Chapter 4

Periodic paralysis

DOREEN FIALHO AND MICHAEL G. HANNA*

Institute of Neurology, London, UK

4.1. Introduction

Periodic paralysis is a disorder of skeletal muscle in which patients experience attacks of muscle weakness of variable duration and severity. The attacks can last from a few minutes to several days. The weakness in an attack can be generalized or focal. Early in the natural history of the disease muscle strength returns to normal after an attack, but later significant fixed muscle weakness often develops. The variability of the symptoms often leads to delays in accurate diagnosis and treatment.

Although the clinical phenotype of periodic paralysis has been recognized for many years, it is only in recent times that the underlying pathophysiology has been deduced at a molecular genetic level. In all forms of this disorder, electrophysiological examination during an attack reveals that the skeletal muscle fiber membrane is in a partially depolarized and inexcitable state. Muscle membrane excitability depends on the coordinated interplay of key voltage-gated ion channels. It is now known that in both genetic and acquired forms of periodic paralysis dysfunction of these key membrane-bound ion channels underlies the pathophysiology and explains the altered muscle excitability. Periodic paralysis was one of the first neurological channelopathies to be characterized at a genetic and cellular level. To a certain extent the current detailed molecular knowledge about periodic paralysis represents a paradigm for our understanding of subsequently discovered muscle and brain channelopathies.

Historically, periodic paralysis was classified according to serum potassium abnormalities during attacks into hypo- and hyperkalemic periodic paralysis (hypoPP and hyperPP). This classification depending on serum potassium is still of use clinically but has now been supplemented by the newer molecular genetic classification which we describe here.

In this chapter we provide a detailed review of current knowledge regarding clinical features, investigations, treatment, genetics and molecular pathophysiology of the periodic paralyses.

4.2. Clinical features

4.2.1. Familial hypokalemic periodic paralysis (hypoPP)

Most of the early original publications on periodic paralysis were probably describing hypoPP, as this is the commonest form of periodic paralysis. Talbott published an extensive review of the literature on periodic paralysis in 1941 (Talbott, 1941). This paper summarized many of the characteristic features of periodic paralysis including age of onset, male predilection, development of fixed weakness and provoking factors. Talbott cites Musgrave's interesting observation from 1727 of a 21-year-old woman who presented with attacks of weakness, and suggests this may be the first description of periodic paralysis (Musgrave, 1727). However, some of the features in Musgrave's original case were atypical, including loss of speech and attacks always occurring on the same day of the week. From the beginning of the 19th century a number of reports started to appear describing cases of sporadic periodic paralysis and the first familial case of an affected father and son was reported by Shakhnowitsch in 1882. Early hypotheses on the pathogenesis of periodic paralysis included the theory of muscle ischemia as the underlying pathology (Westphal, 1885, Holtzapple, 1905, Schmidt, 1919, Mankowsky, 1929). Goldflam (Goldflam, 1890) and others (Crafts,

*Correspondence to: Dr. M.G. Hanna, Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery, University College London Foundation NHS Trust, and Department of Molecular Neuroscience, Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK. E-mail: m.hanna@ion.ucl.ac.uk, Tel: +44-(0)207-837-3611, Fax: +44-(0)207-6921-2085.

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1900, Singer and Goodbody, 1901) suggested that an autotoxin was responsible. Hartwig (1874) was the first to describe electrical inexcitability of muscles during an attack of paralysis. Indeed, Hartwig was so surprised by the lack of response to electrical stimulation that he initially thought that his apparatus was malfunctioning. Biemond and Daniels (1934) provided the first report of low potassium levels during a spontaneous attack. This was confirmed in another case a year later when Walker (1935) reported convincing evidence that there was a 50% decrease of serum potassium during an attack.

p0060   It is now known that hypoPP is the most common form of familial periodic paralysis with a prevalence of 0.4–1:100 000 in Europe (Kantola and Tarssanen, 1992, Fontaine, 1994). The inheritance is autosomal dominant with reduced penetrance in women giving a male:female ratio of ~3:1 (Elbaz et al., 1995).

p0070   There are currently three genes implicated in familial hypoPP including *CACNA1S*, *SCN4A* and *KCNJ2*. Mutations in the voltage-gated calcium channel gene *CACNA1S* account for the majority of cases (~70%; Fouad et al., 1997, Miller et al., 2004). In less than 10% of cases mutations in the voltage-gated sodium channel gene *SCN4A* are reported (Bulman et al., 1999, Davies et al., 2001, Sternberg et al., 2001, Miller et al., 2004). Mutations in *KCNJ2* encoding an inward-rectifying potassium channel can cause Andersen–Tawil syndrome (Plaster et al., 2001). Since this condition is distinct and can present with both hypo- and hyperkalemic periodic paralysis it will be discussed separately. A mutation in *KCNE3* reported as pathogenic in hypoPP was later found to be a benign polymorphism

(Abbott et al., 2001, Sternberg et al., 2003, Jurkat-Rott and Lehmann-Horn, 2004).

p0080   Hypokalemic periodic paralysis generally presents later than hyperkalemic paralysis, usually between the ages of 5 and 20, typically in the teenage years (Fouad et al., 1997, Miller et al., 2004; see Table 4.1). However, onset over the age of 20 has been reported (Miller et al., 2004). Attacks tend to last from several hours up to 2–3 days. It is often difficult for patients to give a precise estimate of attack duration as both onset and resolution tend to be gradual. A sudden onset of weakness leading to a collapse would argue against a diagnosis of periodic paralysis. It is generally considered that hypoPP attacks are longer and more severe than in hyperPP. Although this is our experience, a recent retrospective study did not confirm this. It is possible the use of medication by patients in the study may have influenced attack duration (Miller et al., 2004).

p0090   In a typical hypoPP episode the patient wakes in the night or in the morning with generalized severe weakness being "unable to move". Often intake of a carbohydrate-rich meal or strenuous exercise the preceding day or night can be identified as a triggering factor. Focal episodes of weakness may be triggered by exercise only involving one limb but are more common in hyperPP. Tendon reflexes are diminished or absent. Even in a severe attack cranial muscles are spared so that speech and eye opening remain intact. Impairment of speech, visual symptoms or alterations in consciousness are not expected and should trigger consideration of other diagnostic possibilities. Respiratory muscles are mostly spared but a reduction in vital capacity and consequent

t0010   *Table 4.1*

Clinical features of hyperkalemic periodic paralysis and hypokalemic periodic paralysis

	Hyperkalemic periodic paralysis	Hypokalemic periodic paralysis
Onset of symptoms	First decade	Second decade
Triggers	Rest after exercise, cold, fasting, potassium-rich food	Rest after exercise, carbohydrate load
Time of attack	Any time of the day	Typically when waking up in the morning
Duration of attack	Minutes to hours	Hours to days
Severity of attack	Mild to moderate, may be focal	Moderate to severe
Additional symptoms	Myotonia or paramyotonia	
Serum potassium	Usually high, may be normal	Low
Interictal electromyography	Myotonic discharges in some, positive McManis test	Never myotonic discharges, positive McManis test
Treatment	Acetazolamide, dichlorphenamide, thiazide, beta-agonist	Acetazolamide, dichlorphenamide, potassium supplementation, potassium-sparing diuretics
Gene/ion channel	*SCN4A*: Na$_v$1.4 (sodium channel subunit), *KCNJ2*: Kir2.1 (potassium channel subunit)	*CACNA1S*: Ca$_v$1.1 (calcium channel subunit), *SCN4A*: Na$_v$1.4 (sodium channel subunit), *KCNJ2*: Kir2.1 (potassium channel subunit)

respiratory failure has rarely been reported to occur in severe attacks (Ziegler and McQuarrie, 1952, Rowley and Kliman, 1960, Resnick and Engel, 1967). Strength gradually improves over the course of the next day or two although some patients indicate that it takes up to a week to recover. Even when the patient is not complaining of clear clinical attacks careful quantitative strength measurement has suggested that there is diurnal variation of muscle power, being lowest in the early hours of the morning and highest in the afternoon and evening (Engel et al., 1965). Attacks often become less frequent and severe in later life and in common with hyperPP a permanent myopathy may develop (Biemond and Daniels, 1934). Interestingly fixed weakness has been described to occur even in patients without a strong history of frequent paralytic attacks (Sternberg et al., 2001). For example, in some females the late-onset myopathy may be the only manifestation without any clinically evident paralytic attacks (Links et al., 1990). A study of a large kindred with hypoPP showed that nearly all subjects over the age of 50 years had evidence of fixed muscle weakness (Links et al., 1994). It remains unproven whether active treatment to reduce the frequency of paralytic attacks might reduce the development of fixed weakness later.

