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Skeletal Muscle Channelopathies: New insights into the periodic paralyses and nondystrophic myotonias

Daniel Platt, B.S. and

Medical Student, University of Rochester School of Medicine and Dentistry

Robert Griggs, M.D.

University of Rochester School of Medicine and Dentistry Department of Neurology

Abstract

Purpose of Review—To summarize advances in our understanding of the clinical phenotypes, genetics, and molecular pathophysiology of the periodic paralyses, the nondystrophic myotonias, and other muscle channelopathies.

Recent findings—The number of pathogenic mutations causing periodic paralysis, nondystrophic myotonias, and ryanodinopathies continues to grow with the advent of exon hierarchy analysis strategies for genetic screening and better understanding and recognition of disease phenotypes. Recent studies have expanded and clarified the role of gating pore current in channelopathy pathogenesis. It has been shown that the gating pore current can account for the molecular and phenotypic pathology observed in the muscle sodium channelopathies, and, given that homologous residues are affected in mutations of calcium channels, it is possible that pore leak represents a pathomechanism applicable to many channel diseases. Improvements in treatment of the muscle channelopathies are on the horizon. A randomized controlled trial has been initiated for the study of mexiletine in nondystrophic myotonias. The class IC anti-arrhythmia drug flecainide has been shown to depress ventricular ectopy and improve exercise capacity in patients with Andersen-Tawil syndrome.

Summary—Recent studies have expanded our understanding of gating pore current as a disease-causing mechanism in the muscle channelopathies and have allowed new correlations to be drawn between disease genotype and phenotype.

Keywords

channelopathies; periodic paralysis; myotonia; ryanodine receptor

Introduction

Genetic defects in the genes encoding the calcium, sodium, chloride, and potassium channels in skeletal muscles result in: the periodic paralyses (PP), the nondystrophic myotonias (NDM), and the ryanodinopathies. PPses and NDMs were the first recognized channelopathies, and the group now includes myotonia congenita, paramyotonia congenita (PMC), potassium-aggravated myotonia (PAM), hyper and hypokalemic periodic paralysis (hyperPP and hypoPP), and Andersen-Tawil syndrome (ATS). The ryanodinopathies represent more recent discoveries and include malignant hyperthermia (MH), central core disease (CCD), some forms of multi-minicore disease (MmD), and centronuclear myopathy (CNM). We review new

findings relating to the clinical phenotype, genetics, and pathophysiology of the skeletal muscle channelopathies.

Nondystrophic Myotonias (NDM)

The NDMs are characterized by clinical/electrical myotonia, defined as the prolongation of skeletal muscle relaxation time following sudden voluntary contraction or external mechanical stimulation. In these diseases a defect in muscle ion channel function leads to hyperexcitability. The nondystrophic myotonias have overlapping phenotypes and seldom cause progressive muscle wasting. The NDMs are divided into two groups: the chloride channelopathies, including the dominant and recessive forms of myotonia congenita, and the sodium channelopathies, including paramyotonia congenita and the potassium-aggravated myotonias.

Myotonia Congenita (MC)

MC is the most common skeletal muscle channelopathy and is caused by mutations in the skeletal muscle voltage-gated chloride channel gene, *CLCN1* (chromosome 7q), which encodes the chloride channel protein, ClC-1 (1). Normal muscle requires a high resting chloride conductance for fast repolarization of the t-tubules and stabilization of the electrical excitability of the muscle membrane (2). In MC, mutations cause a reduction in chloride current that results in repetitive depolarization of the muscle fibers.

MC exists in two forms: autosomal dominant (Thomsen), and autosomal recessive (Becker) (3). Both types show a remarkable degree of phenotypic and genotypic variability, such that more than eighty different mutations have been recognized, including several new ones in the past year (4-7). Interestingly, certain mutations occur in both the dominant and recessive forms of MC (4). Moreover, different mutations at the same gene locus can also cause both forms of the disease. One theory to explain this observation suggests that dominant mutations may affect the common outflow chloride channel, whereas recessive mutations may involve two faster flow entry gates; dominant mutations would therefore affect the most important function of the channel, while recessive mutations would alter secondary channel function and would thus require two inherited mutations to cause disease (8).

