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Review Article

Care Recommendations for the Investigation and Management of Children With Skeletal Muscle Channelopathies

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ABSTRACT

The field of pediatric skeletal muscle channelopathies has seen major new advances in terms of a wider understanding of clinical presentations and new phenotypes. Skeletal muscle channelopathies cause significant disability and even death in some of the newly described phenotypes. Despite this, there are virtually no data on the epidemiology and longitudinal natural history of these conditions or randomized controlled trial evidence of efficacy or tolerability of any treatment in children, and thus best practice care recommendations do not exist. Clinical history, and to a lesser extent examination, is key to eliciting symptoms and signs that indicate a differential diagnosis of muscle channelopathy. Normal routine investigations should not deter one from the diagnosis. Specialist neurophysiologic investigations have an additional role, but their availability should not delay genetic testing. New phenotypes are increasingly likely to be identified by next-generation sequencing panels. Many treatments or interventions for symptomatic patients are available, with anecdotal data to support their benefit, but we lack trial data on efficacy, safety, or superiority. This lack of trial data in turn can lead to hesitancy in prescribing among doctors or in accepting medication by parents. Holistic management addressing work, education, activity, and additional symptoms of pain and fatigue provides significant benefit. Preventable morbidity and sometimes mortality occurs if the diagnosis and therefore treatment is delayed. Advances in genetic sequencing technology and greater access to testing may help to refine recently identified phenotypes, including histology, as more cases are described. Randomized controlled treatment trials are required to inform best practice care recommendations. A holistic approach to management is essential and should not be overlooked. Good quality data on prevalence, health burden, and optimal treatment are urgently needed.

Introduction

Skeletal muscle channelopathies (SMC) are a group of heterogeneous genetic disorders.[1] SMC are rare, but pharmacologic treatments are available for symptomatic patients with often dramatic effects on morbidity, emphasizing the utility of making an early diagnosis. Eventually most patients will be cared for by a pediatric neurologist or a neuromuscular specialist, but the initial presentation is usually to general pediatricians or practitioners. Making a diagnosis can be a challenge for several reasons: muscle channelopathies are rare disorders, phenotypes are varied, symptoms are typically episodic, and many routine investigations can be normal.[1,2] Even if a diagnosis is made there are no best practice care recommendations to assist in the management of children.

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Established phenotypes include the non-dystrophic myotonias (NDMs), periodic paralyses, and Andersen-Tawil syndrome (ATS). Point prevalence estimates of these characteristic channelopathies vary geographically being almost twice as high in the Netherlands than in the United Kingdom: 2.38 of 100,000 versus 1.12 of 100,000.[3,4] In the Netherlands study, only 10% (40 of 405) of individuals with a positive genetic diagnosis of SMC were children, (aged three to 18 years); the mean age of the majority was 44 years (range 19 to 93).[4] There are no prevalence figures for more newly recognized phenotypes of severe neonatal episodic laryngospasm (SNEL), congenital myasthenia, and congenital myopathy.

Given that symptom onset is typically in childhood (Table 1) it is unclear if the low prevalence rates among the pediatric population reflect hesitancy in genetic testing or indicate a significant delay in diagnosis. One pediatric series did report a delay of between three and 13 years from first symptom to diagnosis.[2] In this narrative review, we provide a pragmatic guide with illustrated learning from our own experience to the recognition, investigation, and management of these rare but treatable disorders including suggested drug monitoring regimes.

Pathophysiology

The channelopathies derive their name from the knowledge that they are caused by mutations in genes that code for skeletal muscle ion channels. Each of these ion channels is essential for muscle membrane excitability, which controls muscle contraction and relaxation allowing movement. The pathophysiology has been well studied with a clear correlation between mutation effect on channel function and resultant clinical features.[5,6] In broad terms mutations that result in a hyperexcitable sarcolemma cause myotonia that can be detected electrically by neurophysiology and clinically by examination. Mutations that reduce membrane excitability, or cause prolonged states of depolarization, result in muscle weakness. In periodic paralysis and myasthenia weakness is episodic or variable, although progressive development of a

TABLE 1.
Summary of Clinical Features of the Myotonic Muscle Channelopathy Phenotypes