p0100 A useful feature to distinguish between hypo- and hyperkalemic periodic paralysis clinically is the absence of (true) myotonia in hypoPP. The only exception to this rule so far is the *SCN4A* mutation P1158S which has been described in a Japanese kindred causing myotonia and cold-induced hypoPP (Sugiura et al., 2000). Previously in the literature only a single case was reported with myotonia and periodic paralysis where the potassium level was low (1.9 mEq/l) during the attack. However the patient was from a family with typical myotonic dystrophy and the precise diagnosis is unclear (Leyburn and Walton, 1960). There are a handful of other reports of apparent clinical myotonia (mostly myotonic lid lag) in association with hypokalemic periodic paralysis (Odor et al., 1967, Resnick et al., 1967, Griggs et al., 1970). Here the explanation may be that the lid lag was not due to true electrical myotonia, which explains why no EMG myotonia could be demonstrated in any of these patients. Although lid lag is a sensitive marker of myotonia it does not appear to be very specific as it has been found even in healthy volunteers (Odor et al., 1967) and should therefore be interpreted with caution.

p0110 A number of factors may induce or exacerbate attacks. These include ingestion of carbohydrates, administration of insulin and epinephrine injections (Ziegler and McQuarrie, 1952, Rowley and Kliman, 1960, Engel et al., 1965). Stress and excitement and exposure to cold are also often listed by patients as triggers (Miller et al.,

2004). Menstruation and pregnancy have been reported to cause an increase in frequency and severity of attacks (Bender, 1936, Links et al., 1994).

p0120 Although serum potassium levels are often reduced, especially at the beginning of an attack, they may not be below the normal range. The original studies of periodic paralysis in the early 20th century reported a number of other electrolyte changes (for review see Talbott 1941), including a decrease in serum phosphate in parallel with potassium and reduced urinary excretion of sodium, potassium, chloride and water. Serum creatine kinase (CK) may be normal or slightly elevated in between attacks. During paralytic attacks there can be a moderate rise in CK (De Keyser et al., 1987).

p0130 Electrogardiogram (ECG) changes have been observed with very low potassium including prominent U waves, flattening of T waves and ST depression. Inter-ictal ECG is usually normal although affected members of a kindred with hypokalemic periodic paralysis carrying the R528H *CACNA1S* mutation were reported to suffer from cardiac arrhythmias (Fouad et al., 1997). The presence of prominent U waves, frequent ventricular ectopic beats or arrhythmias should alert the clinician to the possibility of Andersen–Tawil syndrome (ATS) (see later section). Familial hypokalemic periodic paralysis is not associated with clinical or echocardiographic evidence of cardiomyopathy (Schipperheyn et al., 1978).

4.2.2. Familial hyperkalemic periodic paralysis (hyperPP)
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p0140 In the early 1950s the Swedish pediatric neurologist Gamstorp recognized a new form of periodic paralysis associated with an elevated serum potassium. In her thesis in 1956 she coined the term "adynamia episodica hereditaria" (Gamstorp, 1956) but later it was referred to as hyperkalemic periodic paralysis.

p0150 Familial hyperPP is due to mutations in *SCN4A* encoding the α-subunit of the skeletal muscle voltage-gated sodium channel $Na_v1.4$. The clinical presentation of hyperPP includes attacks of limb weakness lasting minutes to hours. In contrast to hypoPP the attacks frequently happen during daytime but nocturnal attacks may occur (Gamstorp, 1956, Layzer et al., 1967). From a clinical diagnostic perspective, frequent short daytime attacks favor a diagnosis of hyperPP and nocturnal prolonged attacks may slightly favor hypoPP. The onset of symptoms is typically within the first decade and attacks tend to become milder and less frequent with age. A persistent mild myopathy may develop later in the course of the disease and reports indicate that this is independent of the number of attacks (Saunders et al., 1968, Bradley et al., 1990, Ptacek et al., 1991a).

p0160	The rise of potassium during attacks may be subtle and transient, frequently not exceeding the normal range and can therefore be easily missed (Plassart et al., 1994). For many years normokalemic periodic paralysis was considered to be a distinct disorder based on descriptions of a limited number of families (Poskanzer and Kerr, 1961, Meyers et al., 1972, Danowski et al., 1975). However, the status of normokalemic PP as a distinct entity now looks uncertain. We had the opportunity to analyze the original 1961 family from the northeast of England and showed that they harbored the common M1592V hyperPP *SCN4A* mutation (Chinnery et al., 2002). It seems likely that normokalemic periodic paralysis should be considered a variant of hyperPP.

p0170	HyperPP, potassium aggravated myotonia (PAM) and paramyotonia congenita (PMC) are allelic sodium channel disorders and their phenotypes overlap to varying degrees (Layzer et al., 1967, de Silva et al., 1990). In hyperPP and paramyotonia congenita women may be less severely affected (Layzer et al., 1967).

p0180	Many patients who have both periodic paralysis and myotonia find it difficult to distinguish between stiffness and weakness and attacks are often initially dominated by stiffness leading to paralysis later. EMG myotonia can be demonstrated in at least 50% of patients with the two most common *SCN4A* mutations T704M and M1592V (Plassart et al., 1994, Miller et al., 2004, Fournier et al., 2004) but myotonia on examination is detected in a smaller percentage (Plassart et al., 1994). Interestingly myotonic symptoms are frequently experienced and easily elicited in the cranial musculature (myotonic lid lag, eye closure myotonia) which is not usually involved in the paralytic attack. Consciousness is preserved and respiratory and cranial musculature is usually spared. A number of factors have been identified that can trigger or exacerbate attacks. These include rest following exercise, fasting, cold, stress, intercurrent infection and anesthesia. Hormonal changes may also play a role as menstruation, oral contraception and pregnancy have been associated with an increase in symptoms (Layzer et al., 1967, Ptacek et al., 1993, Kim et al., 2001).

s0050	### 4.2.3. Andersen–Tawil syndrome (ATS)

p0190	Andersen–Tawil syndrome first fully described by Andersen et al. (1971) is characterized by a triad of periodic paralysis, ventricular arrhythmia and distinctive physical features. Many patients do not have all of these features and there can be marked intrafamilial variation and evidence of incomplete penetrance (Plaster et al., 2001). It is the rarest form of periodic paralysis and no reliable data exist on prevalence.

Mutations in *KCNJ2* encoding the inward-rectifying potassium channel Kir2.1 have been identified in about two-thirds of kindreds with ATS (Plaster et al., 2001, Tristani-Firouzi et al., 2002). Up to 20% of individuals carrying pathogenic mutations may not exhibit any phenotypic features (Andelfinger et al., 2002, Tristani-Firouzi et al., 2002, Donaldson et al., 2003). De novo mutations are frequent (Donaldson et al., 2003).

p0200	The original case described by Andersen et al. (1971) had quite marked physical abnormalities with low-set ears, hypertelorism, mandibular hypoplasia, scaphocephalic cranium, clinodactyly, single transverse palm crease, central defect of soft and hard palate and cryptorchidism. Many patients with Andersen–Tawil syndrome have only subtle skeletal or facial abnormalities which become more obvious when the patient's appearance is compared with unaffected family members. The most common features are mandibular hypoplasia, hypertelorism, broad-based nose, low-set ears, clinodactyly and syndactyly (Fig. 4.1; Canun et al., 1999). Other possible associated features described in a small number of cases include hypoplastic kidney (Andelfinger et al., 2002), renal tubular acidosis, dysphonia, cognitive impairment (Davies et al., 2005), valvular heart defects (Andelfinger et al., 2002) and vaginal atresia (Canun et al., 1999).

p0210	Symptomatic onset with episodic weakness is typically in the first or second decade. The periodic paralysis is most commonly hypokalemic but may also be hyper- or normokalemic (Donaldson et al., 2003).

p0220	Electrocardiography may show bidirectional or polymorphic ventricular tachycardia, prolonged corrected QT interval, bigeminy, frequent ventricular ectopy or may be normal (Fig. 4.2). A particularly frequent finding is a prominent 'U' wave even in the presence of a normal serum potassium (Tristani-Firouzi et al., 2002). Due to the cardiac abnormalities Andersen–Tawil syndrome is also classified as long-QT syndrome 7 (LQT7). In comparison to other long-QT syndromes the arrhythmias in Andersen–Tawil syndrome are less malignant (Tristani-Firouzi et al., 2002). However sudden cardiac death does occur and patients require careful cardiac evaluation (Andelfinger et al., 2002, Tristani-Firouzi et al., 2002, Donaldson et al., 2003). A more recent study of ECGs from a large cohort of ATS patients established a distinct T-U-wave pattern that reliably distinguished between *KCNJ2* mutation positive ATS patients and those where no mutation could be found (Zhang et al., 2005). The authors also point out that in many ATS patients the QT interval is in fact within the normal limits and the designation of LQT7 should therefore not be used.

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Fig. 4.1. Patient with ATS.

