

REVIEW ARTICLE

The primary periodic paralyses: diagnosis, pathogenesis and treatment

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Periodic paralyses (PPs) are rare inherited channelopathies that manifest as abnormal, often potassium (K)-sensitive, muscle membrane excitability leading to episodic flaccid paralysis. Hypokalaemic (HypoPP) and hyperkalaemic PP and Andersen-Tawil syndrome are genetically heterogeneous. Over the past decade mutations in genes encoding three ion channels, *CACN1A5*, *SCN4A* and *KCNJ2*, have been identified and account for at least 70% of the identified cases of PP and several allelic disorders. No prospective clinical studies have followed sufficiently large cohorts with characterized molecular lesions to draw precise conclusions. We summarize current knowledge of the clinical diagnosis, molecular genetics, genotype–phenotype correlations, pathophysiology and treatment in the PPs. We focus on unresolved issues including (i) Are there additional ion channel defects in cases without defined mutations? (ii) What is the mechanism for depolarization-induced weakness in Hypo PP? and finally (iii) Will detailed electrophysiological studies be able to correctly identify specific channel mutations? Understanding the pathophysiology of the potassium-sensitive PPs ought to reduce genetic complexity, allow subjects to be stratified during future clinical trials and increase the likelihood of observing true clinical effects. Ideally, therapy for the PPs will prevent attacks, avoid permanent weakness and improve quality of life. Moreover, understanding the skeletal muscle channelopathies will hopefully lead to insights into the more common central nervous system channel diseases such as migraine and epilepsy.

Keywords: Andersen-Tawil syndrome; channelopathy; episodic weakness; periodic paralysis; potassium-sensitive

Abbreviations: ATS = Andersen-Tawil syndrome; CMAP = compound motor action potential; HyperPP = hyperkalaemic periodic paralysis; HypoPP = hypokalaemic periodic paralysis; PMC = paramyotonia congenita; PP = periodic paralysis; K = potassium

Received June 14, 2005. Revised August 22, 2005. Accepted August 26, 2005. Advance Access publication September 29, 2005

Introduction

Primary periodic paralyses (PPs) are autosomal dominant disorders of ion channel dysfunction characterized by episodic flaccid weakness secondary to abnormal sarcolemmal excitability. Classically, PP is classified as hyperkalaemic (HyperPP) or hypokalaemic (HypoPP) based on serum potassium (K) level or response to K administration (Table 1). Although PP is seldom life-threatening, the attacks produce disability and a majority of affected individuals develop

persistent, interattack weakness. Moreover, morbidity and mortality associated with cardiac arrhythmia in a subset of PP patients, those with Andersen–Tawil syndrome (ATS; some authors refer to the disorder as ‘Andersen syndrome’), has yet to be fully appreciated. Although the genotypic spectrum of the PP has expanded over the past decade, molecular lesions in an uncertain proportion of subjects remain unknown.

Table 1 Clinical features of the primary PPs

	HypoPP	HyperPP	Andersen–Tawil
Age at onset	1st or 2nd decade	1st decade	1st or 2nd decade
Duration of attacks	Hours to days	Hours	Hours to days
EMG myotonia	No	Yes	No
Usual triggers	Rest after exercise, carbohydrate load	Rest after exercise, K-rich foods	Prolonged rest after exercise
Ictal K	↓	↑ or normal	↓ or normal or ↑
Fixed proximal weakness	Yes	Yes	+/–
Cardiac arrhythmias	No	No	Yes
Skeletal developmental anomalies	No	No	Yes
Response to potassium	Improves weakness	Triggers weakness	Depends on ictal K
Mutations	CACNA1S (60%) SCN4A (20%)	SCN4A (~50%)	Improves ECG; strength-variable KCNJ2 (~65%)

Clinical features

Hypokalaemic periodic paralysis (MIM 170400)

HypoPP is the most common PP, with a prevalence of ~1:100 000 (Fontaine, 1994). Inheritance is autosomal dominant with reduced penetrance in women (Fontaine, 1994; Elbaz *et al.*, 1995; Fouad *et al.*, 1997; Miller *et al.*, 2004; Sternberg *et al.*, 2001). Approximately one-third of cases may be new dominant mutations (M. Hanna, personal communication). Symptoms typically begin in the first or second decade, attacks of flaccid paralysis usually occurring on awakening in the night or in the early morning. Weakness may be focal or generalized, usually sparing facial and respiratory muscles, and lasting for hours (occasionally days) with gradual resolution. Frequency of individual attacks can vary from daily to a few episodes in a lifetime; attacks often decrease in frequency after age 40. Attacks occur spontaneously or are provoked by prolonged rest after vigorous exercise or a carbohydrate-rich meal on the previous day. Attacks can also be triggered by stress including intercurrent viral illness, lack of sleep, menstruation and specific medications (e.g. beta agonists, corticosteroids and insulin). Many individuals describe a vague prodrome (paraesthesias, fatigue, behavioural and cognitive changes) the day prior to an attack. Attacks of weakness are invariably associated with a low serum potassium concentration. Fixed permanent proximal weakness develops independent of the frequency and severity of attacks (Links *et al.*, 1990) (Table 1).