Channelopathy	Causative Gene	Inheritance	Age of Onset	Muscles Most Affected	Additional Features	Myotonic Triggers	Diagnostic Clue
Myotonia congenita	*CLCN1*	AD or AR	Typically early teens Range first to fourth decade	Legs>face and hands	Warm-up phenomena (myotonia improves with repetitive action) Transient weakness may be observed, also improves with repetitive action Muscle hypertrophy Contractures Scoliosis Toe walking	Cold environment, often improves in warm environment but “too hot” conditions can also exacerbate myotonia Rest after exertion Sudden movement Initiation of movement	Never good at sprinting. Sports day at school—when start of race declared “all the other children ran off and I fell over or couldn't move” “Once I get going I'm ok.” Falls a lot “Funny gait” Climbing stairs difficult
Paramyotonia congenita	*SCN4A*	AD	Typically first decade Often early—birth or within first few weeks	Eyelids, extraocular muscles, jaw, tongue, hands>legs	Paradoxical worsening with repetitive action Can have episodic weakness/paralysis (overlap with hyperPP) Muscle hypertrophy Contractures Scoliosis Strabismus	Extreme sensitivity to cold environment Rest after exertion	Neonatal hypotonia, Stridor—neonate or infant Parents note eye closure myotonia in babies, e.g., if they cry “face gets stuck” Strabismus “Always had it” “After swimming lessons I couldn't use my hands to put my clothes back on”
Sodium channel myotonia	*SCN4A*	AD	Typically first or second decade	Eyelids, extraocular muscles, jaw, tongue, hands, legs	Both warm-up phenomena and paradoxical worsening can be seen Muscle hypertrophy	Extremes of temperature—cold or hot Sometimes high-potassium foods	Has overlap features with MC and PMC Can seem like MC but earlier onset, more prominent involvement of face muscles, extraocular myotonia, and AD family history
SNEL	*SCN4A*	Often *de novo* Can be AD	Birth to 10 months	Generalized but prominent respiratory and laryngeal muscle involvement	Recurrent episodic apnea ± stridor Bradycardia Loss of consciousness Massive muscle hypertrophy Dysmorphic features	Cold, feeding, crying can stimulate apnea	Often mistaken for epilepsy but no EEG correlate Milder episodes mistaken for laryngomalacia or reflux

Abbreviations:
AD = Autosomal dominant
AR = Autosomal recessive
EEG = Electroencephalography
hyperPP = Hyperkalemic periodic paralysis
MC = Myotonia congenita
PMC = Paramyotonia congenita

proximal myopathy is described. In the most severe loss-of-function mutations congenital myopathy occurs. Understanding the pathophysiology has contributed directly to the development of effective therapies.[7,8]

Clinical presentation

The nondystrophic myotonias (NDMs)

The NDMs are composed of myotonia congenita (due to mutations in the *CLCN-1* gene), paramyotonia congenita, and sodium channel myotonia (both due to mutations in the *SCN4A* gene).[1] Myotonia, delayed muscle relaxation after forced contraction, can affect any skeletal muscle, but different patterns of involvement are recognized in each phenotype. Although myotonia is the primary feature, other symptoms including weakness, myalgia, and fatigue can be equally debilitating and should be asked about.[1] Table 1 summarizes the characteristic clinical features that are indicative of each diagnosis. Some important clues and more recently recognized presentations in children should be highlighted.

"Funny gait"

Leg myotonia in children can cause frequent falls, a "funny gait," and intermittent toe walking.[2,9] Both gait and toe walking (Fig 1) may be seen to improve as the child walks through from the waiting room or when observed walking in clinic, i.e., there is a warm-up phenomena. Referral with gait abnormality is common in myotonia congenita but may be erroneously directed to a movement disorders clinic.

Extraocular muscle myotonia

Myotonia of extraocular muscles is typical of paramyotonia congenita (PMC) and SCM[2,10]; this may present as "blurred vision" after a period of focused gaze, for example, reading. Intermittent strabismus (Fig 1) or strabismus with a variable degree of gaze deviation is relatively common; this may prompt referral to ophthalmology.

Musculoskeletal abnormalities

Elbow and Achilles contractures, scoliosis, and short stature (Fig 1) are more recently recognized clinical signs.[2,10] Dysmorphic features including high forehead, low-set ears, short neck (Fig 1), and a high-arched palate are also increasingly described in sodium channel myotonia.[9,11] These features in combination with the striking muscle hypertrophy that can be generalized may have previously deterred physicians from a diagnosis of NDM or led to a misdiagnosis of the much rarer Schwartz-Jampel syndrome.[10]

Neonatal hypotonia

This condition associated with self-limiting minor feeding difficulties (temporary nasogastric tube) and/or episodic oxygen desaturation (supplemental oxygen required) has also been reported in cases with *SCN4A* mutation[2,12] (PMC, SCM, and hyperkalemic periodic paralysis [hyperPP] phenotypes).

Severe neonatal episodic laryngospasm (SNEL)

Severe neonatal episodic laryngospasm (SNEL) is a specific infantile presentation of *SCN4A* gene mutations.[13] Presentation may be at birth or within a few hours postnatally, but it can present later