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4.2.4. Thyrotoxic periodic paralysis (TPP)

p0230 The occurrence of periodic paralysis in association with hyperthyroidism was reported as early as 1902 (Rosenfeld, 1902). This form of periodic paralysis is more common in Asia, particularly China, Korea and Japan, where more than 10% of male thyrotoxic patients may be affected (Chen et al., 1965, McFadzean and Yeung, 1967, Ober, 1992, Kung et al., 2004). The overall incidence in thyrotoxic patients from these populations is approximately 2% (McFadzean and Yeung, 1967) while the incidence in Caucasians has been estimated at only 0.1–0.2% (Kelley et al., 1989). Due to migration, cases of (TPP) are now increasingly seen in the Western world (Ober, 1992). It is also recognized in Caucasians (Linder, 1955), native American Indians (Conway et al., 1974), Blacks (Kilpatrick et al., 1994), Aborigines (Ghose et al., 1996) and Maoris (Wild, 2004). The male-to-female predominance is much more marked in TPP (between 20:1 and 76:1) (Okinaka et al.,

1957, McFadzean and Yeung, 1967) compared to hypoPP (3:1; Elbaz et al., 1995). This is even more significant given that the prevalence of thyrotoxicosis is so much higher in females.

Most cases of TPP are sporadic but a few familial   p0240 cases have been described (Kufs et al., 1989, Dias da Silva et al., 2002a). The onset of symptoms is most frequently between the second and fourth decade in parallel to the highest incidence of hyperthyroidism. A significant proportion of patients have only subtle clinical signs of hyperthyroidism (McFadzean and Yeung, 1967, Kelley et al., 1989). Autoimmune thyrotoxicosis (Graves' disease) is the most common underlying disorder but TPP may be caused by any form of hyperthyroidism in susceptible patients including excessive administration of thyroid hormone replacement.

Thyrotoxic periodic paralysis bears phenotypic   p0250 resemblance to familial hypokalemic periodic paralysis. It is associated with low serum potassium during attacks, may be triggered by glucose/insulin administration and

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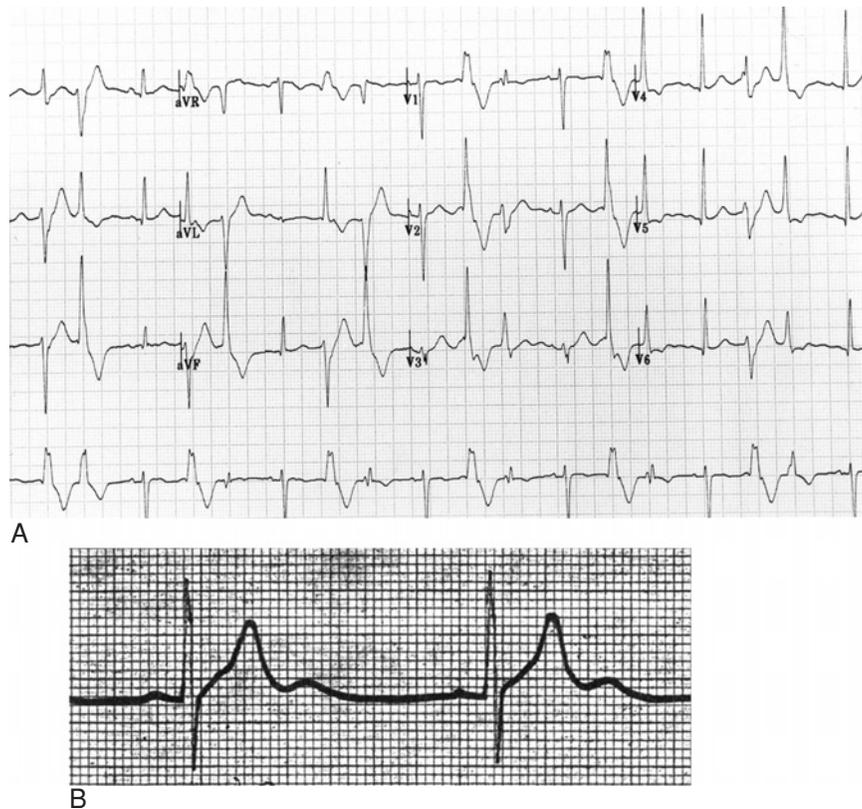
Fig. 4.2. ECG traces from patients with ATS. (A) Frequent polymorphic ventricular ectopy with bidirectional ventricular ectopics detectable in the lateral chest leads. QTc interval borderline prolonged. (B) Prominent U-wave.

may also be triggered by rest following exercise. Focal weakness can develop in more strenuously exercised muscles and attacks typically occur at night or on wakening in the morning (McFadzean and Yeung, 1967). Rare cases with associated normo- or hyperkalemia have been reported, although this was prior to the availability of DNA testing for familial periodic paralysis (Adachihara and Takagi, 1974, Mehta et al., 1990). The respiratory and cranial musculature tend to be spared. Morbidity and mortality is low but significant arrhythmias associated with severe hypokalemia have been reported (McFadzean and Yeung, 1967, Fisher, 1982).

4.2.5. Secondary periodic paralysis

A number of secondary causes of periodic paralysis should to be considered when evaluating a patient with periodic paralysis. Both hypo- and hyperkalemia of any origin can result in muscle weakness or paralysis. Usually the patient remains weak until the underlying cause of potassium alteration is identified and treated. Occasionally patients with a secondary cause may present with intermittent attacks of weakness and this may make the distinction with sporadic genetic periodic paralysis more difficult. In general the electrolyte disturbance tends to be more severe than seen in the familial forms of periodic paralysis. Usually potassium levels have to decline to <3 mmol/l or rise to >7 mmol/l before significant muscle symptoms are experienced. With the exception of barium poisoning and insulin excess there is a loss or excess of total body potassium in secondary periodic paralysis rather than a shift between intra- and extracellular space as is the case in the familial forms and in TPP. Metabolic abnormalities often persist between attacks and this gives an important clue to the underlying diagnosis. The treatment is aimed at correcting the primary abnormality.

A number of conditions mainly causing urinary or gastrointestinal potassium loss leading to hypokalemia have been reported in association with episodic weakness (Table 4.2). With severe hypokalemia there is an associated risk of significant arrhythmias, paralytic ileus and rhabdomyolysis in addition to respiratory failure secondary to muscle paralysis (Weiss-Guillet et al., 2003). The presentation of patients with muscle

t0020 *Table 4.2*

Causes of secondary periodic paralysis

	Conditions leading to hyperkalemia	Conditions leading to hypokalemia
Endocrine	Addison's disease (Pollen and Williams, 1960)	Hyperaldosteronism (primary/secondary) (Conn et al., 1964, Ishikawa et al., 1985, Ma et al., 1986)
	Hypoaldosteronism and hyporeninaemia (Daughaday and Rendleman, 1967)	Cushing's disease/syndrome
	Gordon's syndrome: pseudohypoaldosteronism type II (Pasman et al., 1989)	Hyperreninism (Umeki et al., 1986)
		17α-hydroxylase deficiency (*CYP17*) (Yazaki et al., 1982)
		Hyperinsulinemia
Renal	Chronic renal failure (Cumberbatch and Hampton, 1999)	Bartter's syndrome (Shiah et al., 1994)
		Liddle syndrome
		Gitelman syndrome (Lin et al., 2003)
		Distal tubular acidosis type 1 and 2 +/− Sjögren's syndrome (Owen and Verner, 1960, Raskin et al., 1981)
Gastro-intestinal		Severe diarrhea and vomiting (Ortuno et al., 2002, Haddad et al., 2004)
		Ileostomy
		Uterosigmoidostomy (Angeloni and Scott, 1960, Sataline and Simonelli, 1961)
		Villous adenoma (Keyloun and Grace, 1967)
Drugs/Toxins	Potassium load (Muensterer, 2003)	Licorice (Cumming et al., 1980, Ishikawa et al., 1985)
	Potassium-sparing diuretics (Udezue and Harrold, 1980)	Laxative abuse (Basser, 1979)
	High-dose angiontensin-converting (ACE) inhibitor (Dutta et al., 2001)	Potassium-wasting diuretics (Cohen, 1959)
		Amphotericin B (McChesney and Marquardt, 1964)
		Barium poisoning (Lewi and Bar-Khayim, 1964)
		Toluene exposure (Bennett and Forman, 1980)
		Cocaine (Nalluri et al., 2000, Lajara-Nanson, 2002)
		Gossypol (Wang and Chen, 1991, Waites et al., 1998)

paralysis secondary to hyperkalemia is much less common than hypokalemia (Evers et al., 1998). Most cases of secondary hyperPP are due to potassium-sparing diuretics (spironolactone) often on a background of renal impairment.

p0280 There have been many case reports of primary and secondary renal tubular acidosis (RTA) associated with hypoPP (Koul et al., 1993, Bresolin et al., 2005). Renal tubular acidosis probably due to autoimmune tubulointerstitial nephritis may occur in Sjögren's syndrome and an association with periodic paralysis has been described (Raskin et al., 1981). In some of these cases the muscle symptoms were the presenting complaints (Soy et al., 2005), even leading to respiratory arrest (Poux et al., 1992, Fujimoto et al., 2001). Habitual toluene inhalation (glue sniffing) can also cause RTA and may present with paralysis (Bennett and Forman, 1980).