Thomsen's disease is characterized by early onset, mild to moderate myotonia, and muscle hypertrophy (9). The muscle stiffness is generally painless and transient. Becker's disease is characterized by later onset, moderate to severe myotonia with transient weakness, moderate muscle hypertrophy (especially of the lower extremity), and in some cases by progressive muscle weakness and wasting (9,10). This recessive form of MC is more common and more insidious. Both forms of MC exhibit the warm-up phenomenon, where myotonia diminishes with repetitive muscle contractions. A recent study used trunk sway analysis to quantify the warm-up phenomenon and suggests its potential use as a clinical endpoint for future trials (11).

Both forms of MC are more severe in men than in women, and the Thomsen's variant often worsens during pregnancy. Fialho et al. found that both testosterone and progesterone reversibly inhibit skeletal muscle chloride channels expressed in *Xenopus* oocytes, suggesting that hormonal regulation of chloride current may worsen myotonia in certain individuals (12). It is not clear, however, whether the hormones have an effect at physiologically relevant concentrations.

Paramyotonia congenita and potassium-aggravated myotonias

Missense mutations of the skeletal muscle voltage-gated sodium channel gene, *SCN4A*, produce a spectrum of disorders characterized by myotonia and periodic paralysis. The range of phenotypes includes those with myotonia only (PAMs), myotonia plus periodic paralysis

(PMC and HyperPP), or solely periodic paralysis (hypokalemic periodic paralysis type 2 [HypoPP2]). Several new mutations in the sodium channel gene that produce distinctive phenotypes have recently been reported (13-16).

Paramyotonia congenita (PMC) (Eulenburg's disease) is an autosomal dominant inherited disease whose predominant feature is an episodic cold- or exercise-induced muscle myotonia in exposed areas (mainly the face, neck, and hands) that lasts for minutes to hours (10). The myotonia is denoted as "paradoxical" because the stiffness worsens rather than improves with repeated muscle contractions (17). The disease may also progress later in life, with stiffness giving way to flaccid paralysis and weakness in exposed or exercised muscles (18).

The potassium-aggravated myotonias (PAMs) include three diseases with very similar phenotypes: myotonia fluctuans, myotonia permanens, and acetazolamide-sensitive myotonia. These disorders differ from the other nondystrophic myotonias in that: (1) the myotonia is exacerbated by potassium ingestion; (2) the myotonia does not worsen with cold exposure; and (3) there is no major weakness (10,19).

Periodic Paralysis (PPses)

The primary PPses are autosomal-dominant disorders of skeletal muscle sodium, potassium, and calcium channel genes. They are characterized by episodes of muscle weakness associated with variations in serum potassium concentration.

Hyperkalemic periodic paralysis

HyperPP and PMC have overlapping phenotypes and are both caused by gain-of-function mutations in the α -subunit of the skeletal muscle voltage-gated sodium channel, Nav1.4 (20). HyperPP is characterized by attacks of flaccid limb paralysis or, rarely, weakness of the eye and throat muscles. Triggers for these attacks include ingestion of potassium-rich food, rest after strenuous exercise, and cold exposure. Episodes of weakness may last for up to an hour and disappear as the blood potassium concentration decreases due to elimination by the kidney and reuptake by muscle cells. Overcompensation by these mechanisms may cause transient hypokalemia at the end of an attack, which can lead to misdiagnosis (21). Attacks typically begin in the first decade of life, increase in frequency and severity during puberty, and then decrease in frequency after 40 years of age. Older individuals may develop permanent weakness, which might be related to the number or severity of prior attacks (21,22). Myotonia of the facial or hand muscles supports the diagnosis of HyperPP. The T704M and M1592V mutations in the SCN4A gene account for the majority of cases (23).

Some patients with periodic paralysis have serum potassium levels in the normal physiological range during attacks of weakness, which initially suggested to researchers the existence of an intermediate disease, normokalemic periodic paralysis (NormoPP) (24,25). However, a number of the families diagnosed as NormoPP were subsequently found to have HyperPP mutations (26), and those with the T704M mutation showed increased blood potassium concentration during attacks in 50% of cases (27). Thus, NormoPP may simply be a phenotypic variant of HyperPP. A recent study by Vicart et al., however, reported 4 families with unique mutations of the R3 gating charge in the voltage sensor of domain 2 of the Nav1.4 channel. Patients from these families were normokalemic, but some had phenotypes similar to HypoPP, whereas others had paralysis induced by potassium supplement as in HyperPP (28).