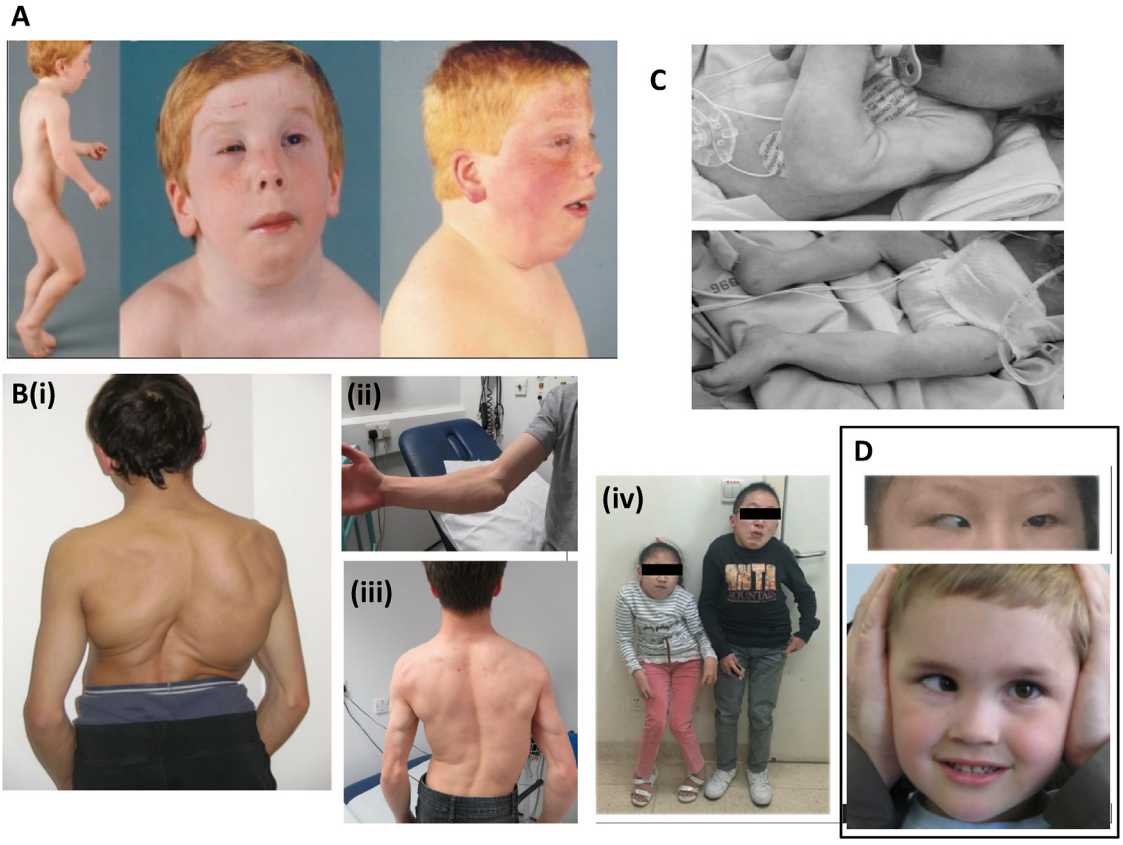

FIGURE 1. Clinical signs in children with myotonic disorders. (A) Toe walking, eyelid myotonia, and facial dysmorphism with short neck and hypertrophic neck and shoulder girdle muscles. (B) Scoliosis (i, iii), elbow contractures (ii), and elbow and knee contractures, short neck, and short stature (iv). (C) Massive muscle hypertrophy in a child with severe neonatal episodic laryngospasm. (D) Strabismus. The color version of this figure is available in the online edition.

in life with reports up to age 10 months.[14] Generalized attacks of myotonia include the respiratory and laryngeal muscles. Infants experience desaturations, apnea, and cyanosis with or without stridor accompanied by whole body "stiffening." Bradycardia and loss of consciousness may occur. Events are relatively brief (seconds to minutes) but may require ventilator support if apneic. Frequency ranges from a single episode to up to 20 per day. More minor episodes can present as brief resolved unexplained events, but recurrent severe events may be managed in an intensive care unit environment.[15] Signs are often misdiagnosed as seizures, although a normal ictal electroencephalography will help differentiate it from this condition. Muscle hypertrophy can be striking (Fig 1), and dysmorphic features may be seen. The episodes of apnea naturally decline with advancing age,[9] but some infants have died and others have required recurrent resuscitation in the first two years of life.[11,16] A positive response to sodium channel blockers can be dramatic.[13,16]

Periodic paralyses

HyperPP refers to episodes of muscle weakness that occur in association with an elevated serum potassium level.[17] Hypokalemic periodic paralysis (hypoPP) is when muscle weakness occurs in association with low serum potassium.[17] Core features are summarized in Table 2. It is important to note that although the name implies paralysis, the severity of any given attack of weakness can be extremely variable. Patients may therefore describe an inability to complete some activities but not all, for example, can walk on the flat but not upstairs. Typically, symptoms are bilateral but certain activities can prompt a focal attack of weakness, for example, the dominant hand after a prolonged period of writing in school examinations. The variability of attacks and abilities during them coupled with their episodic nature can lead to an erroneous diagnosis of a functional neurological disorder. Symptoms can also be misinterpreted as school avoidance especially if associated with examinations and the early morning timing of attacks in the case of hypoPP with recovery by the afternoon.