The first cases of barium poisoning were referred to as p0290 Pa Ping disease due to endemic periodic paralysis in the Pa Ping area of the Szechwan province of China caused by ingestion of table salt contaminated by barium (Allen, 1943). Accidental ingestion of barium salts used as rat poison, industrial accidents, suicidal attempts and administration of barium carbonate instead of the insoluble sulphate in radiodiagnosis have been reported (Lewi and Bar-Khayim, 1964, Berning, 1975, Layzer, 1982, Shankle and Keane, 1988, Ahlawat and Sachdev, 1999). Manifestations of toxicity include hemorrhagic gastroenteritis with vomiting, colic and diarrhea, hypertension, cardiac arrhythmias, muscle twitching, seizures, hypokalemia and muscle paralysis (Johnson and VanTassell, 1991). The hypokalemia in barium poisoning occurs due to a shift of potassium from the extracellular to intracellular compartments. Barium competitively blocks potassium channels causing reduction in potassium

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permeability leading to membrane depolarization and finally inexcitability (Sperelakis et al., 1967, Gallant, 1983). The potassium channels affected include the inward-rectifying channel Kir2.1 which is mutated in the familial periodic paralysis Andersen–Tawil syndrome (Schram et al., 2003). The main treatment consists of oral or intravenous potassium which displaces barium and allows it to be excreted.

4.2.6. Differential diagnosis

Other neuromuscular disorders should also be considered in the differential diagnosis of episodic weakness. The difference between myasthenia and periodic paralysis appears straight forward at first glance. Attacks of weakness are more distinct in PP versus a more long-term fluctuation of muscle strength in myasthenia. Gentle exercise helps to lessen or abort PP attacks while exertion worsens symptoms in myasthenia. The distribution of muscles affected is different (bulbar and extraocular muscles frequently affected in myasthenia and spared in PP). Investigations (neuromuscular junction transmission deficit on repetitive nerve stimulation and single fiber EMG, acetylcholine receptor antibodies, genetic testing) should also easily distinguish between these two disorders. However, diagnostic difficulty may sometimes arise when distinguishing between the limb girdle presentation of myaesthenia and periodic paralysis. In this context it is interesting to note the discovery of a mutation in *SCN4A* leading to loss of sodium channel $Na_v1.4$ function in a patient with attacks of bulbar and respiratory paralysis associated with ptosis and a neuromuscular junction transmission deficit on neurophysiological investigations (Tsujino et al., 2003). This finding indicates that an overlap between periodic paralysis and myasthenia gravis may occur at a molecular level. Of interest is also an Australian family with episodic weakness affecting extraocular, facial, trunk and limb muscles lasting weeks to months (Ryan et al., 1999). The disorder has been linked to the X chromosome but the gene involved has not been identified. Patients with both myotonia congenita and paramyotonia/hyperPP can experience intermittent weakness. In myotonia congenita this is termed transient weakness and presents with brief loss of muscle strength at initiation of movement particularly after a period of rest. Attacks of weakness in patients with hyperPP and paramyotonia congenita are usually more profound and of longer duration. Most other disorders causing acute or subacute muscle weakness (e.g., McArdle's disease, Guillain-Barré syndrome, acute intermittent porphyria) are normally straightforward to exclude by appropriate history, clinical examination and investigations.

4.3. Examination and investigations

4.3.1. General examination and laboratory investigations

General examination of patients between attacks is often normal. Muscle strength testing may reveal evidence of persistent proximal weakness. Patients with hyperPP may show signs of action and percussion myotonia. Lid lag often proves to be the most sensitive indicator of myotonia but it can also be seen in healthy volunteers. Patients with periodic paralysis and myotonia may also exhibit a degree of muscle hypertrophy (McArdle, 1962, Layzer et al., 1967). Attention should be paid to detect any subtle dysmorphic features which may indicate ATS.

Laboratory investigations are directed to establish potassium levels during attacks (ideally soon after the onset of attack) and exclude secondary causes of periodic paralysis. All patients with hypokalemic periodic paralysis should have their thyroid function checked to exclude the possibility of TPP. Routine 12-lead electrocardiography (ECG) should be undertaken in all PP cases since the cranioskeletal features of ATS may be subtle. There is also a risk of cardiac arrhythmias during severe attacks when potassium levels are excessively deranged. Patients with suspected ATS should undergo more thorough cardiological work-up including prolonged ECG recordings, echocardiography and exercise testing.

In the past patients were often subjected to a range of provocative tests, many of which have now been superseded by the availability of genetic analysis and specialized neurophysiological investigations. The principle aim was to induce a clinical focal or generalized attack of paralysis. For hyperPP administration of potassium (orally or intravenously), cooling of limbs and exercise, or a combination has been used. In cases of suspected hypoPP a glucose load with or without additional insulin was the preferred method of inducing attacks. The glucose-insulin test needs to be interpreted with caution as apparent weakness (although without change in reflexes) has also been induced in patients with hyperkalemic periodic paralysis (Layzer et al., 1967). Cardiac monitoring and frequent testing of the serum potassium and glucose level are essential. Another provocative test involved intra-arterial epinephrine together with EMG monitoring.

4.3.2. Genetic testing

DNA testing is now a major diagnostic tool in familial periodic paralysis. However, even with extensive DNA sequencing of the ion channel genes known to be

involved in periodic paralysis, mutations are not detected in one-third of patients with either hyper- or hypokalemic periodic paralysis (Miller et al., 2004). Both *CACNA1S* and *SCN4A* are large genes containing 44 and 25 exons respectively. The genetic testing generally available in DNA diagnostic-service laboratories often only encompasses gene regions containing common mutations. It is therefore important to note that a negative genetic result from such a laboratory reduces the likelihood but does not exclude a diagnosis of familial periodic paralysis. The potassium channel gene *KCNJ2* mutated in ATS is a relatively small single exon gene and direct sequencing analysis of the whole gene is more feasible in the diagnostic laboratory setting. In ATS more than 30 mutations have been identified (Table 4.3) but approximately 30% of kindreds do not harbor mutations in *KCNJ2*. This could be partly because there may be undetected mutations in the promoter or intronic regions of the *KCNJ2* gene (Tristani-Firouzi et al., 2002).

p0350   In patients with clear evidence of hypoPP, analysis for the known mutations in *CACNA1S* should be undertaken first. Mutations have so far only been described at residues 528 (R528H and R528G) and 1239 (R1239G and R1239H) and testing is therefore relatively straightforward. The R528H or R1239H mutations are each found in 40–50% of genotyped hypoPP, patients while the R1239G mutation is much rarer (Ptacek et al., 1994, Elbaz et al., 1995, Fouad et al., 1997, Davies et al., 2001, Sternberg et al., 2001, Miller et al., 2004). The R528G mutation has only been reported in a single Chinese kindred (Wang et al., 2005). Less commonly (<10%) changes are found in *SCN4A* in hypoPP and exon 12 appears to be a hotspot (Bulman et al., 1999, Davies et al., 2001, Sternberg et al., 2001, Miller et al., 2004). Testing of *KCNJ2* may also be helpful even in the absence of cardiac or distinctive physical features as some patients only present with one of the three typical features of ATS.

p0360   DNA of patients with definite hyperkalemic periodic paralysis and/or with evidence of myotonia should be analysed for mutations in *SCN4A*. The two most commonly occurring mutations are T704M and M1592V (Rojas et al., 1991, Ptacek et al., 1991a) accounting for 30–70% and 15–30% respectively of all genotyped patients with hyperPP depending on the population (Plassart et al., 1994, Miller et al., 2004). There are a number of other mutations (Table 4.4). Patients with Andersen syndrome may less commonly suffer from

t0030   *Table 4.3*

KCNJ2 **mutations in Andersen–Tawil syndrome**

Amino acid change	Functional domain	References	Functional effect
R67W	N-terminal	Andelfinger et al., 2002 (gen+funct), Donaldson et al., 2003 (gen)	Strong dominant-negative effect, affinity to PIP$_2$ affected
Y68D	N-terminal	Davies et al., 2005 (gen)	
D71N	N-terminal	Donaldson et al., 2003 (gen)	
D71V	N-terminal	Plaster et al., 2001 (gen+funct), Lange et al., 2003 (funct), Bendahhou et al., 2003 (funct)	Equivalent to D74Y mutation in Bartter's syndrome; strong dominant-negative effect
T74A	N-terminal	Zhang et al., 2005 (gen)	
T75A	N-terminal	Fodstad et al., 2004 (gen +funct)	No clear dominant-negative effect
T75R	N-terminal	Donaldson et al., 2003 (gen)	
T75M	N-terminal	Davies et al., 2005 (gen+funct)	Dominant-negative effect
D78G	N-terminal	Davies et al., 2005 (gen+funct)	Dominant-negative effect
R82Q	M1	Davies et al., 2005 (gen+funct)	Dominant-negative effect
Del 95–98	M1	Plaster et al., 2001 (gen), Tristani-Firouzi et al., 2002 (gen+funct), Lange et al., 2003 (funct), Bendahhou et al. 2003 (funct)	Dominant-negative effect
C101R	M1	Chun et al., 2004 (gen+funct)	
V123G	Extra-cellular loop	Davies et al., 2005 (gen)	
S136F	P	Plaster et al., 2001 (gen), Tristani-Firouzi et al., 2002 (gen+funct); Lange et al., 2003 (funct), Bendahhou et al., 2003 (funct)	Dominant-negative effect