Hypokalemic periodic paralysis

HypoPP is caused by mutations in both the α -subunit of the Nav1.4 channel and the homologous α 1-subunit of the skeletal muscle calcium channel, Cav1.1. Missense mutations were first identified in the calcium channel gene, CACNA1S (HypoPP1), which accounts for

approximately 60% of cases (29-31). Later, it was found that about 10% of cases were due to mutations in the sodium channel gene, SCN4A (HypoPP2) (32-34). In general, HypoPP is characterized by reversible attacks of muscle weakness concomitant with decreased blood potassium concentrations. The attacks may be triggered by rest after strenuous exercise, by a meal rich in carbohydrates, or by exposure to cold. Patients typically wake up paralyzed, and attacks usually last several hours to days. Some older HypoPP patients develop progressive, persistent weakness that takes the form of a proximal myopathy. Phenotypic differences between HypoPP1 (calcium channel) and HypoPP2 (sodium channel) include: (1) earlier onset of disease in HypoPP1; (2) myalgias in HypoPP2; (3) on muscle biopsy, predominance of tubular aggregates in HypoPP2 and vacuoles in HypoPP1; and (4) aggravation of HypoPP2 by acetazolamide (31).

Andersen-Tawil syndrome

The majority of ATS patients have loss-of-function mutations in the KCNJ2 gene, which encodes the voltage-gated inward rectifier potassium channel, Kir2.1 (35). This channel is abundantly expressed in excitable tissues throughout the body, and channel dysfunction thus produces a unique phenotype consisting of periodic paralysis, cardiac arrhythmias, and facial and skeletal malformations (36). Paralysis occurs in the setting of either hyperkalemia or hypokalemia, which can both exacerbate the underlying cardiac arrhythmia. Heart manifestations include ventricular arrhythmia (84% of patients), long QT syndrome (50% of patients), abnormal TU wave patterns (73%), and sudden cardiac arrest (10% of patients) (37,38). A characteristic rhythm disturbance present only in ATS, digitalis intoxication, and ryanodine receptor mutations is bidirectional ventricular tachycardia (BVT) (36). The mechanisms of BVT and the abnormal U wave have recently been elucidated in a canine tissue model of ATS (39).

The distinctive physical features considered characteristic of ATS are: broad forehead, hypoplastic mandible, hypotelorism, low-set ears, digit clinodactyly, and 2-3 syndactyly of the toes (36). Many other features have been described, and it is obvious that the disease has a high degree of phenotypic heterogeneity.

Ryanodinopathies

The ryanodinopathies are congenital muscle disorders caused by defects of the skeletal muscle sarcoplasmic reticulum calcium release channel, the ryanodine receptor (RyR1). Normal muscle function depends on the interaction between the dihydropyridine receptor (voltage-dependent calcium channel, Cav1.1) and the ryanodine receptor, which together couple membrane depolarization to calcium release and subsequent muscle contraction. Dysfunction of RyR1 results in several distinct pathologies, including malignant hyperthermia (MH), central core disease (CCD), some forms of multi-minicore disease (MmD), and centronuclear myopathy (CNM). In this review, only the most common diseases, MH and CCD, will be discussed.

Malignant Hyperthermia (MH)

MH is a potentially lethal disorder in which the administration of certain pharmacological agents, particularly volatile anesthetics and depolarizing muscle relaxants, causes uncontrollable skeletal muscle hypermetabolism. Mutations in RyR1 create hypersensitive channels that allow calcium to leave the sarcoplasmic stores and enter the myoplasm. This calcium efflux leads to muscle contracture, generalized rigidity, and an increase in body temperature. Excess muscle activity depletes ATP and upregulates glycogenolysis, producing lactic acid and a metabolic acidosis. High oxygen consumption and carbon dioxide production lead to hypoxemia and hypercapnia. If the treatment, dantrolene, is not rapidly administered,

patients may develop rhabdomyolysis with subsequent hyperkalemia and renal failure or cardiac arrest (40).

A small number of MH cases are caused by mutations in *CACNA1S*, the gene that encodes the voltage-gated skeletal muscle calcium channel (41). Mutations affecting the voltage sensor of this channel cause HypoPP1, whereas mutations in the myoplasmic loop connecting domains 3 and 4 can give rise to MH (40).

Central Core Disease (CCD)

CCD is characterized by cores that run the length of the muscle fiber and lack mitochondria and oxidative enzymes, with degradation of the contractile apparatus and loss of myofibrillar structure. Patients have muscle hypotonia and proximal > distal weakness. Most patients with CCD carry an autosomal dominant inherited mutation in the hydrophobic pore-forming region of RyR1 (42). There are two hypotheses to explain the functional effect of CCD mutations: the leaky channel theory and the E—C uncoupling theory. The leaky channel hypothesis suggests that defective channels allow calcium to continually leak out of the sarcoplasmic reticulum, so that less calcium is available for muscle contraction (43). The E—C uncoupling theory, on the other hand, posits that mutant channels are functionally uncoupled from sarcolemmal depolarization, so that there is only minimal calcium release in response to any action potential (44). Both mechanisms could account for the characteristic weakness seen in CCD.