Andersen-Tawil syndrome (ATS)

ATS is a syndrome caused by mutations in the *KCNJ2* gene that includes periodic paralysis (usually hypoPP), dysmorphic features, and cardiac manifestations, including prominent U waves, prolonged QT interval, frequent premature ventricular contractions, and ventricular tachycardia[18,19] (Table 2). Distinct physical dysmorphisms are a core feature of ATS and typically include mandibular hypoplasia, low-set ears, and micromelia. The severity of the muscle and cardiac symptoms can be very variable,[20] and the dominant presenting symptoms drive referral to either a neurologist or a cardiologist. Cardiac symptoms can include palpitations, presyncope or "dizziness," and syncope.[21] A sudden and unexpected cardiac arrest is relatively rare but can be the presenting event.[22] Despite frequent ventricular ectopy, many patients do not report any cardiac symptoms and the arrhythmias may be picked up incidentally, for example, during electrocardiography (ECG) or cardiac monitoring for an unrelated procedure. At the severe end of the neurological spectrum we have seen adolescent patients require a wheelchair for long distances.

Congenital myopathy

Mutations in the *SCN4A* and *CACNA1S* genes are now also recognized as a cause of congenital myopathy.[23,24] The majority of cases are autosomal recessive. The clinical phenotype with *SCN4A* is

TABLE 2.
Summary of Clinical Features of the Periodic Paralyses Including Andersen-Tawil Syndrome

Channelopathy	Causative Gene	Inheritance	Age of Onset	Muscles Most Affected	Additional Features	Triggers	Diagnostic Clue
Hyperkalemic periodic paralysis	*SCN4A*	AD	First decade	Limbs and trunk	Neonatal hypotonia Myotonia can be seen	High serum potassium, may be due to potassium-rich foods Cold environment, intercurrent illness Rest after exertion Puberty, menses	Weakness can be any time of day Can last minutes to hours May have additional myotonia and sometimes muscle hypertrophy
Hypokalemic periodic paralysis	*CACNA1S* *SCN4A*	AD	Second decade typical	Limbs and trunk	In very severe attacks facial muscles can be weak—speech slurred, and respiratory muscles affected	Low serum potassium, may be due to carbohydrate-rich food or fasting Intercurrent illness Rest after exertion Puberty, menses	Attacks common during night when wakes to use bathroom or first thing in morning Attacks are typically hours to days Plays football after school, has pizza for tea, wakes next morning unable to move
Andersen-Tawil syndrome	*KCNJ2*	AD	First and second decade	Limbs and trunk	Cardiac conduction abnormalities Ventricular tachyarrhythmia Dysmorphic features—commonly short stature, micrognathia, clinodactyly, syndactyly, low-set ears	Low serum potassium, may be due to carbohydrate-rich food	U waves or prolonged QT interval on ECG 100-1000 s of ventricular ectopics noted during incidental procedure, e.g., appendicectomy Dental anomalies or overcrowding and tooth extraction Attacks of muscle weakness less commonly cause full paralysis than in other forms of PP Short stature is not universal and dysmorphic features may be very subtle

Abbreviations:
AD = Autosomal dominant
ECG = Electrocardiography
PP = Periodic paralysis

a continuum from severe lethal fetal hypokinesia to a classic congenital myopathy correlating with the degree of channel dysfunction seen in *in vitro* studies.[23] In survivors, onset is often antenatal, but some milder cases have presented with motor difficulties in childhood.[25] Neonatal hypotonia with talipes and respiratory and feeding difficulties are common presenting symptoms. As more *SCN4A* cases are reported the phenotype has expanded to include a spectrum of autosomal dominant congenital myopathy and myotonia.[26,27] *CACNA1S* myopathy also ranges from mild to severe.[24] The severe phenotype consists of antenatal onset, a variable degree of polyhydramnios, reduced fetal movements, severe neonatal hypotonia and muscle weakness, and respiratory and feeding difficulties with later acquisition of contractures. Milder cases present with later-onset motor difficulties. Ophthalmoplegia is relatively common. The pattern of muscle weakness appears to be generalized including facial, axial, respiratory, bulbar, and limb muscles.[24,28]

Congenital myasthenic syndromes (CMS)

Congenital myasthenic syndrome (CMS) refers to a group of heterogeneous genetic disorders characterized by fatigable muscle weakness. Congenital myasthenia due to *SCN4A* mutations is rare,[29] and the cases reported often have additional episodic symptoms or fixed weakness suggesting coexisting disorders such as myotonia, myopathy, or periodic paralysis.[30-33] Described severity varies, but respiratory failure, bulbar symptoms, limb weakness, ptosis, and ophthalmoplegia are all reported. Repetitive nerve stimulation (RNS) at 3 Hz may be normal.[29] Even at 10 Hz, a decrement is often absent.[31,33] Response to pyridostigmine may be minimal or none,[29,31] which is not unexpected as the defect is downstream of the acetylcholine receptor. Overall, we feel this phenotype may be best viewed as part of a mixed spectrum of neuromuscular deficits as opposed to a "pure" myasthenic syndrome.