(continued)

Table 4.3

(Continued)

Amino acid change	Functional domain	References	Functional effect
G144S	P	Plaster et al., 2001 (gen), Tristani-Firouzi et al., 2002 (gen+funct), Lange et al., 2003 (funct), Bendahhou et al., 2003 (funct)	First G of GYG motif; weak dominant-negative effect
G146D	P	Donaldson et al., 2003 (gen)	Second G of GYG motif
C154F	Extra-cellular loop	Bendahhou et al., 2005 (gen+funct)	Dominant-negative effect
Del 163–164	M2	Fodstad et al., 2004 (gen+funct)	No clear dominant-negative effect
P186L	C-terminal	Tristani-Firouzi et al., 2002 (gen+funct)	Alters PKKKR m otif (AA 186–9) implicated in PIP_2 binding
R189I	C-terminal	Donaldson et al., 2003 (gen)	Affinity to PIP_2
T192A	C-terminal	Ai et al., 2002 (gen+funct)	Region 175–206 binding of PIP_2; also region necessary for multimerization, only minimal dominant-negative effect
G215D	C-terminal	Hosaka et al., 2003 (gen+funct)	Dominant-negative effect
N216H	C-terminal	Tristani-Firouzi et al., 2002 (gen+funct), Bendahhou et al., 2003 (funct)	Region 207–246 thought to be involved in PIP_2 interaction; weak dominant-negative effect
L217P	C-terminal	Davies et al., 2005 (gen+funct)	Dominant-negative effect
R218W	C-terminal	Plaster et al., 2001 (gen+funct), Donaldson et al., 2003 (gen), Lange et al., 2003 (funct)	Affinity to PIP_2; weak dominant-negative effect
R218Q	C-terminal	Plaster et al., 2001 (gen), Tristani-Firouzi et al., 2002 (gen+funct), Lopes et al., 2002 (funct), Bendahhou et al., 2003 (funct)	Dominant-negative effect, decreases PIP_2 binding
G300D	C-terminal	Donaldson et al., 2003 (gen), Davies et al., 2005 (gen+funct)	Dominant-negative effect, affinity to PIP_2 probably through allosteric interaction
G300V	C-terminal	Plaster et al., 2001 (gen), Tristani-Firouzi et al., 2002 (gen+funct), Lopes et al., 2002 (funct), Lange et al., 2003 (funct), Bendahhou et al., 2003 (funct)	Weak dominant-negative effect, decreases PIP_2 binding
V302M	C-terminal	Tristani-Firouzi et al., 2002 (gen+funct), Bendahhou et al., 2003 (funct)	Affects trafficking and/or assembly, mutant channels don't reach membrane; effect through haploinsufficiency
E303K	C-terminal	Plaster et al., 2001 (gen), Tristani-Firouzi et al., 2002 (gen+funct), Lopes et al., 2002 (funct), Lange et al., 2003 (funct), Bendahhou et al., 2003 (funct)	Strong dominant-negative, decreases PIP_2 binding
T309I	C-terminal	Bendahhou et al., 2005 (gen+funct)	Dominant negative
R312C	C-terminal	Donaldson et al., 2003 (gen)	Affinity to PIP_2
Del 314–315	C-terminal	Plaster et al., 2001 (gen), Tristani-Firouzi et al., 2002 (gen+funct), Lange et al., 2003 (funct), Bendahhou et al., 2003 (funct)	Strong dominant-negative, trafficking of channels containing mutant subunits impaired

gen: genetic; funct: functional; del: deletion; PIP_2: phosphatidylinositol 4,5-bisphosphate

Table 4.4

SCN4A mutation causing periodic paralysis and/or myotonia

Amino acid change	Domain/ segment	Exon	Phenotype	References	Functional effect; comments	
L266V	DI/S5	6	Cold-aggravated myotonia	Wu et al., 2001 (gen+funct)	Impaired fast inactivation	Au1
V445M	DI/S6	9	Myotonia	Rosenfeld et al., 1997 (gen), Takahashi and Cannon, 1999(funct)	Impaired fast inactivation, enhanced slow inactivation	Au2, 3
R669H	DII/S4	12	HypoPP	Bulman et al. 1999 (gen), Struyck et al., 2000 (funct), Kuzmenkin et al., 2002 (funct)	Enhanced fast and slow inactivation	
R672G	DII/S4	12	HypoPP	Jurkat-Rott et al., 2000b (gen+funct), Sternberg et al., 2001 (gen), Kuzmenkin et al., 2002 (funct)	Enhanced fast and slow inactivation	
R672S			HypoPP	Bendahhou et al., 2001 (gen+funct), Sternberg et al., 2001 (gen), Davies et al., 2001 (gen)	Enhanced fast and slow inactivation	
R672H			HypoPP	Jurkat-Rott et al., 2000b (gen+funct), Sternberg et al., 2001 (gen), Kuzmenkin et al., 2002 (funct)	Enhanced fast inactivation	
R672C			HypoPP	Kim et al., 2004 (gen), Miller et al., 2004 (gen)		
R675G	DII/S4	13	PP	Vicart et al., 2004 (gen)		
R675W			PP	Vicart et al., 2004 (gen)		
R675Q			PP	Vicart et al., 2004 (gen)		
L689V	DII/S4–5	12	PP	Miller et al., 2004 (gen)		
L689I			HyperPP	Bendahhou et al., 2002 (gen+funct)	Impaired slow inactivation, enhanced activation	Au4
I693T	DII/S4–5	13	PMC; PP	Plassart et al., 1996 (gen), Hayward et al., 1999(funct)	Impaired slow activation	Au5
T704M	DII/S5	13	HyperPP	Ptacek et al., 1991a (gen), Cannon and Strittmatter, 1993b (funct), Hayward et al., 1999	Impaired slow inactivation	Au6
V781I	DII/S6	13	HyperPP	Baquero et al., 1995 (gen), Miller et al., 2004 (gen), Green et al., 1997(funct)	?benign polymorphism	
S804F	DII-III	14	Myotonia	McClatchey et al., 1992a (gen), Green et al., 1998 (funct)	Impaired fast inactivation	Au7, 8
A1156T	DIII/S4–5	19	HyperPP	McClatchey et al., 1992a (gen), Yang et al., 1994, Hayward et al., 1999 (funct)	Impaired fast inactivation	Au9
P1158S	DIII/S4–5	19	Cold-induced hypoPP + heat-induced myotonia	Sugiura et al., 2000 (gen), 2003 (funct)	Temperature-dependent shift of voltage dependence	
I1160V	DIII/S4–5	19	PAM	Richmond et al., 1997b (gen+funct)	Impaired fast inactivation	
V1293I	DIII/S6	21	PMC	Koch et al., 1995 (gen), Green et al., 1998 (funct)	Impaired fast inactivation and enhanced activation	Au10
G1306V	DIII-IV	22	PMC	McClatchey et al., 1992b (gen), Mitrovic et al., 1995 (funct)	Impaired fast inactivation	Au11

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(continued)

Table 4.4

(Continued)

