



Skeletal Muscle Channelopathies

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Abstract

Skeletal muscle channelopathies are rare heterogeneous diseases with marked genotypic and phenotypic variability. These disorders cause lifetime disability and impact quality of life. Despite advances in understanding of the molecular pathology of these disorders, the diverse phenotypic manifestations remain a challenge in diagnosis, therapeutic, genetic counseling, and research planning. Electrodiagnostic testing is useful in directing the diagnosis, but has several limitations: patient discomfort, time consuming, and significant overlap of findings in muscle channelopathies. Although genetic testing is the gold standard in making a definitive diagnosis, a mutation might not be identified in many patients with a well-supported clinical diagnosis of periodic paralysis. In the recent past, there have been landmark clinical trials in non-dystrophic myotonia and periodic paralysis which are encouraging as they demonstrate the ability of robust clinical research consortia to conduct well-controlled trials of rare diseases.

Key Words Channelopathies · ion channel · non-dystrophic myotonia · periodic paralysis · electrophysiology

Introduction

Skeletal muscle ion channelopathies are rare heterogeneous disorders and are caused by mutations in genes encoding sodium channel (SCN4A), chloride channel (CLCN1), calcium channel (CACNA1S), or potassium channel (KCNJ2 and KCNJ18) [1–3]. They are characterized by episodic and fluctuating symptoms, exacerbation by environmental factors, and frequently autosomal dominant inheritance patterns. Symptoms are lifelong and impact quality of life. The diverse clinical manifestations remain a challenge in diagnosis and management. For instance, SCN4A mutations can cause various phenotypes such as paramyotonia congenita, sodium channel myotonia, hyperkalemic periodic paralysis, or hypokalemic periodic paralysis. Similarly, myotonic disorders can occur due to SCN4A or CLCN1 ion channel defects. Treatment options are also few and most of them are not FDA-approved. In this article, we review clinical features, diagnostic studies, pathophysiology, and treatment options in non-dystrophic myotonia and periodic paralyses.

Non-Dystrophic Myotonia

The non-dystrophic myotonias (NDM) include myotonia congenita, paramyotonia congenita, and sodium channel myotonias. Myotonia congenita is autosomal dominant or autosomal recessive, whereas paramyotonia congenita and sodium channel myotonias are autosomal dominant. These disorders are caused by mutations in the skeletal muscle chloride (CLCN1) and sodium (SCN4A) channels [4–11]. These are rare disorders, with a prevalence of < 1:100,000 [5, 9]. Patients typically present in the first two decades of life with muscle stiffness in the absence of severe fixed weakness or muscle wasting; this is in contrast to the dystrophic myotonias, such as myotonic dystrophies type 1 and type 2, which present with both progressive muscle weakness and multisystem involvement [2]. However, these myotonic dystrophies can also present with a pure myotonic phenotype that may be clinically indistinguishable from myotonia congenita [6]. Thus, in any young adult patient presenting with myotonia, DM1 and DM2 should always be considered. Clinical manifestations may range in severity from severe neonatal myotonia with respiratory compromise [12] to milder late-onset myotonic muscle stiffness. Symptoms of muscle stiffness are brought on by voluntary muscle contraction, leading to sustained bursts of action potentials originating from muscle fibers which persist for several seconds after motor neuron activity has ceased. This sustained activity causes an involuntary delay in the

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relaxation of muscle contraction, or myotonia. Patients describe this delayed relaxation as “stiffness” [4]. Patients may also report fatigue and pain associated with muscle stiffness. Symptoms may be worsened with pregnancy, cold temperatures, hunger, emotional stress, fatigue, and dietary potassium; some of these have traditionally been thought to help distinguish some of the NDM subtypes [13–16]. Symptoms of myotonia can be reduced with a variety of anti-epileptic, anesthetic, and anti-arrhythmic drugs. Co-existence of CLCN1 or SNC4A mutations with DM2 mutations has been reported in certain families. Patients with such dual mutations can have early-onset and more severe clinical and electrical myotonia [17–19]. Thus, DM2 patients with atypical presentation or severe myotonia should be screened for CLCN1 or SCN4A mutations.