Hyperkalaemic periodic paralysis (MIM 170500)

Episodic weakness manifests at an earlier age in HyperPP than HypoPP kindreds, most commonly in the first decade. There is high penetrance. The allelic disorder paramyotonia congenita (PMC) presents with muscle stiffness, worsening with activity and cold temperature; affected individuals may have attacks of weakness in addition to muscle stiffness. Episodes of weakness in HyperPP usually last 1–4 h

(infrequently days), are generalized and triggered by rest after exercise and are K-sensitive. Attacks may also be precipitated by stress and fatigue. Rarely, bulbar and respiratory muscles will be involved in severe paralysis. Interictally, lid lag and eyelid myotonia may be the only clinical signs present. A large proportion of subjects with HyperPP develop a progressive proximal myopathy, similar to HypoPP, which is unrelated to attack frequency (Bradley *et al.*, 1990; Miller *et al.*, 2004) and seen with increasing age (Plassart *et al.*, 1994). Electrical myotonia is found in 50–75% of affected individuals (Plassart *et al.*, 1994; Miller *et al.*, 2004) yet is clinically apparent in <20% (Plassart *et al.*, 1994). Although typically associated with elevated ictal serum K levels, many individuals are normokalaemic during attacks. In such patients K-sensitivity symptoms may be ameliorated by exercising.

Andersen–Tawil syndrome (MIM 170390)

Andersen–Tawil syndrome (ATS), first described in 1971 (Andersen *et al.*, 1971), is characterized by the triad of PP, ventricular ectopy and skeletal anomalies (Tawil *et al.*, 1994; Sansone *et al.*, 1997). Prevalence is unknown but estimated at one-tenth that of HypoPP. Symptomatic onset typically is with episodic weakness in the first or second decade. Intermittent weakness occurs spontaneously or may be triggered by prolonged rest or rest following exertion; permanent proximal weakness often develops. Attack frequency, duration and severity are variable between and within affected individuals and may not correlate with ictal serum K levels, which may be reduced, normal or elevated. ECG manifestations (Fig. 1) include prolongation of the corrected QT interval (QTc), prominent U waves, premature ventricular contractions, ventricular bigeminy and polymorphic ventricular tachycardia. A subset of patients manifests a unique form of ventricular tachycardia, bidirectional ventricular tachycardia, which is characterized by beat-to-beat alternating QRS axis polarity (Fig. 1). While many patients with ventricular ectopy are asymptomatic, others present with palpitations, syncope or rarely cardiac arrest (Tristani-Firouzi *et al.*, 2002). Unlike

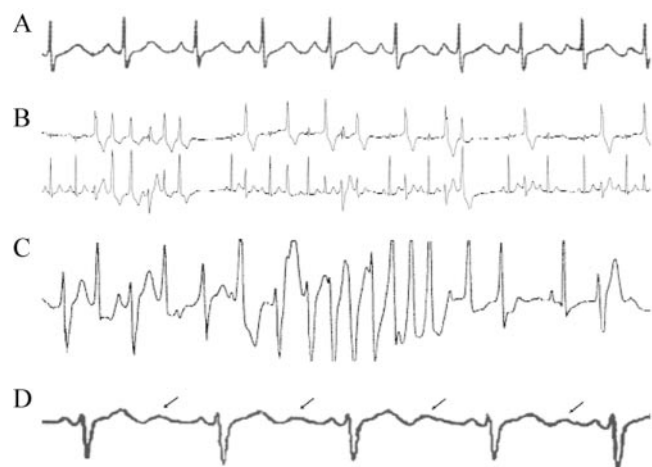


Fig. 1 Representative ECGs from ATS patients. (A) Prolonged QT interval. (B) Non-sustained polymorphic ventricular tachycardia followed by bigeminy. (C) Bidirectional ventricular tachycardia (alternating QRS axis polarity). (D) Prominent U wave indicated by arrows. Reprinted with permission, Tristani-Firouzi *et al.*, *J Clinical Invest* 2002;110: 381–8.