Amino acid change	Domain/ seg-ment	Exon	Phenotype	References	Functional effect; comments	
G1306E			Myotonia	Lerche et al., 1993 (gen), Mitrovic et al., 1995 (funct)	Impaired fast inactivation and enhanced activation	Au12
G1306A			Myotonia	Lerche et al., 1993 (gen), Mitrovic et al., 1995 (funct)	Impaired fast inactivation	
T1313M	DIII-IV	22	PMC	McClatchey et al., 1992b (gen), Richmond et al., 1997a (funct)	Impaired fast inactivation	
M1360V	DIV/S1	23	HyperPP	Lehmann-Horn et al., 1993 (gen), Wagner et al., 1997 (gen+funct)	Impaired inactivation	Au13, 14
I1363T	DIV/S1	23	?	Miller et al., 2004 (gen)		
M1370V	DIV/S1	23	HyperPP and PMC	Okuda et al., 2001(gen)		Au15
L1433R	DIV/S3	24	PMC; hyperPP	Ptacek et al., 1993 (gen), Yang et al., 1994 (funct)	Impaired inactivation	
V1442E	DIV/S3–4	24	Myasthenic syndrome	Tsujino et al., 2003 (gen+funct)	Enhanced fast inactivation, found together with S246L (possible benign polymorphism)	
R1448C	DIV/S4	24	PMC; PMC + hyperPP	Ptacek et al., 1992 (gen), Chahine et al., 1994 (funct), Richmond et al., 1997a (funct)	Impaired fast inactivation	Au16, 17
R1448S			PMC	Bendahhou et al., 1999a (gen+funct)	Impaired fast inactivation	
R1448P			PMC	Wang et al., 1995 (gen), Mitrovic et al., 1999 (funct)	Impaired inactivation	
R1448H			PMC+PP	Ptacek et al., 1992 (gen), Chahine et al., 1994 (funct)	Impaired fast inactivation	
G1456E	DIV/S4	24	PMC	Sasaki et al., 1999 (gen)		
V1458F	DIV/S4	24	PMC	Lehmann-Horn et al., 1993 (gen)		
F1473S	DIV/S4–5	24	PMC	Fleischhauer et al., 1998 (gen+funct)	Impaired fast inactivation	Au18
F1490L + M14931	DIV/S5	24	HyperPP	Bendahhou et al., 2000 (gen+funct)	Enhanced slow activation	
I1495F	DIV/S5	24	HyperPP	Bendahhou et al., 1999b (gen+funct)	Impaired fast inactivation, enhanced activation and enhanced slow inactivation	
V1589M	DIV/S6	24	Myotonia	Heine et al., 1993 (gen), Mitrovic et al., 1994 (funct)	Impaired fast inactivation	Au19
M1592V	DIV/S6	24	HyperPP	Rojas et al., 1991 (gen), Cannon and Strittmatter, 1993b (funct), Hayward et al., 1999 (funct)	Impaired slow activation	
E1702K	C-terminal	24	PMC	Miller et al., 2004 (gen)		
F1705I	C-terminal	24	PMC	Wu et al., 2005 (gen+funct)	Impaired fast inactivation	

gen: genetic; funct: functional, PMC: paramyotonia congenita

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hyperkalemic periodic paralysis (without myotonia) and testing of *KCNJ2* may be indicated in selected cases.

p0370 In patients where the clinical data is insufficient to decide whether the patient is suffering from hypo- or hyperkalemic periodic paralysis testing for the common mutations in both *SCN4A* and *CACNA1S* is a reasonable strategy.

s0120 **4.3.3. Neurophysiological examination**

p0380 Routine nerve conduction studies between attacks are normal. EMG may show myopathic changes, particularly in those patients who have developed fixed weakness. In patients with hyperPP evidence of sarcolemmal hyperexcitability in the form of myotonic discharges, increased insertional activity and spontaneous fibrillation and positive sharp waves may be found. Myotonic discharges can be present even in the absence of clinical symptoms or signs of (para)myotonia but the degree of abnormality tends to correlate with the clinical picture. The presence of myotonic discharges has important implications as they are not seen in hypokalemic periodic paralysis regardless of the underlying genetic defect (*CACNA1S*, *SCN4A* or *KCNJ2*) (Fournier et al., 2004). The detection of myotonia is therefore helpful in directing gene analysis to SCN4A.

p0390 During an attack the compound motor action potential (CMAP) amplitude and area are reduced. Needle EMG shows fibrillation potentials and positive sharp waves, a decrease in insertional activity, and there is an increased proportion of polyphasic motor unit potentials (Engel et al., 1965). With severe paralysis the muscle may become completely inexcitable.

p0400 More specific tests include the use of provocation such as exercise, rest and cold, all in combination with EMG or CMAP monitoring.

p0410 McManis et al. introduced the long exercise test in 1986 (McManis et al., 1986). This involves sustained maximal isometric exercise for 2–5 min (with a short rest period every 15–30 s) in one of the small hand muscles (typically abductor digiti minimi; ADM) with CMAP monitoring every 1–2 minutes during and after the exercise for approximately 30–40 minutes or until no further decrement occurs. The authors observed a significant delayed CMAP amplitude decline in 75% of patients with clinically definite or possible familial periodic paralysis with positive family history using a cutoff point of 40% CMAP decrement. In this study the decline was greater and more frequently seen in patients with hyperPP compared to hypoPP. When familial and secondary causes of periodic paralysis are considered together the long exercise test has been found highly specific (97.8%) in one study (Kuntzer et al., 2000). Prior to the availability of genetic testing McManis et al. (1986)

found a sensitivity of approximately 73% for the long exercise test (including acquired and familial periodic paralysis). Kuntzer et al. (2000) quoted a sensitivity of 81% for periodic paralysis caused by sodium- or calcium-channel mutations. In a study of two families with hypoPP the long exercise test only identified 55% of subjects who where found to carry the *CACNA1S* mutation R528H (Tengan et al., 2004). All subjects who were mutation positive but had a negative exercise test were either asymptomatic carriers or had not had an attack of paralysis in the year prior to the examination. This indicates that the exercise test reflects disease activity, which needs to be taken into account when assessing patients. Patients with frequent or recent attacks of paralysis and a normal exercise test are unlikely to suffer from periodic paralysis. With less recent attacks a negative exercise test has to be interpreted with caution. In hyperPP the CMAP decrement in response to exercise may become more profound after cooling. Successful treatment, such as with mexiletine, can lead to an improvement in the neurophysiological abnormality (Kim et al., 2001). In thyrotoxic periodic paralysis the exercise test normalizes after correction of the hyperthyroidism (Jackson and Barohn, 1992).

p0420 Simple limb immobilization can lead to a decline in CMAP in affected patients. The effect seems to be slightly delayed compared to post-exercise measurements but the percentage decline after 1 hour was not significantly different in a group of three patients (Subramony and Wee, 1986). This phenomenon may also explain why it is impossible at times to obtain a stable baseline CMAP in some patients (McManis et al., 1986).

p0430 The short exercise test was originally described by Streib and colleagues (1982) investigating patients with myotonia. The technique involves a short period (10 s) of isometric contraction of one of the small hand muscles followed by CMAP monitoring every 10 s usually up to one minute. In normal individuals a transient small increase in CMAP amplitude may be observed (Streib et al., 1982, Fournier et al., 2004). The short exercise test has been found helpful in the evaluation of patients with myotonia congenita where a transient decrease in CMAP amplitude mirrors the transient weakness elicited clinically (Streib et al., 1982, Fournier et al., 2004). In paramyotonia congenita there is a decrease in CMAP following exercise which is exacerbated or may only become apparent after cooling (Streib et al., 1983, Jackson et al., 1994). Not many reports exist on the use of the short exercise test in periodic paralysis. Fournier et al. (2004) tested six patients with hyperkalemic periodic paralysis with the common T704M *SCN4A* mutation and found a more pronounced and sustained CMAP increase compared to normal controls (23%± 3% vs 5±1%). Further increase in CMAP amplitude

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was seen with repeated short exercise test (+64%± 11%). This correlates well with the experience of patients that light activity may improve or even abort an attack of paralysis. In the same study patients with paramyotonia congenita (*SCN4A* mutations T1313M and R1448C) showed a moderate decrease in CMAP amplitude which in contrast to patients with myotonia congenita persisted for at least one minute and worsened with repeated exercise. Patients with hypokalemic periodic paralysis (13 with *CACNA1S* mutation and 2 with *SCN4A* mutation) showed no abnormalities in the short exercise test. In a different study no changes were demonstrated in two subjects with ATS (Bendahhou et al., 2005).

p0440   Exposure to cold may trigger attacks of weakness in patients with hyperPP, typically in those who suffer with an overlap of paramyotonia and periodic paralysis. This phenomenon is exploited in the cooling test. Different methods of limb cooling have been applied. Bathing the hand or forearm in ice water is the quickest way but can be uncomfortable. It is important to note that the aim is to reduce the muscle temperature which is usually only indirectly measured through surface temperature. Using a cold water bath which is kept at a constant temperature may achieve more even cooling with less discomfort to the patient but takes much longer than the ice-bath method. In normal subjects CMAP amplitude and duration increases with lower temperatures. In general the cooling test is most helpful in patients with paramyotonia congenita where a significant drop in CMAP amplitude or EMG signal or complete electrical silence may be observed. Similar findings can be seen in some subjects with hyperPP particularly those who have additional signs or symptoms of myotonia (de Silva et al., 1990, Kim et al., 2001). In addition the CMAP amplitude decrement seen during the long exercise test may be exacerbated by cold exposure (Kim et al., 2001).

p0450   A reduction of average muscle fiber conduction velocity (MFVC) between attacks in familial hypoPP was found by Troni et al. (1983) using needle EMG and direct muscle stimulation. Similar changes were later seen in familial and sporadic hypoPP utilizing high-resolution surface EMG signals (Zwarts et al., 1988, Brouwer et al., 1992, Cruz-Martinez and Arpa, 1997). This technique is less invasive and involves the estimation of MFVC computed from the delay between surface EMG signals detected from at least two different muscle locations along the fiber direction during voluntary contraction. Although initially considered promising as a non-invasive test, a major disadvantage has been the poor reproducibility (Rainoldi et al., 2001). Reproducibility can be improved by recording from multiple channels using a linear electrode array

(Farina et al., 2004). Abnormalities in MFVC are not specific for muscle channelopathies but can be detected in other neuromuscular disorders (van der Hoeven et al., 1993, Huppertz et al., 1997). These factors, together with the need for specialist equipment, have prevented this technique from becoming widely accepted as a major diagnostic tool in clinical practice.