Clinical Features

Myotonia Congenita Myotonia congenita (MC) is the most common skeletal muscle channelopathy and is caused by a mutation in the CLCN-1 gene encoding for the main skeletal muscle chloride channel CIC-1. Prevalence of MC varies by region between 0.2 and 7.3 per 100,000 [5, 20]. MC may be inherited as an autosomal dominant (Thomsen’s disease) or recessive (Becker’s disease) trait, with a more severe and earlier-onset phenotype in recessively inherited disease [1, 6, 21]. Myotonia typically presents in the first or second decades of life, and patients classically have a hypertrophic, muscular build with percussion myotonia on exam [22]. Clinical heterogeneity within a family is common. Patients are most symptomatic during rapid voluntary movements following a period of rest (action myotonia), and an improvement of myotonia with exercise is typically seen in MC. This improvement is referred to as “warm-up phenomenon” [23]. The most common site of stiffness is the legs, although the face is less commonly affected [24]. Patients with dominantly inherited MC (Thomsen’s disease) do not report muscle weakness, but patients with recessively inherited MC (Becker’s disease) can experience brief, transient weakness with the initiation of movement that improves with exercise [2]. This transient weakness is unique to MC and is distinct from the more prolonged post-exercise weakness that can occur with paramyotonia congenita (see next section) [25].

Paramyotonia Congenita Paramyotonia congenita (PMC) is autosomal dominant and is caused by missense mutations of the muscle sodium channel SCN4A gene on chromosome 17. Prevalence of PMC is ~1:250,000 [26]. PMC is allelic with other SNC4A disorders which include sodium channel myotonias, hyperkalemic periodic paralysis, and hypokalemic periodic paralysis (discussed separately); these disorders have

some characteristics in common, including the precipitation of symptoms by rest after exercise, fasting, and cold [26, 27]. In contrast to MC, myotonia in PMC worsens with sustained exercise. This is referred to as “paradoxical myotonia,” hence the term paramyotonia. Exercise-induced myotonia typically lasts for seconds to minutes following exercise. Facial stiffness and eye closure myotonia are more common in PMC than in other NDMs, and paradoxical eye closure myotonia is unique to PMC [24]. Patients with PMC may additionally describe prolonged muscle weakness following sustained exercise that can last from several hours to 2 days [28]. This is different from the transient weakness that can be seen in the recessive form of MC. Besides episodic weakness, PMC patients can also develop permanent weakness; however, this is not commonly seen [29, 30].

Sodium Channel Myotonias Sodium channel myotonias (SCMs) are autosomal dominant and typically present in the first decade of life. SCMs may also be referred to as the potassium-aggravated myotonias (PAM). Subtypes include acetazolamide-responsive myotonia (painful myotonia that responds remarkably to acetazolamide), myotonia fluctuans (markedly fluctuating myotonia that develops about 10–20 min after exercise), and myotonia permanens (severe persistent myotonia associated with a unique EMG pattern of persistent myotonic activity). Common to these variants is exacerbation by potassium and lack of cold sensitivity or weakness; however, pure myotonic syndromes that do have cold sensitivity have been linked to the SCN4A gene [13, 31–34]. The presence of warm-up phenomenon and variable cold sensitivity can make these patients difficult to distinguish from other NDM patients.

Pediatric Manifestations Although pediatric patients with NDM often share similar phenotypic features with adult patients, they may have additional symptoms; awareness and recognition of these can reduce delay in diagnosis and subsequently limit the physical and psychological impact on children. In the SCN4A patients, these symptoms include abnormal gait, leg cramps, eyelid or extraocular myotonia, strabismus, stridor, and choking episodes. Episodic neonatal and infantile laryngospasm in these patients occur rarely, but can be life-threatening and respond remarkably well to carbamazepine [35]. The CLCN1 patients may have a “funny gait,” frequent falls, and below average running compared to peers. NDM children can also have ankle contractures and rarely scoliosis. Neonatal hypotonia may be seen in SCN4A mutations that cause NDM and hyperkalemic periodic paralysis (HyperPP). Given this and the potential for respiratory/bulbar compromise in SCN4A patients, expectant mothers and obstetric physicians should be counseled to take appropriate precautions and to avoid unnecessary testing [36].

Diagnosis

Diagnosis of non-dystrophic myotonias is based on history of symptoms, exam findings of muscle hypertrophy, and clinical myotonia/paramyotonia described above, often a positive family history, electrodiagnostic testing, exclusion of other causes of myotonia such as myotonic dystrophy and Pompe disease, and genetic testing.

Creatine kinase can be normal to mildly elevated in patients with NDM. Thyroid function should be checked because hypothyroidism can cause clinical and electrical myotonia [37]. Electromyography is useful in confirming a myotonic disorder in that it reveals electrical myotonia in proximal and distal limb muscles [24].