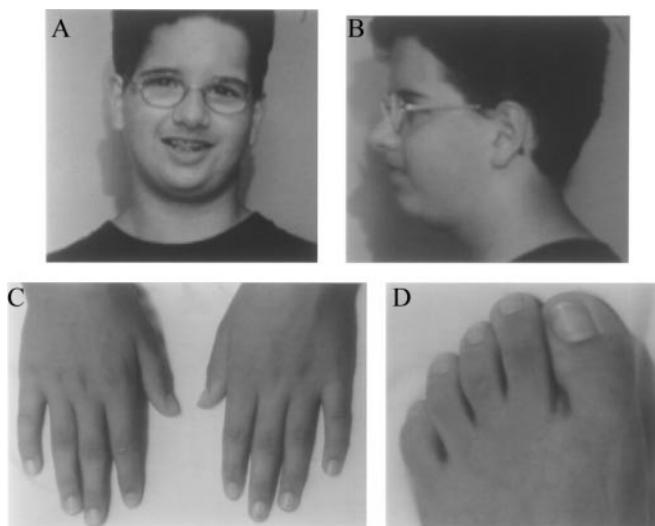


Fig. 2 Developmental features are critical in the assessment of patients with PP and the LQT syndrome to make the appropriate diagnosis and include: hypertelorism, small mandible, low set ears (A and B) and clinodactyly (C and D). Mankodi A, Tawil R. PP and related disorders. In: Gilman S, editor. *MedLink Neurology*. San Diego: MedLink Corporation. Available at www.medlink.com. Accessed February 9, 2005.

other forms of arrhythmia-susceptibility syndromes, many ATS patients remain asymptomatic despite frequent runs of tachycardia (Tristani-Firouzi *et al.*, 2002). Furthermore, there appears to be a lower incidence of syncope and sudden death in ATS compared with other long QT (LQT) syndromes (Tristani-Firouzi *et al.*, 2002). Distinctive physical findings (Fig. 2) include a small mandible, ocular hypertelorism, low set ears, clinodactyly, syndactyly and broad nasal root (Donaldson *et al.*, 2003; Tristani-Firouzi *et al.*, 2002). Short stature, unilateral hypoplastic kidney (Andelfinger *et al.*,

2002), vaginal atresia and brachydactyly (Canun *et al.*, 1999) have been reported. Detailed study has also identified microcephaly, short palpebral fissures, thin upper lip, small hands/feet, residual primary dentition and delayed bone age (Yoon and Ptacek, unpublished).

Clinical diagnosis

Diagnosis of PP requires a history of transient episodes of weakness, determination of ictal serum potassium levels, EMG and exclusion of secondary causes. During an attack, weakness is evident either diffusely or in recently exercised muscle groups. Muscle stretch reflexes are usually hypoactive. In primary HypoPP the K level is low during attacks. In HyperPP, K levels may be elevated; however, the K level remains within the normal range in up to 50% of cases (Plassart *et al.*, 1994; Chinnery *et al.*, 2002). The term K-sensitive may be more appropriate since weakness is typically provoked by K administration. HypoPP attacks respond to oral K ingestion; between episodes serum K should be normal. A provocative K challenge may be necessary to determine K-sensitivity (Griggs, 1983).

Assessment of thyroid status is mandatory for diagnosis of HypoPP. Thyrotoxic PP (MIM 188580) is often indistinguishable from HypoPP. All patients without a family history and any patient presenting after age 20 should be assessed for suppressed TSH and elevated free T4 (fT4) or fT3 levels. In thyrotoxic PP the associated hypokalaemia is often profound. There is a predilection, which can be inherited, for men and in particular Asians, although thyrotoxic PP may be seen in all races.

A diagnosis of ATS (Table 3) can be made when an individual has two of the three cardinal features: (i) PP; (ii) ventricular ectopy and (iii) typical ATS facies (Tawil *et al.*, 1994; Sansone *et al.*, 1997; Tristani-Firouzi *et al.*, 2002). However, the phenotypic variability in ATS may obscure the diagnosis in the absence of a family history of all three cardinal features. Therefore, ATS should be considered in any individual presenting with isolated PP or polymorphic ventricular ectopy. A prolonged QU interval or large amplitude U wave may be more sensitive than the QTc interval, which overlaps with the upper limit of normal (Zhang *et al.*, 2005) (Fig. 1). The episodic weakness seen in affected individuals with ATS has been associated with normal, elevated but most commonly, reduced serum K levels (Tawil *et al.*, 1994; Sansone *et al.*, 1997; Tristani-Firouzi *et al.*, 2002).

During an episode of weakness, the compound motor action potential (CMAP) may be reduced, and rarely, absent on motor nerve conduction studies; insertional activity is reduced, fibrillation potentials and positive sharp waves are seen and there is an increased proportion of polyphasic motor unit potentials on needle examination (Engel *et al.*, 1965). Surface and invasive EMG studies document reduced muscle fibre conduction velocity (Links and van der Hoeven, 2000). Interictal clinical electrophysiological testing (Table 2) is

Table 2 Electrodiagnostic features of the primary PPs

	HyperPP (SCN4A)	HypoPP1 (CACNIAS)
Mutation	T704M	R528H
EMG pattern	IV	V
Electrical myotonia	Yes	No
Short exercise protocol		
Post-exercise myotonic potentials	No	No
Post-exercise CMAP	Increase	No change
Long exercise protocol		
Immediate post-exercise CMAP	Increase	No change
Delayed post-exercise CMAP	Decrease	Decrease