Assessment and diagnosis

Assessment of episodic symptoms, their triggering factors, and diurnal pattern alongside a family history is essential in the clinical history. Examination findings to specifically consider in the myotonic disorders include muscle hypertrophy, contractures, scoliosis, short stature, strabismus, dysmorphic features, and myotonia.[2] One should look for gait myotonia in the waiting room, toe walking, and eyelid and grip myotonia with either paradoxical worsening (repeat test three to five times) or warm-up. Examination is often unremarkable in the periodic paralyses unless seen during symptom onset. One should look for the dysmorphic features of ATS including short stature, micrognathia, clinodactyly, syndactyly, and low-set ears.[21] Signs of congenital myopathy and congenital myasthenia are more evident as described in clinical presentations, but there are currently no discerning features to indicate *SCN4A* or *CACNA1S* specifically as the causative gene.

Blood tests are aimed at excluding other causes of clinical symptoms, for example, renal disease causing potassium imbalance,[34,35] thyroid function to exclude thyrotoxic periodic paralysis[36] (very rare in children but treatable), alpha-glucosidase for Pompe disease[37] (may see florid myotonia on electromyography but usually absent clinical myotonia), acetylcholine receptor (including clustered assay), and MUSK antibodies for autoimmune myasthenia. Creatine kinase can be normal or elevated but is nonspecific.

Cardiac investigations

ATS is the only SMC to inherently affect cardiac muscle, given that the causative gene *KCNJ2* is expressed in both skeletal and cardiac muscle. An ECG can be useful in anyone suspected of having periodic paralysis as the dysmorphic features of ATS may be subtle and the diagnosis not initially considered. An ECG may demonstrate findings that are typical of ATS, for example, U waves, prolonged QT or QU intervals, or ventricular ectopy, including bigeminy and trigeminy, but it can also be within normal limits.[38] It should be noted that cardiac symptoms such as palpitations are often a poor indicator of cardiac disease in ATS. Patients may not report palpitations at all or describe only nonconcerning sounding events despite a corresponding prolonged ventricular tachycardia, (typically bidirectional but may be polymorphic), being seen on a cardiac Holter. False reassurance can be taken from patients who report being "asymptomatic," and we recommend a prolonged Holter be included in the routine investigation of anyone suspected of having ATS.[21,22] Unexplained syncope or documented sustained ventricular tachycardia are risk factors for life-threatening events.[22] Aside from an ECG, prolonged Holter monitoring is recommended at least yearly or sooner if new symptoms arise in anyone with a confirmed diagnosis of ATS.[21]

For patients with hypoPP and hyperPP presenting with flaccid paralysis associated with dyskalemia acute cardiac monitoring is needed for secondary rhythm disturbance until their potassium normalizes.

Neurophysiology

EMG will identify myotonia. A short exercise test may additionally help to differentiate myotonia due to different genotypes to some extent.[39] A positive long exercise test can indicate periodic paralysis, although it cannot indicate which subtype and cannot differentiate between primary or secondary causes.[40] A negative long exercise test can reduce the likelihood of periodic paralysis being the diagnosis; it does not fully exclude it, however, as negative tests are reported in a significant minority with a genetically confirmed diagnosis, reducing its sensitivity.[41] RNS performed in a weak muscle may demonstrate neuromuscular junction dysfunction but as *SCN4A* CMS is postsynaptic very-high-frequency stimulation (more than the standard 3 Hz) may be needed to demonstrate a decrement. Specialist neurophysiology can be painful (high frequency RNS) or prolonged (a long exercise test is approximately 50 minutes to complete). A child's ability to tolerate such investigations can be limited especially in the very young, although exercise tests can usually be performed in those aged older than five years. Specialist neurophysiology may also only be offered in tertiary centers, which can limit its practical utility, and genetic testing should not necessarily be deferred to wait for these tests.

Muscle biopsy

Biopsy is only indicated in cases of congenital myopathy, and no consistent diagnostic histologic features have been described.

Genetic tests

Genetic analysis is ultimately diagnostic. The exact testing available will differ geographically and in different health care systems. In the United Kingdom and European countries it is frequently offered as parallel sequencing of candidate genes via next-generation sequencing panels; this has significant advantages in reducing diagnostic times.[42] The newer phenotypes of congenital