Pathophysiology

Over the past several years, research into the pathophysiology of the skeletal muscle channelopathies has led to a better understanding of skeletal muscle and channel function.

Chloride Channel

In normal muscle, a high sarcolemmal chloride conductance sets the resting potential of the muscle fiber close to the chloride reversal potential, which allows for rapid repolarization of the t-tubules following an action potential. The skeletal muscle chloride channel, *ClC-1*, also stabilizes and regulates the electrical excitability of the muscle membrane. In MC, mutations in the chloride channel decrease the chloride current at the physiological range and destabilize the muscle membrane, predisposing it to the hyperexcitability created by the accumulation of potassium in the t-tubules. Though potassium is normally present in the t-tubular lumen after an action potential, repetitive depolarization of the sarcolemma (myotonia) only occurs when the chloride current cannot adequately buffer the cation load (40).

Most human chloride channels are double-barrelled homodimers with two independent fast-opening pores and one common slow-opening gate shared between the subunits (45). Recessive mutations (Becker) are thought to affect the fast opening mechanism of each channel, such that both subunits have decreased function and the total chloride flux is only about 30% of normal (46,47). Dominant mutations (Thomsen) exert a dominant negative effect on the other, normal subunit, which shifts the activation threshold of the channel toward more positive potentials (48). It is thought that the dominant mutations may affect the common slow-opening gate (46). A recent paper demonstrated a dosage effect of the dominantly inherited T310M mutation, where a young patient with 2 copies of the mutant allele displayed a strikingly severe phenotype, while his parents and siblings with 1 copy had only slight myotonia on EMG (9).

Various effects of the nonsense and missense mutations in *CLCN1* have been reported, including alternative protein splicing, premature truncation and degradation, altered selectivity, and defective endoplasmic reticulum export (3,49-51). Interestingly, Wheeler et al. have showed that correcting *ClC-1* splicing can eliminate the myotonia in the myotonic dystrophy

mouse (52). Furthermore, it is possible that pharmacological chaperones may be able to repair folding defects, as in cystic fibrosis (53).

Sodium Channel

The voltage-gated sodium channel, Nav1.4, generates the action potentials that initiate muscle contraction in response to nerve stimulation. Immediately after the action potential, the channels undergo fast inactivation to prevent repetitive discharge. Mutations in SCN4A result in multiple defects in channel gating and produce different disease phenotypes depending on the location of the mutation. Sodium channelopathies characterized primarily by myotonia, such as PMC and the PAMs, have altered channel gating that causes slowed or incomplete inactivation, or enhanced activation (20,40,54). Furthermore, the worsening of myotonia in response to low temperatures may result from cold-induced disruption of sodium channel slow inactivation (55,56). The net effect of these disturbances is an increase in sodium entry into the cell, which prolongs the action potential duration and encourages persistent depolarization of muscle fibers (myotonia). These mutations are known as gain-of-function because they promote increased cell excitability.

The sodium channelopathies characterized predominantly by PP, namely HyperPP and HypoPP2, produce weakness by two different mechanisms. In HyperPP, as in the closely related disease PMC, failure of the inactivation process results in continual sodium influx and cell depolarization; however, stronger depolarization in HyperPP leads to general inactivation of sodium channels and depolarization block, which manifests as paralysis (21). Therefore, myotonia and paralysis, though clinically opposite, stem from the same pathomechanism. Serum potassium is increased in HyperPP because the sustained membrane depolarization amplifies potassium efflux from muscle, and because sodium influx into muscle draws water into the cells, which elevates potassium concentration and serum osmolality (41).

In HypoPP2, on the other hand, sodium channel mutations cause a loss-of-function by enhancing channel inactivation, mainly by stabilizing the inactivated state (57). Mutations specifically target positively-charged arginine residues in the S4 voltage sensor in domains II or III (29,58,59), which triggers voltage sensor dysfunction. Recently, however, several researchers have suggested a new pathomechanism to explain HypoPP2. Sokolov et al. first showed that three common HypoPP2 mutations induced a hyperpolarization-activated cationic leak through the voltage sensor of the sodium channel, which they called 'gating pore current' (60). According to their model, HypoPP2 mutations are essentially gain-of-function because the cation leak increases resting membrane conductance and sodium influx, leading to excessive depolarization. This hypothesis was amended by Struyk and Cannon, who found that the gating pore permitted transmembrane permeation of protons but not larger cations (61). The predicted magnitude of this leak was not large enough to produce aberrant depolarization by itself, but the authors theorized that sustained proton leak could indirectly contribute to instability of the resting membrane potential by interfering with pH balance inside the cell (61). More cation selective and proton selective gating pore currents have since been described (62).