Adapted from Fournier *et al.*, 2004**Table 3** Diagnostic criteria for ATS

- (1) A clinically definite diagnosis requires two of the following three features:
- PP
 - Prolonged QTc interval or ventricular ectopy (identified on ECG or Holter)
 - The typical ATS facies including:
 - Low set ears, ocular hypertelorism, small mandible, fifth digit clinodactyly, syndactyly
- (2) Alternatively, a diagnosis may be made with one of the three features above and an affected family member meeting two of three.

helpful in the diagnosis of PP. Changes in CMAP after exercise may correlate with exercise-induced symptoms (McManis *et al.*, 1986) and channel mutation (Fournier *et al.*, 2004). Myotonia on EMG needle examination occurs in ~75% of individuals with HyperPP and in all patients with PMC; EMG myotonia does not occur in HypoPP. Electrodiagnostic studies at room temperature and after cooling the extremity may be more sensitive for HyperPP and PMC. The long exercise protocol also may detect a delayed decrement in ATS patients (Katz *et al.*, 1999).

Muscle biopsy changes are non-specific in the PP. Tubular aggregates are more commonly seen in ATS. A vacuolar myopathy, resulting from reduplication of the sarcoplasmic reticulum and transverse tubules, may be seen in HypoPP and HyperPP. Such changes were detected in 21 out of 29 (72%) of affected individuals with either HyperPP or HypoPP (Miller *et al.*, 2004). Patients with fixed weakness may have non-specific myopathic changes, with or without vacuolar change.

Genetics

The PPs are autosomal dominant, have high penetrance and are genetically heterogeneous (Table 1). Family history may be overlooked because of non-penetrance in previous generations and intra-familial variability. Sporadic cases from *de novo* mutations are frequent in HypoPP and have also been documented in HyperPP and ATS.

HypoPP is caused by mutations in the alpha subunits of either the skeletal muscle L-type calcium channel gene *CACNIAS* (HypoPP1) (Jurkat-Rott *et al.*, 1994; Ptacek

et al., 1994a; Fontaine *et al.*, 1994; Elbaz *et al.*, 1995) or the skeletal muscle sodium channel gene *SCN4A* (HypoPP2) (Bulman *et al.*, 1999; Jurkat-Rott *et al.*, 2000; Struyk *et al.*, 2000; Bendahhou *et al.*, 2001; Sternberg *et al.*, 2001). Two of three missense mutations in the calcium channel gene account for up to 70% of HypoPP cases (Fouad *et al.*, 1997; Jurkat-Rott *et al.*, 2000; Davies *et al.*, 2001; Miller *et al.*, 2004) while 10–20% of affected individuals will have a point mutation in the sodium channel gene (Bulman *et al.*, 1999; Jurkat-Rott *et al.*, 2000; Davies *et al.*, 2001; Sternberg *et al.*, 2001; Kim *et al.*, 2004; Miller *et al.*, 2004; Vicart *et al.*, 2004). A small number of definitely affected kindreds do not have a mutation in the calcium or sodium genes and are not linked to these loci. The possibility that HypoPP may be caused by mutations in *KCNE3* (Abbott *et al.*, 2001) has not been substantiated (Sternberg *et al.*, 2003; Jurkat-Rott and Lehmann-Horn, 2004).

Most cases of HyperPP, as well as the allelic disorders paramyotonia congenita and K-aggravated myotonia, are caused by mutations in *SCN4A* (Fontaine *et al.*, 1990; Ptacek *et al.*, 1991, 1992; Rojas *et al.*, 1991; McClatchey *et al.*, 1992a; Heine *et al.*, 1993). The most common are the missense mutations T704M and M1592V (Ptacek *et al.*, 1994a) accounting for 75% of affected individuals (Miller *et al.*, 2004) while other point mutations account for the remainder of affected individuals (McClatchey *et al.*, 1992a; Plassart *et al.*, 1996; Wagner *et al.*, 1997; Bendahhou *et al.*, 1999a, 2000, 2002).

ATS is caused by missense mutations or small deletions (Plaster *et al.*, 2001; Tristani-Firouzi *et al.*, 2002; Ai *et al.*, 2002; Andelfinger *et al.*, 2002; Donaldson *et al.*, 2003; Hosaka *et al.*, 2003) in *KCNJ2*, encoding the inwardly rectifying K channel, Kir 2.1 (Plaster *et al.*, 2001), in approximately two-thirds of the affected individuals (ATS1) (Plaster *et al.*, 2001; Tristani-Firouzi *et al.*, 2002; Donaldson *et al.*, 2003). The molecular lesion(s) have not been identified in ~30% of subjects including kindreds not linked to *KCNJ2*.