TABLE 3.
Pharmacologic Treatment Options and Suggested Monitoring Regimes

Disorder	Medication	Suggested Dosing Regime*	Monitoring Requirements	Other Comments
NDM	Mexiletine	2-5 mg/kg in 2 or 3 divided doses Maximum 10 mg/kg	ECG, FBC, LFTs, clotting before starting ECG after each dose increment and yearly on stable regime	Those with MC may need higher doses than those with *SCN4A*-related myotonia Some children will find a BD regime more acceptable to avoid taking a lunchtime dose at school High-cost drug in the United Kingdom and Europe for those aged >18 years with NDM but license does not include pediatric population and generics can be prescribed
	Carbamazepine	Child 1 month-11 years Initially 5 mg/kg once daily, dose to be taken at night, alternatively initially 2.5 mg/kg twice daily, then increased in steps of 2.5-5 mg/kg every 3-7 days as required; maintenance 5 mg/kg 2-3 times a day, increased if necessary up to 20 mg/kg daily. Child 12-17 years Initially 100-200 mg 1-2 times a day, then increased to 200-400 mg 2-3 times a day, increased if necessary up to 1.8 g daily, dose should be increased slowly.	FBC and LFT before starting	May be easier to obtain than mexiletine and many pediatricians have more experience of using CBZ than mexiletine
	Lamotrigine	Child 2-11 years Initially 300 μg/kg daily in 1-2 divided doses, for 14 days, then 600 μg/kg daily in 1-2 divided doses, for further 14 days, then increased in steps of up to 600 μg/kg every 7-14 days; maintenance 1-10 mg/kg daily in 1-2 divided doses Child 12-17 years Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7-14 days; maintenance 100-200 mg daily in 1-2 divided doses		Little evidence or experience reported in children with NDM
SNEL	Mexiletine, carbamazepine, flecainide	As above	As above	Can result in almost complete cessation of apneic episodes and infants in ICU can be discharged Some *in vitro* evidence that flecainide may be the most efficacious treatment for this phenotype
Hypokalemic periodic paralysis	Acetazolamide	Child 1 month-11 years Initially 2.5 mg/kg 2-3 times a day, followed by maintenance 5-7 mg/kg 2-3 times a day; maximum 750 mg per day. Child 12-17 years 250 mg 2-4 times a day.	U+Es before starting and 7-10 days after repeat U+Es after each dose increment Renal USS before starting and yearly thereafter	
	Potassium-sparing diuretics, e.g., amiloride or spironolactone		U+Es before starting and 7-10 days after repeat U+Es after each dose increment	Caution with spironolactone in boys and avoid if prepubertal Recommend diuretics prescribed under care of expert services
	Potassium supplements	PRN at onset of attack Can be taken daily as a maintenance dose if attacks frequent		
Hyperkalemic periodic paralysis	Acetazolamide	Child 1 month-11 years Initially 2.5 mg/kg 2-3 times a day, followed by maintenance 5-7 mg/kg 2-3 times a day; maximum 750 mg per day. Child 12-17 years 250 mg 2-4 times a day.	U+Es before starting and 7 to 10 days after Repeat U+Es after each dose increment Renal USS before starting and yearly thereafter	
Potassium-wasting diuretics, e.g., bendroflumethiazide			U+Es before starting and 7 -10 days after repeat U+Es after each dose increment	Recommend diuretics prescribed under care of expert services
Salbutamol		PRN rescue medicine		We do not use routinely and limited report of efficacy but can be adjunctive especially if child takes incidentally for asthma
Andersen-Tawil syndrome	Acetazolamide		U+Es before starting and 7-10 days after repeat U+Es after each dose increment Renal USS before starting and yearly thereafter	Other meds dependent on nature of attacks of muscle weakness but the majority are of a hypoPP nature.

(*continued on next page*)

TABLE 3 (*continued*)

Disorder	Medication	Suggested Dosing Regime*	Monitoring Requirements	Other Comments
	Flecainide	Initial: 1-3 mg/kg/day divided every 8 hrs Maintenance: 3-6 mg/kg/day divided every 8 hrs	Holter monitor or event recorder before and after therapy initiation	Implantable devices—ICD may be required for unexplained syncope or ventricular tachycardia
Congenital myasthenia	Acetazolamide, pyridostigmine, fluoxetine, salbutamol			Limited report of cases and benefit for any of these treatments. Pyridostigmine generally not helpful in *SCN4A* cases and in other forms of CMS can be detrimental. In the case of *SCN4A* CMS acetazolamide may be the first choice but would recommend discussing treatment with experts.
Congenital myopathy	Acetazolamide		As above	Limited report of benefit and may be mutation specific

Abbreviations:
BD = Twice per day
CBZ = Carbamazepine
CMS = Congenital myasthenic syndromes
ECG = Electrocardiography
FBC = Full blood count
hypoPP = Hypokalemic periodic paralysis
ICD = Implantable cardioverter
ICU = Intensive care unit
LFT = Liver function tests
MC = Myotonia congenita
NDM = Nondystrophic myotonia
PRN = As required
SNEL = Severe neonatal episodic laryngospasm
U+E = Urea and electrolytes
USS = Ultrasound scan
* Doses given are a guide—always refer to prescribing information.

myopathy and myasthenia for which there are not yet many specific clinical clues are also more likely to be increasingly diagnosed by large umbrella panels, for example, for congenital myopathy. In myotonia cases we would highlight that myotonic dystrophy type 1 (DM1) is far more common than NDM and genetic testing for DM1 should always be considered in the differential diagnosis. It should be noted that some patients have "double trouble" carrying both a *DMPK* or *ZNF9* gene expansion associated with DM1 or 2 and an *SCN4A* or *CLCN-1* mutation4[43,44]; this often exacerbates myotonia, increasing the likelihood of them presenting to medical attention.