The differential diagnosis of electrical myotonia is extensive and includes myotonic dystrophies, some of the distal myopathies, inflammatory myopathy, toxic myopathy, and Pompe disease [38, 39]. Notably, in these conditions, patients will have muscle weakness, atrophy, and markedly elevated CK.

The short exercise and long exercise tests have been used in further characterization of NDM. For the short exercise test, the patient is asked to perform maximum voluntary contraction for 5 to 10 s and compound muscle action potential (CMAP) is recorded immediately after exercise (e.g., stimulating the ulnar nerve at the wrist, recording over the abductor digiti minimi). Subsequently, CMAPs are recorded every 10 s up to 1 min after exercise. This test is repeated 3 times with 60 s in between trials. The short exercise test may help distinguish CLCN1 and SCN4A mutations via the following patterns:

- I. A reduction in CMAP amplitude, facilitated by repetition or cold. This can be seen in PMC.
- II. A transient drop in CMAP amplitude that rapidly returns to baseline. This can be seen in recessive MC.
- III. No change in CMAP amplitude. This can be seen in patients with dominant MC or SCM.

For the short exercise test, a CMAP amplitude reduction of > 10% is considered abnormal [40, 41].

For the long exercise test, patients are instructed to contract the abductor digiti minimi (usually alternating 15-s contractions with 3–4 s of rest) for up to 5 min against fixed resistance, and then CMAPs are recorded every 1 to 2 min for up to 50 min. For the long exercise test, the following patterns may be seen:

- I. A slight decrease in CMAP amplitude. This is seen with MC.
- II. A persistent CMAP amplitude decrement that starts immediately after exercise. This is seen with PMC.

For the long exercise test, a CMAP amplitude reduction of > 40% from the maximum CMAP during or after exercise is considered abnormal. Sensitivity of this test is 70% in diagnosing PP (discussed later) [40, 42, 43].

Limitations of electrodiagnostic testing include the following:

- Some CLCN1 mutations are associated with both dominant and recessive inheritance of MC.
- Certain SCN4A mutations can manifest either as SCM or PMC.
- Significant overlap may be seen with the short exercise test, suggesting that these patterns may not be sensitive or specific enough to make a definitive diagnosis based on electrodiagnostic testing alone.

MRI abnormalities have been noted in NDM patients. In a cohort of 21 genetically confirmed NDM patients, T1-weighted changes supportive of fatty infiltration were seen in almost half the patients. The fatty infiltration suggests that there is some amount of permanent muscle damage in NDM patients. STIR abnormalities, which include a unique “central stripe” and mild to extensive hyperintensity, were detected in the calves in 90% of the patients [44]. These abnormal findings suggest that MRI could potentially be used as a biomarker in treatment trials.

Over 100 CLCN1 mutations and over 30 SCN4A mutations have been identified [31, 45]. Genetic testing is the gold standard in making a definitive diagnosis of NDM, and this is commercially available.

Pathophysiology

The skeletal muscle channelopathies, including NDMs, are caused by alterations of the electrical excitability of the skeletal muscle fiber membrane.

CLCN1 Gene Mutations The chloride channel CLC-1 is a homodimer with each individual subunit forming a gated pore. The channel has two main gating modes referred to as the fast gate, which can operate the two pores independently, and the slow gate, which regulates the open probability of both pores simultaneously [46]. Under normal conditions, chloride accounts for 2/3 of muscle membrane conductance, and chloride conductance contributes significantly to repolarization of action potentials.

Bryant and colleagues demonstrated a greatly diminished sarcolemmal chloride conductance in affected muscle fibers from myotonic goats and this has been established as the basis for the enhanced muscle excitability in MC [47]. In the absence of the chloride conductance, the repolarizing influence of the chloride current is lost and the length constant of the sarcolemma is significantly increased allowing for summation

of electrical potentials [47]. Therefore, elevations of the potassium concentration in the T-tubular lumen during electrical activity cause a greater depolarized shift in the resting potential of the sarcolemmal membrane, which leads to muscle hyperexcitability and myotonic discharges [48].

The dominant forms of MC occur due to effects of the mutated subunit when dimerized with the wild-type (WT) subunit (dominant negative effect); this mutation causes a large shift in gating potential and prevents the chloride channels from opening when required in repolarization [49]. Recessive MC occurs due to homozygous or compound heterozygous loss of function mutations [49], and this loss of conductance leads to the accumulation of potassium ions and after depolarization bursts that manifest as myotonia [48].