The expression of thyrotoxic PP may be a result of an inherited predisposition that is uncovered by thyrotoxicosis. An initial report of an R83H mutation in the *KCNE3* gene causing thyrotoxic PP (Dias Da Silva *et al.*, 2002) proved erroneous as 1% of healthy controls, in addition to patients affected with familial PP, thyrotoxic PP and PMC have this missense polymorphism in *KCNE3* (Sternberg *et al.*, 2003; Jurkat-Rott and Lehmann-Horn, 2004).

Genotype–phenotype correlations

No prospective study has followed a sufficiently large cohort with characterized molecular lesions to draw precise conclusions. Intuitively, since the mutations are invariant they cannot completely explain the intrakindred and interkindred phenotypic variations in PP. The marked phenotypic variability in a large Quarter horse pedigree affected by a missense mutation in the equine sodium channel orthologue was attributed to the ratio of mutant and normal sodium channels

expressed in skeletal muscle (Zhou *et al.*, 1994). Prospective studies as well as further experimental electrophysiology data are necessary to understand the factors that trigger attacks and produce the varying phenotypic severity of human PPs.

What is remarkable is the striking phenotypic heterogeneity evident with discrete sodium channel mutations causing the allelic disorders HypoPP (Bulman *et al.*, 1999; Jurkat-Rott *et al.*, 2000), HyperPP (Fontaine *et al.*, 1990; Cannon *et al.*, 1991; Ptacek *et al.*, 1991), paramyotonia congenita (McClatchey *et al.*, 1992a; Ptacek *et al.*, 1992) and K-aggravated myotonia (Heine *et al.*, 1993; Ptacek *et al.*, 1994b; Ricker *et al.*, 1994), in addition to a congenital myasthenic syndrome (Tsujino *et al.*, 2003). Missense mutations in the highly conserved arginine residues (R699 and R672) of the voltage sensing segment 4 (S4) of domain II (DII) are associated with HypoPP (Bulman *et al.*, 1999; Jurkat-Rott *et al.*, 2000). However, four kindreds with mutations in the adjacent R675 residue had clinical features of HyperPP, were always normokalaemic on repeated ictal testing and yet two individuals had inducible hypokalaemia (Vicart *et al.*, 2004). Moreover, there is also a kindred with a P1158S mutation in exon 19 of *SCN4A* and temperature-dependent shifts of voltage dependence in the sodium channel activation. Affected individuals present with heat-induced myotonia and cold-induced HypoPP (Sugiura *et al.*, 2000). HypoPP may also have an allelic disorder—malignant hyperthermia susceptibility without PP has been described with mutation in *CACNIAS* (Monnier *et al.*, 1997). All PP patients undergoing surgery should be monitored for malignant hyperthermia-like reactions that may be life-threatening; however, prolonged paralysis post-operatively without the usual signs of malignant hyperthermia (rigidity, marked elevation in CK) is more likely related to the stress of surgery.

There are some useful distinguishing features nevertheless. The largest retrospective series involved 226 patients with characterized molecular lesions for HypoPP1 (42), HypoPP2 (7), HyperPP (81) and PMC (49) providing clinical data for patients with and without identifiable mutations (Miller *et al.*, 2004). Age of onset was earlier and the duration of episodes was longer in HypoPP1 (10 years; ~20 h) versus HypoPP2 (16 years; ~1 h). Earlier age of onset and more severe hypokalaemia were also seen in HypoPP1 patients with the R1239H (7 years; 1.9 mEq/l) *CACNIAS* mutation versus R528H (14 years; 2.9 mEq/l). In HypoPP1 patients, >70% had fixed proximal weakness compared with none of the HypoPP2 patients. Similarly, in HyperPP cases, there was a younger age of onset, more frequent attacks and shorter duration with T704M (0.8 years; 28/months; 8 h) *SCN4A* mutation versus M1592V (5 years; 3/month; 89 h). Patients without mutations were slightly atypical with an older age of onset, absence of diet as a trigger and non-specific myopathic changes, rather than a vacuolar myopathy, on muscle biopsy (Miller *et al.*, 2004).

In addition, an EMG study in 51 genetically characterized channelopathy patients with HypoPP1 (13), HypoPP2 (2), HyperPP (12), PMC (16), K aggravated myotonia (2) and

myotonia congenita (6) provides important electrodiagnostic clues (Fournier *et al.*, 2004). Needle EMG, post-exercise myotonic potentials and change in CMAP amplitude after short and long exercise protocols revealed five distinct electrophysiological patterns that could be correlated with patient groups based on known mutations. This protocol differentiated HypoPP1 patients with the R528H *CACNIAS* mutation from HyperPP patients with a T704M *SCN4A* mutation (Table 2) (Fournier *et al.*, 2004). It remains to be seen whether these patterns will differentiate between patients with HypoPP1 and HypoPP2.