Treatment

No care recommendations or randomized controlled trial data exist for the treatment of children with muscle channelopathies. Treatment options are generally extrapolated from anecdotal case reports or evidence based in adult cohorts.[45-47] With a lack of published data the recommendations made here include our own clinical expertise and experience of treating children (Table 3). Where a mixed or overlapping clinical phenotype exists, a trial of different treatments may be indicated, for example, for periodic paralysis and myasthenia, which may then highlight the dominant cause of the symptoms as well as the most useful treatment (Table 3). No pharmacologic therapy is available for congenital myopathy with the exception of acetazolamide, which may have mutation-specific benefits.[48] Aside from pharmacologic options we would emphasize the benefits of holistic care.

Understanding what triggers symptoms for any individual can allow them to take some control over their illness and adjust lifestyle factors accordingly. As the child grows older they will also learn to make their own considered choices, for example, pizza may provoke symptoms of hypokalemic periodic paralysis. Rather than never eating pizza again they may choose to limit the intake to special occasions or for a weekend when they do not have the risk of missing school the next day. Physical activity or rest after activity is a common trigger.[49] Activity should still be encouraged, and children are able to take part in sports clubs, games, etc., but simple modifications can help. These modifications include warming up and warming down before and after activity and continuing to move at half-time, for example, walking or stepping on the spot. It can be extremely useful to have a physiotherapist work with the child to identify activities they enjoy and how to make any modifications so they may still take part without becoming frustrated or provoking symptoms. For those with hypoPP eating a banana before activity may prevent symptoms. High-carbohydrate snacks can help with hyperPP but should be taken sparingly as these tend to contain high sugar carrying a risk of obesity or tooth decay.

School

Educating teachers about the condition is essential, and reasonable adjustments at school can be requested. Guidance often includes being able to wear extra warm clothes, gloves, and hat if playing outside in the cold or allowing children to stay inside during breaks if very cold; extra breaks to reduce prolonged writing time in examinations or a scribe or typing; and allowing children to leave class early to have time to move to the next class without being rushed or pushed in a crowd. Sudden movement to correct position can provoke myotonia with resultant falls especially on stairs, so use of elevators is recommended, if available. Duplicate school books (one copy at home, one at school) should be provided to decrease the weight of the schoolbag. Frequent episodes of periodic paralyses can lead to significant absences and detrimentally affect school performance. Allowing children to come in later in the day after an attack has subsided or ensuring school work is sent home can help with this.

Peer support

Channelopathies are rare conditions. Peer support is often sought by families. We have found patient and family engagement days alongside charities very effective in facilitating these networks.

Anesthetic advice

There are minimal case reports of *CACNA1S* gene variants or patients with hypoPP associated with malignant hyperthermia syndrome (MHS),[50,51] and from these there is an extrapolated concern that MHS is a risk for any patient with SMC receiving anesthetic. This risk is poorly quantified, but it is recommended to avoid suxamethonium and depolarizing anesthetic agents for any patient with SMC.[52] For those with myotonic disorders depolarizing reagents can induce masseter spasms and stiffness of respiratory muscles, which can impair intubation and mechanical ventilation.[53] Generalized severe exacerbation of myotonia or a myotonic crisis can mimic MHS with generalized body stiffness and elevated creatine kinase.[54] Suxamethonium-induced hyperkalemia with arrhythmia can be a particular concern for those with hyperPP or PMC.[55]

For those with periodic paralysis, respiratory distress and generalized weakness may occur in the recovery room after surgery and general anesthesia. Maintaining a normal body temperature, keeping serum potassium in the normal range, avoiding hypoglycemia for hyperPP, and avoiding intravenous glucose for hypoPP will help to prevent such attacks.[56]

Emergency treatment

Those experiencing flaccid quadriparesis with hypoPP may attend the emergency department and require acute treatment for dyskalemia (Fig 2).

Cardiac management

Only ATS inherently affects the heart, but abnormal serum potassium levels in other forms of periodic paralysis can induce ECG changes, which may predispose to arrhythmia. Cardiac monitoring and potassium correction is required as for any cause of dyskalemia. Care must be taken that potassium replacement does not "overshoot" and cause hyperkalemia in those with hypoPP. During attacks of weakness potassium is held intracellularly causing low serum potassium but returns to the serum as an attack abates. If combined with potassium supplementation there is a risk of hyperkalemia and potassium monitoring should continue for some hours after normalization.[57] β-Blockers and flecainide are often required for arrhythmia management in ATS, but more severe ventricular tachyarrhythmias can occur necessitating an implantable cardioverter (ICD) insertion.[22,58]