4.3.4. Histopathology   s0130

p0460   Muscle biopsy is not usually indicated in making the diagnosis of periodic paralysis. Commonly observed changes in muscle biopsies include vacuolar changes and tubular aggregates. Histopathological features generally do not distinguish between the subtypes of periodic paralysis. Occasionally, a biopsy with typical changes may be helpful in patients who are evaluated with prominent myopathy in the absence of paralytic attacks. The changes appear to be more closely related to the degree of fixed weakness rather than the number of attacks. Histopathological abnormalities including glycogen accumulation have been reported in the absence of paralytic attacks or clinical myopathy (Buruma and Bots, 1978).

p0470   Vacuolization of muscle fibers in familial periodic paralysis first discovered by Goldflam (1895, 1897) has been shown repeatedly in cases with the hypo- and hyperkalemic variants of the disorder. Studies on histopathological and ultrastructural abnormalities prior to 1970 where extensively reviewed by Engel, who also summarized his own observations (Engel, 1970). The vacuoles are usually empty but at times contain granular material with an affinity for glycogen staining. Periodic acid-Schiff (PAS)-positive material occasionally fills the entire vacuole but is more frequently located in one of the vacuolar compartments or in small subsarcolemmal or intermyofibrillar spaces. Regions with increased acid phosphatase activity may be seen associated with vacuoles. The same regions often also show NADH dehydrogenase and cytochrome oxidase activity. Engel studied the development of vacuoles in detail and concluded that they originated from proliferated T tubules and dilated sarcoplasmic reticulum components.

p0480   Tubular aggregates consisting of subsarcolemmal proliferations of longitudinal components of the sarcoplasmic reticulum are another feature described in periodic paralysis (Engel, 1970). They may be particularly frequent finding in Andersen–Tawil syndrome (Tawil et al., 1994). However, tubular aggregates can be a nonspecific feature seen in a number of other neuromuscular disorders (Morgan-Hughes, 1998).

p0490   Many other non-specific findings, including variation in fiber diameter, excess of internal nuclei and regional rarefaction, have been described (Engel, 1970).

4. Treatment

4.1. Treatment of familial periodic paralysis

4.1.1. Lifestyle and dietary advice

Simple advice on lifestyle changes to avoid recognized triggering factors can be helpful and should be given to all patients. In all patients with periodic paralysis excessive exertion, particularly when followed by a long period of rest, such as sleep overnight, should be avoided. During an attack gentle physical activity can be helpful in aborting symptoms. Many patients benefit from "warming down" after exercise. Dietary advice includes regular meals (to prevent fasting) and avoidance of potassium-rich foods (banana, melon and a number of other fruits) in hyperPP. Ingestion of carbohydrate-containing drinks or snacks may abort attacks in hyperPP while patients with hypoPP should avoid large carbohydrate-rich meals, particularly late in the evening.

3.4.1.2. Medication options

Potassium chloride can be used in the treatment of an acute attack in hypoPP. Oral preparations are preferable as there is a higher risk of rebound hyperkalemia with intravenous administration. Regular use may reduce the frequency of attacks. Agents that reduce urinary potassium loss such as spironolactone (100 mg/day) or triamterene (150 mg/day) can also improve symptoms in hypoPP.

Patients with hyperPP may benefit from treatment to prevent hyperkalemia including thiazide diuretics (McArdle, 1962) and inhaled β-agonists (Wang and Clausen, 1976, Bendheim et al., 1985, Hanna et al., 1998).

Inhibitors of carbonic acid anhydrase (acetazolamide, dichlorphenamide) are useful in both hypoPP and hyperPP (McArdle, 1962, Resnick et al., 1968). Studies in hypoPP suggest that interictal low-grade weakness may also improve (Griggs et al., 1970, Dalakas and Engel, 1983). However, at present none of the treatments used in periodic paralysis have been proven to prevent the progressive myopathy seen in both hypoPP and hyperPP. The exact mechanism underlying the beneficial effect of carbonic anhydrase inhibitors remains unclear. One of several possibilities includes acidification of the channel microenvironment. The channel defect may be alleviated by a reduction in the muscle pH as shown in expression studies for some mutations (Kuzmenkin et al., 2002). A similar mechanism may explain why gentle exercise (known to cause transient hyperkalemia) can improve symptoms during a mild attack. In vitro studies also show that carbonic anhydrase inhibitor improve weakness in K^+-deficient rats (an animal model for hypoPP) through activation of calcium-activated potassium channels rather than direct inhibition of carbonic anhydrase (Tricarico et al., 2000, 2004).

Acetazolamide has been evaluated in a number of case studies although evidence from a randomized double-blind placebo-controlled trial is lacking. The dosage should be started low at 62.5 or 125 mg daily and increased gradually until a satisfactory response is achieved but usually not higher than 1000 mg/day given in two or three divided doses. Distal paresthesiae, headaches and occasionally mood disturbance including depression can be experienced. An important long-term complication is the development of renal calculi in 10–20% of patients (Tawil et al., 1993). Therefore, all patients should undergo baseline and yearly follow-up renal imaging to enable early detection and treatment of nephrolithiasis. Regular intake of citrus drinks reduces the development of renal calculi.

The efficacy of dichlorphenamide (50–300 mg/day) was demonstrated in a double-blind placebo-controlled crossover trial (Tawil et al., 2000). Despite the limitations of this study such as the dropout rate and unblinding of patients and investigators, the effectiveness of dichlorphenamide to prevent or reduce the severity and frequency of attacks in both hyperPP and hypoPP was clearly shown. Side-effects and consequent precautions are similar to acetazolamide.

Some reports suggest that acetazolamide can exacerbate symptoms in patients with hypoPP due to sodium channel mutations (Bendahhou et al., 2001, Sternberg et al., 2001) but others report benefit (Kuzmenkin et al., 2002, Kim et al., 2004). Treatment-induced worsening with carbonic anhydrase inhibitors can also occur with other mutations and patient should be warned and monitored accordingly.

Patients with hyperPP and myotonia may also benefit from antimyotonic agents such as mexiletine (200–600 mg/day in two or three divided doses). Due to its cardiac side-effects mexiletine should be monitored with baseline and follow-up ECGs.

Potassium-channel openers have been investigated as potential treatment agents in hypoPP. Theoretically, by increasing potassium conductance, the muscle membrane could be repolarized and attacks prevented. Diazoxide, cromakalim and pinacidil, drugs with an antihypertensive vasodilator effect, are known to directly activate ATP-sensitive potassium channels. Diazoxide was initially effective in preventing attacks in patients with hypoPP but became ineffective after a few months (Johnsen, 1977). In vitro studies in human hypoPP muscle fibers showed that cromakalim did repolarize the muscle membrane and restore twitch force (Grafe et al., 1990). Ligtenberg et al. (1996) found

some increase in muscle strength following carbohydrate challenge in two out of four hypoPP patients after using pinacidil. Clinically the use of K-ATP openers has been limited due to severe side-effects including hypotension and hyperglycaemia. Nevertheless more selective channel modulators may improve management in the future.

s0180 4.4.2. Periodic paralysis and anesthesia

p0590 There are case reports of patients with periodic paralysis having episodes of malignant hyperthermia (Paasuke and Brownell, 1986, Lambert et al., 1994, Rajabally and El Lahawi, 2002). In one of these patients a mutation in the ryanodine receptor has been identified (Marchant et al., 2004). Whether another unidentified mutation in a voltage-gated channel is responsible for the periodic paralysis in this particular case is uncertain. From a practical point of view it is advisable to avoid volatile anesthetics although there is no definite evidence of an increased risk of malignant hyperthermia in this patient group. The more frequent anesthetic complication is an attack of paralysis following an intervention (Fouad et al., 1997). This is not unexpected given the known trigger factors (stress, immobility, cold, exertion during labor) in addition to anesthetic drugs. The management plan should take these factors into account (avoidance or minimization of pain, carbohydrate loads in hypoPP, fasting and cold in hyperPP, sympathomimetics, prolonged labor, etc.). Non-depolarizing muscle relaxants, propofol, and regional anesthesia have been found to be relatively safe (Aarons et al., 1989, Ashwood et al., 1992, Cone and Sansome, 1992, Weller et al., 2002).