Currently, individuals with clinically defined ATS are phenotypically indistinguishable, regardless of the presence (ATS1) or absence of *KCNJ2* mutation (Tristani-Firouzi *et al.*, 2002; Donaldson *et al.*, 2003). Phenotypic variability is high, only 60% of affected individuals manifest the complete triad while ~80% express two of the three cardinal features (Tristani-Firouzi *et al.*, 2002). This variability is evident even within kindreds carrying the identical *KCNJ2* mutation (Tristani-Firouzi *et al.*, 2002; Andelfinger *et al.*, 2002; Donaldson *et al.*, 2003). Non-penetrance may be seen in up to 20% of individuals with a defined Kir2.1 mutation (Tristani-Firouzi *et al.*, 2002; Andelfinger *et al.*, 2002; Donaldson *et al.*, 2003).

Pathophysiology

All forms of familial PP share a common final mechanistic pathway: aberrant depolarization, which inactivates sodium channels and renders the muscle fibre electrically inexcitable (Lehmann-Horn *et al.*, 2002). Differences in attack frequency, severity and precipitating factors probably reflect which channel gene is affected, and the specific alterations in mutant channel function. Other factors, such as relative expression level or variations in other determinants of cellular excitability must also have an influence, since phenotypic variability is observed in unrelated kindreds with the same mutation or even among affected members in a single family.

Based on early microelectrode studies in PP, an increase in sodium permeability was hypothesized (McComas *et al.*, 1968). However, membrane depolarization was later shown to be caused by abnormal inactivation of voltage-gated sodium channels (Lehmann-Horn *et al.*, 1987). Direct measurement of channel activity in isolated membrane patches from myotubes (Cannon *et al.* 1991) as well as in muscle fibres from patients with HyperPP (Lehmann-Horn *et al.*, 1991) showed the impaired inactivation. Operationally, this defect in mutant channel gating creates a gain-of-function, and the increased sodium current will excessively depolarize affected muscle. Over 20 sodium channel (*SCN4A*) mutations with gain-of-function defects due to impaired inactivation, or in some cases enhanced activation, have been established as the cause of HyperPP or PMC (Lehmann-Horn and Jurkat-Rott, 1999; Cannon, 2002). Electrophysiological correlates in affected patients are thought to be the reduced ictal CMAP (Engel *et al.*, 1965), slowing of muscle fibre conduction

velocity (Zwarts *et al.*, 1988; Links *et al.*, 1994), and decrement on the long exercise protocol (McManis *et al.*, 1986; Kuntzer *et al.*, 2000; Fournier *et al.*, 2004).

In HyperPP and PMC, gain-of-function mutations occur in highly conserved amino acids on the cytoplasmic face of the channel (Ptacek *et al.*, 1991; Rojas *et al.*, 1991), the inactivation gate (McClatchey *et al.*, 1992*b*) or the voltage sensor (S4) of DIV (Ptacek *et al.*, 1992; Lerche *et al.*, 1996) resulting in impaired fast (Cannon *et al.*, 1991; Wagner *et al.*, 1997; Bendahhou *et al.*, 1999*b*) or slow inactivation (Cummins and Sigworth, 1996; Hayward *et al.*, 1999; Ruff and Cannon, 2000) and, therefore, persistent increased sodium current and sarcolemmal depolarization. It is the degree of depolarization and inactivation of normal sodium channels that dictates whether the muscle fibre membrane is hyperexcitable (myotonia) or inexcitable (weakness).

The mechanism for depolarization-induced attacks of weakness in HypoPP is not understood. Missense mutations in the $\alpha 1$ subunit of the L-type calcium channel (Jurkat-Rott *et al.*, 1994; Ptacek *et al.*, 1994*a*), or less commonly in the voltage-gated sodium channel (Bulman *et al.*, 1999; Jurkat-Rott *et al.*, 2000), cause HypoPP. Curiously, for both channel types the mutations occur in highly conserved arginine residues in the voltage-sensing segments. The calcium channel mutations cause a loss-of-function manifest as reduced current density (Lapie *et al.*, 1996) and slower activation (Morrill *et al.*, 1998). This observation does not readily explain the episodes of depolarization, weakness and hypokalaemia. *In vitro*, muscle fibres from patients with HypoPP depolarize in low K solution (Rüdel *et al.*, 1984). A study on fibres biopsied from a patient with the R528H calcium channel mutation detected a reduction in ATP-sensitive K current (Tricarico *et al.*, 1999), which is more easily tied to depolarization with hypokalaemia and suggests a secondary channelopathy stemming from altered calcium homeostasis. The sodium channel mutations associated with HypoPP2 enhance inactivation to produce a net loss-of-function defect (Jurkat-Rott *et al.*, 2000; Struyk *et al.*, 2000; Bendahhou *et al.*, 2001). This behaviour is the converse of the gain-of-function changes observed in HyperPP, but the mechanism linking this defect to depolarization and hypokalaemia in HypoPP remains obscure.