Mutations in Nav1.4 also cause the periodic paralysis variant known as NormoPP. Sokolov et al. recently investigated 3 unique NormoPP mutations in the R3 gating charge and found gating pore current that was activated by depolarization, which would lead to abnormal persistent sodium influx and depolarization of the muscle fiber. The authors also hypothesized that sodium overload is the main pathogenic factor in both HypoPP and NormoPP, either by increased sodium influx through hyperactivation of the sodium-proton pump or by direct entry of sodium through the gating pore (63). They maintain that the gating pore current theory can account for all aspects of the pathophysiology of these two diseases (63).

Calcium and potassium channels

In normal muscle, the calcium channel, Cav1.1, initiates excitation-contraction coupling in response to depolarization. Mutations in Cav1.1 upset this mechanism and cause a muscle paralysis syndrome with progressive myopathy, HypoPP1. As in HypoPP2, the mutations replace arginine residues in the S4 voltage sensor in domains II, III, or IV with neutral amino acids (58,64). A widespread hypothesis suggests that the pathological effect of these mutations is caused by voltage sensor dysfunction and impaired channel gating; however, this theory does not account for the sarcolemmal depolarization or the hypokalemia that characterize the disorder. Kuzmenkin et al. showed that HypoPP1 mutants stabilize the second open state of the calcium channel and proposed that the low selectivity of the channel in this state would allow monovalent ions to pass into the cell and promote depolarization (58). In opposition to this theory is the discovery of gating pore current in the sodium channel, which lends credence to the idea that a similar structural defect in Cav1.1 may underlie HypoPP1 pathogenesis. This hypothesis could account for the common downstream phenotype of the periodic paralyses, but there is currently no evidence to support it. The gating pore current hypothesis would also explain the susceptibility of patients to hypokalemia: the leak sensitizes myofibers to reduced serum potassium, which results in a paradoxical membrane depolarization due to the low potassium (65). Essentially, the reduced serum potassium sets a new resting potential at -60 mV, and the cation leak increases action potential generation from this level, resulting in weakness and paralysis.

Potassium channels differ from other cation channels in that they are comprised of homo or heteromultimers of α -subunits, rather than being made up of one large monomeric protein. In normal heart and skeletal muscle, the inwardly rectifying potassium channel, Kir2.1, stabilizes the resting membrane potential and regulates action potential duration, especially in myocytes (66). Mutations in the KCNJ2 gene cause ATS by suppression of outward potassium currents and/or enhancement of inward currents, which can occur by dominant negative effects or haploinsufficiency (36). Many cellular modulators affect potassium channel activity and are necessary for proper channel function; the loss-of-function mutations in ATS have been linked to decreased PIP₂ sensitivity and an exaggerated inhibitory effect of intracellular Mg²⁺ (67, 68). Another possible pathological mechanism involves dysfunction of a portion of the channel known as the slide helix, which represents a cluster point for ATS mutations (69). It is thought that interaction of the slide helix with the C-terminus may be required for normal gating of the Kir2 family of channels (69).

Diagnosis and Treatment

Improvements in genetic testing and redefinition of the clinical phenotypes of the skeletal muscle channelopathies have led to earlier and more accurate diagnosis of these diseases. Some recent studies suggest new treatments for certain channelopathies.

Nondystrophic myotonias

Diagnosis of the NDMs is based primarily on clinical history, physical examination, and DNA studies. A recent study sought to redefine the phenotypic characteristics of these diseases in order to improve differentiation between chloride and sodium channelopathies. The authors discovered that MC patients reported a higher frequency of muscle weakness, the warm-up phenomenon, and difficulties in running or climbing stairs, while patients with sodium channelopathies reported an earlier onset, paradoxical, and painful myotonia (70). The authors found a higher incidence of leg myotonia for MC and of eyelid myotonia for the other NDMs (70). A further aid to diagnosis has been electromyography based on short and long exercise tests and cooling protocols (14,71). Additionally, Weber et al. have pioneered the use of MRI

to measure changes in intra-muscular sodium concentration and have recorded differences between each of the sodium channel nondystrophic myotonias (72,73).