Distinct allelic mutations in *CLCN1* have been identified in a large number of autosomal dominant and autosomal recessive myotonia cases [50, 51]. Notably, several *CLCN1* mutations have been reported to cause both autosomal dominant and autosomal recessive forms in different families [11, 52–55]. The exact mechanism by which mutations in the same gene cause both dominant and recessive diseases remains unclear.

SCN4A Gene Mutations *SCN4A* encodes the pore-forming α subunit of the sodium channel $\text{Na}_v1.4$, which consists of four domains, each with six transmembrane segments. In the 1980s, electrophysiological studies on human muscle revealed that chloride conductance was normal in patients with PMC and with hyperkalemic periodic paralysis (discussed later) [56, 57]. These patients had an anomalous persistent inward current that was blocked by tetrodotoxin, suggesting a voltage-gated sodium channel defect. Missense mutations in *SCN4A* that cause a variety of gating defects of the sodium channel are responsible for PMC, SCMs, and hyperkalemic periodic paralysis (discussed later) [58, 59]. The gating defects result in gain-of-function changes that increase Na^+ influx by disruption of fast inactivation of mutant $\text{Na}_v1.4$ channels, or enhancement of activation in some cases [60].

Therapeutic Options in NDM

There are no FDA-approved treatments for NDM at this time. NDM patients experience constant, lifelong symptoms and their impact on quality of life is comparable to that of some muscular dystrophies [61, 62]. A quarter of subjects in a natural history study of NDM were disabled or unemployed due to NDM [24]. Sodium channel blockers are effective in reducing myotonia by reducing sarcolemmal excitability, irrespective of the underlying channel defect, be it *CLCN1* or *SCN4A* [63]. This suggests that the effects may be due to modulation of normal sodium channels, rather than due to the effect on mutant channels. The sodium channel blockers are used off-label

and include anti-epileptics, anesthetics, and anti-arrhythmic drugs (Table 1).

Anecdotal data support the use of quinine [74], procainamide [74, 75], and phenytoin [75] in patients with myotonia. Additionally, there is evidence that the symptoms of autosomal recessive MC and PMC may be more effectively managed with class 1B anti-arrhythmics, tocainide (withdrawn from the market), or mexiletine [76, 77].

In a prospective multinational NDM study, about 40% patients were not on any anti-myotonic treatment [24]. Subsequently, a randomized double-blind placebo-controlled study was performed to study effects of mexiletine in NDM. Mexiletine 200 mg three times a day both significantly reduced stiffness and improved severity of graded myotonia on electromyography and quality of life measures [65]. However, 15% of the subjects experienced GI side effects and a third of the subjects had suboptimal or no response. Further, there is a black box warning regarding increased mortality in asymptomatic non-life-threatening ventricular arrhythmias in patients who had a myocardial infarction 6 days to 2 years prior. Due to this pro-arrhythmogenic potential, patients using mexiletine should have EKG monitoring.

Ranolazine, an anti-anginal drug, demonstrated anti-myotonic properties in a MC mouse model leading to a pilot study in NDM patients. It significantly improved self-reported severity of stiffness and weakness, reduced Timed Up and Go and grip times, and reduced myotonia during electromyography. Dosage was 500 mg twice a day and was further increased to 1000 mg twice a day. Larger studies are needed to confirm the benefits of treatment [66].

Lamotrigine, another sodium channel blocker, was found to have anti-myotonic properties at submaximal serum level concentrations [72]. In a recent double blind, placebo-controlled clinical trial in NDM, it effectively reduced myotonia and had a low frequency of side effects. It has been suggested that lamotrigine should now be considered for first line of treatment for myotonia in treatment-naïve NDM patients [73].

