	Cold environment Activity Rest after activity	Warm environments	No	Characteristic finding	Prolonged weakness or paralysis (can have clinical overlap with hyperPP).	Yes can be generalised
Sodium Channel Myotonia*	SCN4A	Autosomal dominant	Either pattern	Prolonged rest or sitting(especially after activity) Activity Temperature extremes hot or cold	Warm environments (although extremes can provoke myotonia)	Can occur	Can occur	No	Yes can be generalised

*before the genetic basis of channelopathies was known many clinical phenotypes were described including potassium aggravated myotonia, acetazolamide responsive myotonia but these were subsequently all shown to be due to mutations in the *SCN4A* gene and are now collectively called sodium channel myotonia.

Table 1: Clinical features of the non-dsytrophic myotonias

Diagnosis	Comment
Myopathies – Pompe's disease, myofibrillar myopathy	May have electrical myotonia on EMG.
Myopathies – Metabolic, McArdles disease, RYR1 related	Episodic symptoms, often related to physical exertion, can be confused with periodic paralysis. A specific RYR1/PP overlap syndrome has recently been identified.
Becker muscular dystrophy	Large calves occasionally confused with calf hypertrophy seen in myotonia congenita.
Secondary causes of hypokalaemia e.g. renal disease, drug induced	Profound hypokalaemia can induce muscle weakness in any individual in the absence of a genetic predisposition.
Thyrotoxic periodic paralysis	Can present with hypokalaemic periodic paralysis, most commonly seen in Asian males. Essential to check TFTs in all first presentations of hypoPP as treatment of the thyrotoxicosis abolishes the episodes of periodic paralysis.
Migraine (hemiplegic migraine)	Usually there is a headache history to guide diagnosis but non-headache symptoms may predominate.
Paroxysmal movement disorders e.g. PKD, GLUT1 deficiency, episodic ataxia	Patients may use the term "weakness" erroneously when it is difficult to quantify a symptom
Functional disorder	Most commonly a functional episodic weakness confused with periodic paralysis

Table 2: differential diagnoses of skeletal muscle channelopathies

Figure Legends

Figure 1: the skeletal muscle channelopathies – causative genes, dysfunctional ion channel and resultant clinical symptom

Figure 2: discerning features in hypokalaemic and hyperkalaemic periodic paralysis

Figure 3: MRI STIR images of both calves in a patient with myotonia congenita demonstrating the "central stripe" in both left and right medial gastrocnemius muscles (arrowheads). Fig reproduced[26]

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