Kir2.1 channels stabilize the resting membrane potential in skeletal and cardiac muscle, and contribute significantly to the most terminal repolarization phase of the cardiac action potential (Plaster *et al.*, 2001; Tristani-Firouzi *et al.*, 2002). The majority of *KCNJ2* mutations exert a dominant-negative effect on channel function (Plaster *et al.*, 2001; Lange *et al.*, 2003; Donaldson *et al.*, 2004). Most mutant channels traffic normally to the cell surface, but fail to conduct appropriately (Bendahhou *et al.*, 2003). Many mutations alter the binding of phosphatidylinositol 4,5 biphosphate, which is an important regulator of Kir2.1 channel function (Lopes *et al.*, 2002; Donaldson *et al.*, 2003). While limited *in vivo* data are available, reduced Kir2.1 channel function in skeletal muscle may cause sustained membrane depolarization, leading to failure of action potential propagation and flaccid paralysis (Cannon,

2002). In the heart, altered Kir2.1 function may prolong the most terminal phase of repolarization, leading to delayed after-depolarizations and $\text{Na}^+/\text{Ca}^{2+}$ -dependent triggered activity (Tristani-Firouzi *et al.*, 2002; Miake *et al.*, 2003). A broad range of possible molecular candidates for ATS2 includes genes homologous to Kir2.1 and gene products that modulate Kir2.1 channel expression, trafficking and function. The development of an animal model of ATS will probably advance our understanding of the skeletal and cardiac muscle pathophysiology.

Animal models

Equine hyperPP is a dominantly inherited disorder characterized by episodic weakness associated with elevated serum potassium and muscle stiffness due to a single point mutation in S3/DIV of the skeletal sodium channel α subunit (Rudolph *et al.*, 1992) causing impaired fast inactivation (Cannon *et al.*, 1995). Mouse models such as knock-in, knock-out and cDNA transgenics may provide more accessible alternatives to the equine model, allow specific questions to be addressed *in vivo*, and well characterized mouse models can then be used for screening possible therapeutic agents. There are no published reports of viable mouse models to date; the Kir2.1 knock-out is lethal (Zaritsky *et al.*, 2000).

Natural history

The natural history of the PPs has not been documented by prospective studies. Published case series suggest the highest frequency of attacks in the teenage years followed by a decreasing attack frequency with increasing age in both HyperPP and HypoPP. Approximately two-thirds of the patients will develop progressive fixed weakness (Miller *et al.*, 2004) unrelated to frequency of episodic weakness (Links *et al.*, 1990); risk factors other than a specific molecular lesion have yet to be determined. Estimated at one-tenth the prevalence of HypoPP, there is even less appreciation for the natural history of ATS, although there is some evidence to suggest that the cardiac arrhythmias may be less likely to degenerate into a fatal arrhythmia than occur with other LQT syndromes. Many unanswered questions remain, including the relationship of K to the cardiac and skeletal muscle manifestations, the risk of fixed weakness and the outcome of the cardiac arrhythmias. The presence of Kir2.1 in the CNS raises the question of whether there may be a CNS phenotype.

Treatment

The management of PP has been symptomatic and behavioural; affected individuals learn to avoid precipitating triggers through lifestyle and dietary modification. Patients with hypokalaemic attacks eat frequent small meals to avoid large carbohydrate loads. In contrast, those with

hyperkalaemic attacks stay away from K rich foods, medications that increase serum K (e.g. spironolactone) and fasting.

There are no randomized clinical trials in the acute management of paralytic attacks, which targets normalization of serum K levels. For HypoPP, the administration of oral K (20–30 mEq/l orally every 15–30 min until serum K is normalized) is usually sufficient for resolution of weakness. Patients may take oral potassium (15–30 mEq) at the beginning of an attack to alleviate or shorten the episode. Conversely, patients with HyperPP will continue with mild activity or ingest sweets to prevent or shorten attacks. Beta agonist inhalers (1–2 puffs of 0.1 mg salbutamol or albuterol) attenuate hyperkalaemic attacks (Ricker *et al.*, 1989).

Anecdotal evidence showed benefit with sodium restriction and potassium supplementation (Conn *et al.*, 1957) in HypoPP as well as with acetazolamide (125–1000 mg/day) treatment in HyperPP (McArdle, 1956) and HypoPP (Resnick *et al.*, 1968). Dichlorophenamide (50–200 mg/day) is another carbonic anhydrase inhibitor that reduces attack frequency (Dalakas and Engel, 1983). These observations led to the only randomized, double blind clinical trial in PP. Dichlorophenamide, when compared with placebo, significantly reduced attack frequency in patients with HyperPP and HypoPP (Tawil *et al.*, 2000). HypoPP2 patients, i.e. those with *SCN4A* mutations, may have been excluded from the trial because of reports of worsening of attacks with acetazolamide treatment (Torres *et al.*, 1981; Sternberg *et al.*, 2001) although there are other reports of patients with *SCN4A* mutations deriving benefit with acetazolamide (Davies *et al.*, 2001; Venance *et al.*, 2004; Vicart *et al.*, 2004). A clinical trial is currently underway comparing treatment with dichlorophenamide and acetazolamide on the primary outcome, attack frequency. Despite this, <50% of affected individuals are prescribed prophylactic medication (Tawil *et al.*, 2000). The observation that prophylactic treatment improves fixed weakness (Griggs *et al.*, 1970; Dalakas and Engel, 1983) is also under investigation in the randomized controlled trial.