Periodic Paralysis

The primary periodic paralysis are autosomal dominant and include hyperkalemic periodic paralysis, hypokalemic periodic paralysis, and Andersen–Tawil syndrome [78]. These disorders are caused by mutations in sodium, calcium, and potassium channel genes that reduce muscle membrane excitability, leading to susceptibility to episodes of paralysis [63, 78]. Patients typically present with episodes of focal or generalized weakness that start in the first two decades of life [2, 79, 80]. Attacks are typically brought on by triggers which include diet or rest after exercise and are often associated with changes in extracellular potassium. Later in the disease

Table 1 Anti-myotonic drugs used to treat symptoms of NDM [64]

Anti-myotonic drugs	Dosage	Side effects	Monitoring
Mexiletine [65]	Start 150 mg BID with slow titration to 200–300 mg TID	GI distress, tremor, ataxia	LFTs, EKG
Ranolazine [66]	500–1000 mg BID	GI distress, dizziness, headache, prolonged QT interval, vasovagal syncope	Renal function periodically with creatinine clearance < 60 mL/min
Quinine [67]	200–1200 mg/day	Cardiac arrhythmias, hypersensitivity reactions, bone marrow suppression, liver damage, GI distress, visual disturbance	CBC with platelet count, LFTs, blood glucose, EKG, ophthalmologic evaluation
Procainamide [67, 68]	125–1000 mg/day	Rash, GI distress, positive ANA	EKG, creatinine, CBC, ANA
Phenytoin [67, 68]	300–400 mg/day	Gingival hypertrophy, agranulocytosis, pancytopenia, rash, cognitive impairment, liver damage	CBC, LFTs
Flecainide [69]	Start 100 mg/day, titrate to 100 mg BID	Cardiac arrhythmias, dizziness, rash	EKG, periodic drug serum concentrations
Carbamazepine [70]	20 mg/kg divided TID	Rash, agranulocytosis, pancytopenia, liver damage	LFTs, CBC, TSH
Acetazolamide [67, 71]	125 mg BID with slow titration to goal dose 250 mg TID	GI distress, electrolyte abnormalities (hypokalemia, hyponatremia), paresthesias, nephrolithiasis, rash, agranulocytosis	Serum electrolytes, LFTs, CBC
Lamotrigine [72, 73]	Start at 25 mg qday and titrate slowly to 300 mg qday	Headache, fatigue, and skin rash	LFTs, renal function as hepatic and renal impairment will drive dose reduction

ANA = antinuclear antibodies; BID = twice a day; CBC = complete blood count; GI = gastrointestinal; LFTs = liver function tests; NA = not applicable; TID = 3 times a day; TSH = thyroid-stimulating hormone

course, many patients will develop fixed proximal weakness [79, 81–85]. Attack frequency and severity can be reduced with carbonic anhydrase inhibitors.

Clinical Features

Hyperkalemic Periodic Paralysis Prevalence of HyperPP is less than 1:200,000 and is caused by mutations in the SCN4A gene on chromosome 17. HyperPP lies on one end of a spectrum of allelic SCN4A disorders which include paramyotonia congenital and sodium channel myotonia (see the “NDM” section). HyperPP typically presents in the first decade of life with transient episodic muscle paralysis. Attacks most commonly last 1 to 4 h and are triggered by fasting, rest after exercise, ingestion of potassium-rich foods, stress, and fatigue [79, 80]. Respiratory and cardiac muscles are typically spared; however, rarely during severe attacks, respiratory muscles may become involved. Strength is typically normal between attacks but many patients can develop fixed proximal weakness later in life. Electrical myotonia can be seen in the majority of patients [79, 86], but less than 20% will have clinical myotonia [86].

Hypokalemic Periodic Paralysis Hypokalemic periodic paralysis (HypoPP) is the most common PP and has a prevalence of ~0.13 per 100,000 [87]. It is caused by mutations involving mostly the muscle calcium (CACNA1S, chromosome 1) and less frequently the sodium (SCN4A, chromosome 17) channel

genes. HypoPP is characterized by episodic attacks of weakness associated with low serum potassium beginning in the first or second decade of life and without clinical or electrical myotonia. Patients experience attacks of flaccid paralysis that typically occur upon awakening in the night or in the early morning. The attacks can be of variable severity, ranging from mild weakness to profound paralysis, each lasting from hours to days [79]. Attack frequency can be daily or few episodes in a lifetime and typically reduces after age 40 [80]. Carbohydrate-rich foods, stress, alcohol, rest after exercise, menstruation, and certain medications (β agonists, insulin, and corticosteroids) can trigger attacks. Potassium levels can drop to < 3.0 mmol/L during attacks. Rarely, ocular, bulbar, and respiratory muscles can be involved in severe attacks. Although many attacks may be mild in nature, patients still experience significant lifetime morbidity due to the unpredictable and disabling nature of attacks, and variable degrees of fixed weakness that occur over time [81, 83].