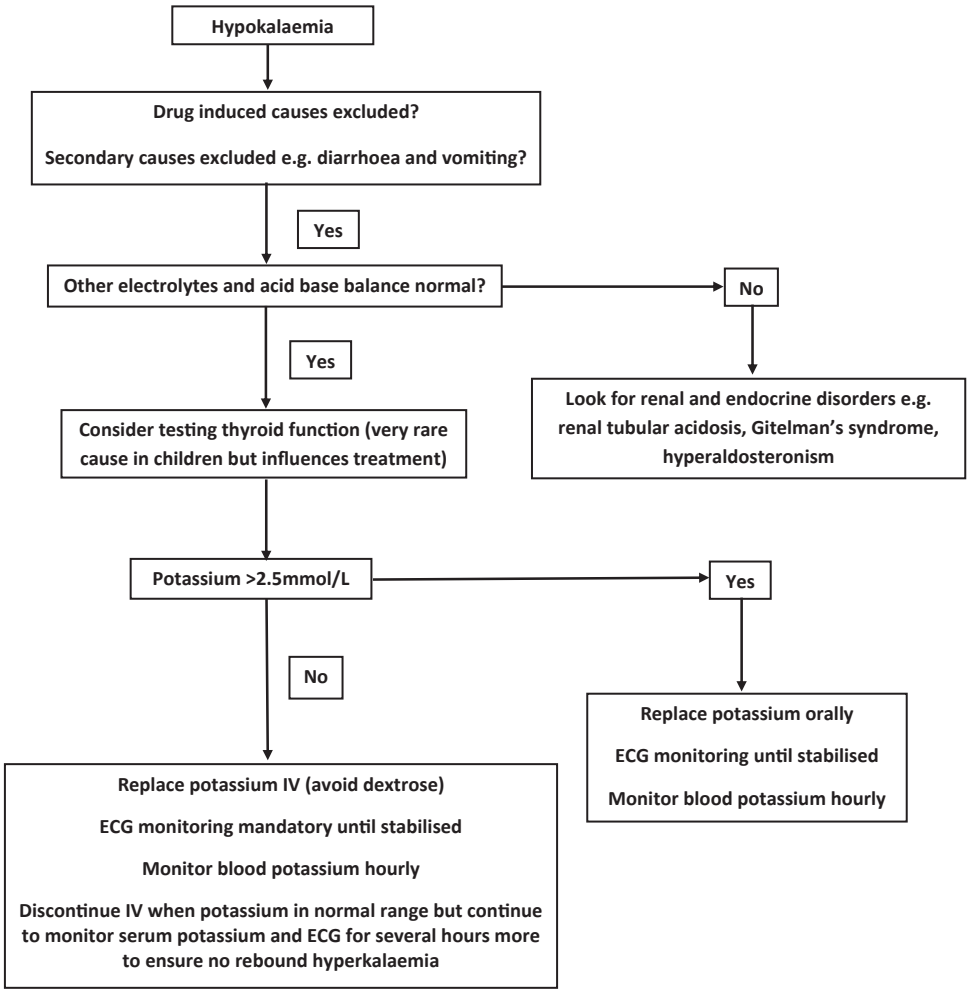

FIGURE 2. Flow chart for the emergency management of a child presenting with hypokalemia and flaccid paralysis.

Congenital myopathy and myasthenia

Children with congenital myopathy or myasthenia due to the channelopathy genes will benefit from the same multidisciplinary team approach including cardiorespiratory care, feeding abilities, therapies, orthotics, etc., as for any child with congenital myopathy or myasthenia. Pyridostigmine is usually unhelpful, but other specific medicines may be tried to support fatigable or episodic symptoms in the myasthenic cases (Table 3).

Prognosis

The vast majority of patients will have normal life expectancy, although life-threatening morbidity can occur in SNEL, congenital myopathy, congenital myasthenia, and ATS. Careful cardiac monitoring can allow for pre-emptive management and avoid cardiac complications in ATS. Life-threatening apneas in SNEL can be ameliorated with sodium channel blockers, and time to diagnosis may be improved with expanded access to genetic testing. Although not usually fatal, NDM and periodic paralysis may impact on every activity making daily life challenging. Symptomatic treatments can have dramatic benefit, but it is our experience that parents may decline treatment due to lack of conclusive data on the safety and efficacy of using these medicines to treat children with muscle channelopathies. The biggest cause of untreated morbidity, however, usually lies in delayed diagnosis.

Conclusions

Data are needed on the epidemiology and natural history of children living with SMC. The next-generation sequencing era is likely to facilitate better diagnosis and help to refine newly identified phenotypes. Evidence-based treatments in pediatric cohorts remain elusive and are urgently required if clinicians are to be able to offer optimal care. A future Delphi process focusing on pharmacologic treatment and management strategies, involving a larger group of expert clinicians, could be an interim way to proceed.

Declaration of Competing Interest

The authors declare no conflict of interest or financial disclosures concerning the materials or methods used in this study or the findings specified in this article.

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