The mechanism of action of carbonic anhydrase inhibitors is unclear and is independent of carbonic anhydrase inhibition. *In vitro* studies show that carbonic anhydrase inhibitors relieve weakness in K⁺-deficient rats through activation of calcium-activated K channels (Tricarico *et al.*, 2000, 2004) rather than direct inhibition of carbonic anhydrase.

No prospective, randomized therapeutic trials have been completed in ATS. Anecdotal evidence suggests that like HyperPP and HypoPP, carbonic anhydrase inhibitors may be effective in the prevention of attacks of PP. K-wasting diuretics and other drugs that prolong the QT interval may be hazardous. There is very limited data demonstrating clear efficacy of any antiarrhythmic agent, alone or in combination, to control the frequent ventricular ectopy manifested by ATS patients. While many ATS subjects are treated empirically with beta-blockers, there is little evidence that beta-blockers alter the frequency of ventricular tachycardia. The primary question as to whether asymptomatic patients with

frequent runs of non-sustained ventricular tachycardia are better off without therapy remains to be determined from natural history cohort studies. For patients with tachycardia-induced syncope or aborted sudden cardiac death, an implantable cardioverter-defibrillator is a prudent option (Chun *et al.*, 2004). Kir2.1 channels are paradoxically sensitive to external K⁺ concentration, increasing their conductance with increasing external K⁺. Likewise, the hERG K channel is also paradoxically sensitive to external potassium and this effect was recently exploited to shorten the QT interval in LQT2 subjects with *hERG* mutations by combining spironolactone and oral K supplementation (Etheridge *et al.*, 2003). Prospective studies are needed to determine whether a similar approach may benefit ATS patients.

Acknowledgements

This report is dedicated to the memory of Philip G. McManis (1953–2004). The authors thank Shirley Thomas for organizing the IPP conference and assisting in the preparation of this manuscript. The authors belong to the Consortium for Clinical Investigation of Neurological Channelopathies (CINCH) supported by NIH RU54 RR019482-03 (NINDS/ORD).

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Appendix

This report summarizes the findings of an International Conference on the Pathogenesis and Treatment of the PPs (Rochester NY, October 31, 2004). The conference was generously supported by an NIH conference grant 1R13 NS050966-01 as well as the Muscular Dystrophy Association and the Association Française contre les Myopathies.

Members of the International Meeting on the Pathogenesis and Treatment of the PPs listed alphabetically:

Anthony Amato (Brigham and Women's), Robert Barchi (Thomas Jefferson University), Richard Barohn (University of Kansas), Dennis Bulman (Ottawa Health Research Institute), Domenico Tricarico (University of Bari), Stephen Cannon (University of Texas Southwestern), Emma Ciafaloni (University of Rochester), James Cleland (University of Rochester), Patrick Cochran (Periodic Paralysis Association), Marinos Dalakas (NINDS, NIH), Magnus Dias DaSilva (UCSF), Nick Davis (Queen Elizabeth Hospital, UK), Erik Ensrud (Nora Neurological Clinic), Doreen Fialho (Institute of Neurology, UK), Bertrand Fontaine (Pitié-Salpêtrière, France), Tracey Graves (Institute of Neurology), Robert C.

Griggs (University of Rochester), Angelika Hahn (London Health Sciences Ctr, Canada), Michael Hanna (Institute of Neurology, UK), Lawrence Hayward (University of Massachusetts), Barbara Herr (University of Rochester), Ellen Hess (Johns Hopkins), Joanna Jen (UCLA), Bethan Lang (Weatherall Institute of Molecular Medicine, UK), Jake Levitt (Taro Pharmaceuticals, Inc), Thera Links (Hospital Groningen, Netherlands), Giovanni Meola (University of Milan, Italy), Hiroshi Mitsumoto (Columbia Presbyterian), Louis Ptacek (UCSF), Ming Qi (University of Rochester), Goran Rakocevic (NINDS, NIH), Seward Rutkove (Beth Israel Deaconess), Robert Ruff (Cleveland VA Medical Center), Valeria Sansone (University of Milan, Italy), David Saperstein (University of Kansas), Damien Sternberg (Pitié-Salpêtrière, France), Randall Stewart (NINDS, NIH), Arie Struyk (Massachusetts General Hospital), Rabi Tawil (University of Rochester), Charles Thornton (University of Rochester), Martin Tristani-Firouzi (University of Utah), Shannon Venance (London Health Sciences Center, Canada), Savine Vicart (Pitié-Salpêtrière, France), Grace Yoon (UCSF).