Andersen–Tawil Syndrome Andersen–Tawil syndrome (ATS) is a rare autosomal dominant disorder with a prevalence of ~1:1,000,000 characterized by the clinical triad [88]:

- Episodic flaccid muscle weakness, in the setting of high, low, or normal potassium
- Ventricular arrhythmias and prolonged QT interval
- Dysmorphic features

Approximately 60% of ATS patients will have a mutation in a potassium inward rectifier *KCNJ2* on chromosome 17. Attacks of weakness usually start in the first or second decade of life; duration and frequency are variable and potassium levels are either low, high, or normal during attacks [80]. Characteristic physical features include short stature, low-set ears, hypertelorism, broad nasal bridge, micrognathia, clinodactyly, syndactyly, scoliosis, and toes joined at the base [88]. Cardiac manifestations consist of premature ventricular contractions, prominent u-wave, ventricular bigeminy, bidirectional ventricular tachycardia, and polymorphic ventricular tachyarrhythmia. Most cardiac arrhythmias will remain asymptomatic; however, some may experience palpitations or syncope or, very rarely, sudden cardiac death [89].

Thyrotoxic hypokalemic periodic paralysis (TPP) is characterized by episodes of weakness, hypokalemia, and thyrotoxicosis. These transient attacks resemble those of patients with familial hypokalemic periodic paralysis (hypoKPP) and resolve with treatment of the underlying hyperthyroidism. It is most prevalent in Asian and Latin American men. Approximately, a third of the patients will have a mutation in the *KCNJ18* gene which encodes an inwardly rectifying KCN channel Kir2.6 [90].

Diagnosis

Diagnosis of primary periodic paralysis is based on history of attacks of flaccid paralysis, positive family history, characteristic ictal changes in serum potassium (high or low), prolonged exercise test, and exclusion of secondary causes of hypokalemia and hyperkalemia. Thyroid testing should be performed to evaluate for thyrotoxicosis-related HypoPP. Of note, lack of family history should not preclude a diagnosis of periodic paralysis. Although genetic testing is the gold standard to confirm definite PP, significant number of patients will have no identifiable mutation.

During an acute attack, neurological examination will reveal flaccid paralysis and loss of muscle stretch reflexes in affected limbs. Ictal potassium will be low in primary HypoPP, often < 3.0 mmol/L; in HyperPP, elevations in potassium > 5 mmol/l or increases > 1.5 mmol/L are often seen. In about 50% cases of primary HyperPP, the potassium level will remain within normal range during an attack [86, 91]. In ATS, potassium can be low, high, or normal during attacks. It is important to always verify that the disorder is primary PP and not secondary to metabolic disorders resulting in low or high potassium and subsequent paralysis (Table 2). At the minimum, basic electrolyte studies and thyroid studies should be performed in all patients. Non-specific elevations in serum creatine kinase may be seen during attacks. Diagnosis of ATS can be made when an individual has two of the three cardinal features: PP, ventricular arrhythmia, or the dysmorphic features described above. However, not all features might be

Table 2 Conditions associated with secondary periodic paralysis [64]

Low potassium
Thyrotoxic
Primary hyperaldosteronism
Renal tubular acidosis
Juxtaglomerular apparatus hyperplasia
Gastrointestinal potassium wastage
Laxative abuse
Licorice
Corticosteroids
Potassium-depleting diuretics
High potassium
Addison's disease
Hypoaldosteronism
Potassium-sparing diuretics
Excessive potassium supplementation

present and so, ATS should also be suspected in isolated PP or polymorphic ventricular ectopy [89, 92, 93]. Muscle biopsies show non-specific myopathic changes. Vacuoles may be seen in HypoPP or HyperPP [79]. Tubular aggregates can be seen in HypoPP and ATS.

Electrodiagnostic testing is an important diagnostic tool in PP. On needle electromyography, myotonic discharges can be seen in HyperPP. The long exercise test is a sensitive test performed routinely prior to genetic testing. In this test, focal attack of weakness is induced by exercise of a single muscle. During testing, patients are instructed to contract the abductor digiti minimi muscle in an isometric fashion (usually alternating 15-s contractions with 3–4 s of rest) for up to 5 min against fixed resistance and then compound muscle action potentials (CMAPs) are recorded every 1 to 2 min for up to 1 h after exercise. Characteristic reduction in CMAP amplitude of $> 40\%$ from the maximum CMAP during or after exercise is considered abnormal. Sensitivity of this test is 70% in diagnosing PP [40, 42, 43].