A number of mutational hotspots have been recognized for the nondystrophic myotonias. Sodium channel paramyotonia congenita shows genetic clustering of mutations in exons 22 and 24 of the SCN4A gene (16), while mutations causing the dominant form of myotonia congenita were recently found to cluster in exon 8 of the CLCN1 gene (74).

Agents that reduce sodium channel opening frequency or duration tend to be the most effective therapies for alleviating myotonia. The anticonvulsants phenytoin and carbamazepine have shown some efficacy in these diseases, as have several classes of anti-arrhythmic drugs, notably those of class IB (mexiletine, tocainide) and class IC (flecainide, propafenone) (75). A recent Cochrane review highlights the lack of sufficient randomized controlled trials of treatments for the nondystrophic myotonias (76). A controlled trial of mexiletine versus placebo started in late 2008 (clinicaltrials.gov).

Periodic paralyses

Diagnosis of the PPs is based on clinical findings, neurophysiology studies, and genetic testing. The history and serum potassium level during attacks often differentiate these diseases. It is also important to rule out thyrotoxic hypokalemic periodic paralysis. Other tests that may aid in diagnosis include an ECG, nerve-conduction studies, needle electromyography (71), and long exercise testing (McManis test). Genetic testing should focus on the common sites of mutations in SCN4A and CACNA1S, such as the voltage sensor residues in HypoPP1 and HypoPP2, and the T704M and M1592V mutations in HyperPP.

The first step in treatment should be to counsel the patient on avoiding known triggers, such as strenuous exercise, cold exposure, or certain foods. Pharmacologic therapies can be separated into two categories, treatments used for acute attacks and prophylactic treatments. In HyperPP, acute attacks may respond to inhaled salbutamol or glucose/insulin therapy, whereas in HypoPP, acute attacks are usually treated with oral potassium chloride (75). The most effective medications for the prevention of attacks in both disorders are the carbonic anhydrase inhibitors, particularly acetazolamide and dichlorphenamide. These drugs may ameliorate paralysis by opening muscular calcium-activated potassium channels (77), or by intracellular acidification and the stabilization of serum potassium levels (78). Acetazolamide has also recently been shown to prevent vacuolar myopathy in the skeletal muscle of potassium depleted rats, which implies that it may avert the progressive myopathy seen in HypoPP (79). A Cochrane review of treatment in the PPs lists only three studies that meet its inclusion criteria, including a randomized trial showing the efficacy of dichlorphenamide in both HypoPP and HyperPP (80).

Andersen-Tawil syndrome

Diagnosis of ATS is based on clinical history, physical examination, ECG, and genetic testing. Cardiac involvement in ATS manifests as long QT interval, TU complex formed by prominent U waves, and ventricular arrhythmias, including the otherwise rare bidirectional ventricular tachycardia (BVT) and torsades de pointes (39). The McManis test and the long exercise nerve conduction study may be helpful in confirming the presence of periodic paralysis (36). ATS should always be considered in the differential diagnosis of a patient with periodic paralysis because facial features may be subtle and cardiac symptoms are not always present, despite an abnormal ECG. Ultimately, confirmation of the diagnosis requires genetic testing for KCNJ2 mutations, which are present in 80%-90% of patients (36).

The necessity of treating two distinct excitable tissues, skeletal muscle and cardiac muscle, complicates the treatment of ATS. For the periodic paralysis, therapy involves minimizing known triggers and prophylaxis against recurrent attacks with the carbonic anhydrase inhibitors. Potassium supplementation may also prevent paralytic attacks while simultaneously shortening the QT interval and lessening arrhythmogenicity. Treatment for the cardiac symptoms of ATS is based on anecdotal evidence supporting the use of β -blockers or calcium-channel blockers (81,82). Recent evidence has shown flecainide to be particularly successful in the treatment of BVT, ventricular ectopy, and tachycardia-induced cardiomyopathy in ATS (83-85).

Conclusion

Recent research into the pathomechanisms of the skeletal muscle channelopathies and the role played by gating pore current may lead to novel therapeutic targets for these rare diseases. Improvements in clinical testing, recognition of disease phenotypes, and genetic screening should improve diagnostic capabilities and patient access to appropriate treatments. Randomized clinical trials of pharmacological agents are necessary and should be easier to obtain as more patients are identified and included in shared international patient databases, such as the CINCH group.

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