Genetic testing is required for confirmation and will identify a mutation in ~60 to 70% of patients. Although a known pathogenic mutation is confirmatory, a variant of unknown significance should be interpreted with caution. In such cases, family members should be tested or functional testing of the variant should be performed to understand its significance.

Pathophysiology

In all forms of primary PP, there is aberrant depolarization which inactivates sodium channels and leads to muscle membrane inexcitability [94]. HyperPP, caused by missense mutations in the α pore-forming unit of the *SCN4A* gene, is unique in that it demonstrates both myotonia and paralysis in the same patient. Modeling studies have suggested that development of myotonia or paralysis depends on the extent of

persistent inward sodium currents [4]. Most mutations alter the rate of sodium channel inactivation, but mutations associated with HyperPP also result in incomplete inactivation and thus larger persistent inward depolarizing currents. When inward currents are large enough to shift the resting membrane to depolarized potentials, SCN4A channels switch to an inactive configuration subsequently leading to paralysis. The differences in clinical severity of attacks and triggers are dependent on the type of affected channel gene and the change in the mutant channel function.

Almost all mutations associated with HypoPP in both calcium and sodium channels occur at arginine residues in the fourth transmembrane (S4) segment of the voltage sensor domains [95]. More recent studies have shown that in response to changes in membrane potential, the S4 segment translocates through a crevasse, or “gating pore,” in the channel protein. In patients with HypoPP, mutations in the S4 region cause this “gating pore” to conduct ions at rest. Typically, this depolarizing gating pore current is small, but in low potassium conditions, the repolarizing potassium current becomes small and so the net balance may shift to depolarization. This causes the membrane to depolarize and sodium channels to switch to an inactive configuration—making the sarcolemma inexcitable. This anomalous gating pore current has been demonstrated in mouse models for both sodium and calcium channel HypoPP [96, 97].

The exact pathophysiological mechanism of ATS is not known. The potassium inward rectifier (Kir2.1) helps set the resting membrane potential in the skeletal and cardiac muscle, and contributes to the terminal repolarization phase of the cardiac action potential [88, 89]. Mutations are thought to result in sustained depolarization, leading to failure of action potential propagation and flaccid paralysis [88].

Therapeutic Options

A multipronged approach should be used in treating patients with primary PP. Importantly, lifestyle and behavioral modifications such as recognition and avoidance of triggers are crucial in reducing paralytic attacks. Patients with HypoPP benefit from smaller but frequent meals, low salt, and avoidance of large amounts of carbohydrates. In contrast, HyperPP patients benefit from carbohydrate snacks, but should avoid potassium-rich foods, fasting state, and medications that increase potassium (e.g., spironolactone). For all the periodic paralyses, mild exercise at the attack onset can help prevent a full-blown attack of paralysis.

Pharmacologic treatment comprises of abortive therapy and preventive therapy with a goal of reducing attack frequency and severity (Table 3). Treatment options are limited and dichlorphenamide is the only FDA-approved treatment for primary PP. For patients who cannot tolerate or do not respond to dichlorphenamide or acetazolamide, potassium-sparing

diuretics may prove useful for HypoPP. For HyperPP, hydrochlorothiazide may be effective.

Carbonic anhydrase inhibitors, acetazolamide and dichlorphenamide, have been used for decades to treat PP, but the mechanism of action is not well understood. They promote kaliuresis and increase urinary bicarbonate excretion thereby leading to metabolic acidosis which may reduce susceptibility to PP [98]. An alternative mechanism may be enhanced opening of calcium-activated K channels and the mild diuretic effects [99]. Common side effects of carbonic anhydrase inhibitors include paresthesias, fatigue, mild cognitive disturbance, and nephrolithiasis [100–102]. In a recent randomized placebo-controlled trial of dichlorphenamide in PP, the median attack rate was lower in HypoPP compared to that of placebo (0.3 vs 2.4, $p = 0.02$). It was found to be safe and also improved quality of life in HypoPP. In HyperPP, the attack rate was lower, but did not reach statistical significance (0.9 vs 4.8, $p = 0.10$). Dosage was 50 mg bid in treatment-naïve patients and the mean dose was 82 mg per day [100].

Management of HypoPP or ATS due to hypokalemia:

Abortive therapy: Potassium supplementation can be effective in treating acute attacks of paralysis; preferred route of administration is oral. Treatment options include the following [2, 81]:

- I. Oral potassium: 0.2 to 0.4 mEq/kg every 30 min not to exceed 200 to 250 mEq/day.
- II. Intravenous potassium: 40 mEq/L in 5% mannitol solution to run at a maximum of 20 mEq/h, not to exceed 200 to 250 mEq/day. Avoid potassium in glucose- and saline-containing solutions as this may worsen weakness [103]
- III. Arrhythmias have been reported in HypoPP and so cardiac monitoring is recommended during an acute paralytic attack as well as during treatment of hypokalemia [104].

Chronic therapy: Approximately, only 50% of genotyped patients with hypokalemic periodic paralysis respond to acetazolamide, most of whom have calcium channel mutations [105]. Exacerbation has been reported with acetazolamide in sodium channel mutations [106–108]. Treatment options include the following:

- I. Low sodium and low carbohydrate diet; daily slow release potassium salt
- II. Acetazolamide 125 to 1000 mg/day [109, 110]
- III. Dichlorphenamide 50 mg bid; maximum dosage 200 mg per day [100].
- IV. Potassium-sparing diuretics: triamterene 50 to 150 mg per day, spironolactone 25 to 100 mg per day, or eplerenone 50 to 100 mg per day [2, 111]. Eplerenone is preferred over spironolactone as the latter can cause gynecomastia.

Table 3 Treatment strategies for primary periodic paralyses [64]

Treatment	Hypokalemic periodic paralysis	Hyperkalemic periodic paralysis	Andersen-Tawil syndrome
Acute therapy			
Behavioral			
Oral potassium	Mild exercise at attack onset 0.2–0.4 mEq/kg every 30 min not to succeed 200–250 mEq per day	Mild exercise at attack onset Not indicated	Mild exercise at attack onset If potassium is low during attacks, 0.2–0.4 mEq/kg every 30 min not to succeed 200–250 mEq per day
Oral carbohydrate	Not indicated	Oral carbohydrate up to 2.0 g/kg	Not typically indicated
Intravenous potassium	Only if cannot take orally, 40 mEq/L in 5% mannitol solution to run at maximum of 20 mEq/h; not to exceed 200–250 mEq per day	Not indicated	If potassium is low during attack and cannot take orally, 40 mEq/L in 5% mannitol solution to run at maximum of 20 mEq/h not to exceed 200–250 mEq per day
β Agonist			
Intravenous calcium gluconate	Not indicated	1–2 puffs inhalation 0.1 mg salbutamol	Not typically indicated
Chronic therapy			
Diet			
Oral potassium	Low salt, low carbohydrate; avoid alcohol 10–20 mEq up to three times daily	Avoid potassium-rich foods Not indicated	If potassium is low during attacks: low salt; low carbohydrate; avoid alcohol If potassium is low during attacks, 10–20 mEq up to three times daily
Carbonic anhydrase inhibitor	Acetazolamide 125–1000 mg/day or dichlorophenamide 50–200 mg/day	Acetazolamide 125–1000 mg/day or dichlorophenamide 50–200 mg/day	Acetazolamide 125–1000 mg/day or dichlorophenamide 50–200 mg/day
Potassium-sparing diuretic	Triamterene 50–150 mg/day; spironolactone 25–100 mg/day; eplerenone 50–100 mg/day	Not indicated	If potassium is low during attack, triamterene 50–150 mg/day; spironolactone 25–100 mg/day; eplerenone 50–100 mg/day
Oral hydrochlorothiazide	Not indicated	25–50 mg/day—monitor potassium	Not typically indicated

Management of HyperPP or ATS due to hyperkalemia:

Abortive therapy: Usually mild exercise or oral carbohydrate snacks are enough to abort attacks. If attacks persist or are severe, inhaled β -agonist or intravenous calcium gluconate can be used. Salbutamol dosage is 1 to 2 puffs (0.1 mg) [112]. As in HypoPP, severe attacks requiring repeat interventions should be monitored on telemetry.

Chronic therapy: Treatment options include the following:

- I. Avoid potassium-rich foods; multiple carbohydrate snacks during the day
- II. Acetazolamide 125 to 1000 mg/day [109, 110]
- III. Dichlorphenamide 50 mg bid; maximum dosage 200 mg per day [100]
- IV. Hydrochlorothiazide 25 to 50 mg per day [113]

ATS requires a multidisciplinary approach to patient care with yearly follow-up with cardiology. Patients may require yearly Holter monitor evaluation, and if symptomatic arrhythmias develop, they may require implantable ICDs.

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