s0190 4.4.3. Treatment of Andersen–Tawil syndrome

p0600 Treatment of ATS presents a particular problem as muscle and cardiac symptoms often occur independently and treatment of one may exacerbate the other. Carbonic anhydrase inhibitors appear to be beneficial and are probably the first line treatment for the muscle symptoms. A single report suggested efficacy of terbutaline, a β_2-agonist, reducing the frequency of paralytic attacks (Djurhuus et al., 1998). The same patient had also responded to potassium and spironolactone. It is curious that a β_2-agonist, usually helpful in hyperPP, and medication often given in hypoPP, should be beneficial in the same patient. The lack of evidence from randomized controlled trials in this rare condition is unlikely to change soon.

p0610 The management of cardiac arrhythmias can range between simple monitoring to necessity of pacemaker or implantable cardioverter defibrillator. Case reports exist on the successful use of amiodarone (Junker et al., 2002) and imipramine (Gould et al., 1985, Tawil et al., 1994). Imipramine does not interact with Kir2.1 channels (Kobayashi et al., 2004) but it has inhibitory effects on many other cardiac potassium, sodium and calcium channels (Garcia-Ferreiro et al., 2004). Beta-blockers have been tried (Sansone et al., 1997). Verapamil has been found beneficial in one patient (Kannankeril et al., 2004) but worsened muscle symptoms in another (Sansone et al., 1997).

4.4.4. Treatment of thyrotoxic periodic paralysis   s0200

p0620 Effective treatment of TPP requires the correction of the endocrine abnormality. Once the patient becomes euthyroid the paralytic attacks cease and neurophysiological abnormalities disappear (Jackson and Barohn, 1992). The underlying susceptibility however remains and excessive thyroid supplementation may induce recurrence of attacks. Correcting thyrotoxicosis can sometimes take weeks or months during which time prevention and treatment of acute attacks may be desirable in severely affected patients.

p0630 In contrast to the familial periodic paralyses no convincing benefit from carbonic anhydrase inhibitors has been described in TPP (Norris, et al., 1971, Yeung and Tse, 1974). Most centers use potassium supplementation, a beta-blocker, or a combination to treat acute attacks. Lu et al. (2004) conducted a small study comparing intravenous potassium chloride in 20 patients with no potassium chloride administration in 12 patients. Patients in the untreated group all recovered spontaneously but took twice as long as the treated cohort (13.5 ± 7.5 vs 6.3 ± 3.8 hours, $p<0.01$). However, in 40% of patients receiving potassium rebound hyperkalemia developed with $K^+>5.5$ mmol/l. Intravenous potassium chloride for the acute treatment of paralysis in TPP should therefore probably be reserved for severe cases with associated cardiac arrhythmias where rapid normalization of serum potassium level is required. In other cases oral potassium supplement or simple monitoring with no potassium supplementation may suffice.

p0640 Beta-blockers can be used both in acute attacks as well as a preventive measure. It has been postulated that hyperadrenergia during thyrotoxicosis contributes to the muscle weakness. Indeed, a 6-day course of propranolol (40 mg four times daily) prevented or lessened the severity of paralysis induced by a high carbohydrate diet in five out of seven patients with TPP (Yeung and Tse, 1974). Oral propranolol without potassium supplementation has been found by other authors to be beneficial (Conway et al., 1974, Lin and Lin, 2001). Intravenous propranolol together with potassium supplementation has also been described (Payne et al.,

1979, Shayne and Hart, 1994, Birkhahn et al., 2000). Again, rebound hyperkalemia with cardiac arrhythmias was observed.

4.5. Genetic and in vitro electrophysiological characteristics

4.5.1. Calcium channel periodic paralysis

Missense mutations in the pore-forming α-subunit of the dihydropyridine-sensitive (L-type) calcium channel $Ca_v1.1$ of skeletal muscle are the main cause of familial hypokalemic periodic paralysis. In 1994, in a genome-wide search in three affected European families, Fontaine et al. (1994) discovered linkage to chromosome 1q31–q32. They also established that the *CACNA1S* gene mapped to the same region and cosegregated with the disease with no recombinants in two families. The first mutations were identified by Ptacek et al. (1994) and Jurkat-Rott et al. (1994). A founder effect has not been established (Elbaz et al., 1995, Grosson et al., 1996).

The $Ca_v1.1$ gene spans about 73 kb, and consists of 44 exons (Drouet et al., 1993). Similarly to other voltage-gated sodium and calcium channels, $Ca_v1.1$ is made up of the main pore-forming α-subunit which is associated with accessory units (α2, δ, β and γ). Within the α-subunit four homologous domains can be distinguished (DI–IV). Each domain correlates to a single subunit of the voltage-gated potassium channel, which requires four subunits to assemble a complete pore-forming channel. Evolutionarily, the α-subunit of the calcium and sodium channels developed through gene duplication from these potassium channels. Each domain of $Ca_v1.1$ is made up of six transmembrane segments. The fourth transmembrane segment (S4) contains regularly-spaced positively charged amino acids and functions as the voltage sensor. This segment is thought to move outward upon depolarization and channel openings (Mannuzzu et al., 1996, Yang et al., 1996). Other important structures are the loops between segments five and six of each domain which re-enter the membrane and come together to provide the lining of the pore and determine the ion selectivity. In skeletal muscle conformational changes of $Ca_v1.1$ have been shown to activate the ryanodine receptor, facilitating calcium release from the sarcoplasmic reticulum, thus mediating excitation-contraction coupling.

Some controversy exists regarding the precise sub-unit topology and voltage sensor movement, following the crystallization of a bacterial voltage-gated potassium channel (Jiang et al., 2003). Two main models for the voltage sensor movement exist (Ahern and Horn, 2004). In the conventional model, which seems to be more in keeping with most of the experimental data obtained so far, S4 moves in a helical screw or in a helical twist pattern inside the densely packed channel protein. However, the "paddle" model assumes that the S4-charged helical segment and portions of S3 form a paddle that lies at the periphery of the channel, parallel to the intracellular membrane–water interface. During depolarization, the paddle-like motif moves across the membrane toward the extracellular side, thus triggering channel opening.

All four mutations identified in *CACNA1S* causing periodic paralysis occur at positively charged arginines in the voltage-sensing region of the channel. Interestingly, the sodium channel mutations identified causing hypoPP also affect positively charged arginines in the voltage sensing region of *SCN4A*. Two other changes in *CACNA1S* have been identified in a few families causing malignant hyperthermia. These mutations (R1086H and R1086C) occur in the loop connecting domains III and IV (Monnier et al., 1997, Jurkat-Rott et al., 2000a).

The exact mechanism through which mutations in *CACNA1S* cause periodic paralysis is unknown. The channel does not contribute on its own to membrane excitability. Expression studies of mutant channels as well as primary cultures of affected muscle have shown only moderate functional changes. These range from reduced current density, slowing in activation rate to enhanced rate of closing (Lapie et al., 1996, Jurkat-Rott et al., 1998, Morrill and Cannon, 1999). The effect of these changes is a reduction in calcium influx into the muscle. It has been suggested that an indirect effect on other channels is responsible for the clinical presentation. In keeping with this, patch recordings from fibers with the R528H mutation showed a loss of potassium conductance of an ATP-sensitive K^+ channel (Tricarico et al., 1999). Ruff (1999) also reported an insulin-induced reduction in potassium currents. How this is linked to the calcium channel remains unclear. One hypothesis for the pathogenesis of hypoPP is that a disruption of the calcium homeostasis due to mutant $Ca_v1.1$ channels alters the transcription, expression or regulation of other ion channels including potassium channels. A reduced potassium current in turn could then explain the depolarized resting potential and the intracellular trapping of potassium during attacks.

Even at baseline the resting potential in hypoPP muscle is depolarized by 5–10 mV compared to normal (Rudel et al., 1984, Ruff, 1999). Hypokalemia in hypoPP results from the physiological effect of glucose intake and the release of insulin which in turn stimulates the sodium–potassium pump and shifts potassium from the extracellular to the intracellular space. In normal muscle fibers this leads to hyperpolarization. In contrast, in hypoPP muscle fibers hypokalemia

causes depolarization and induces an attack of paralysis (Rudel et al., 1984, Minaker et al., 1988).

4.5.2. Sodium-channel periodic paralysis

Clinically the sodium channelopathies of skeletal muscle can be divided into three main allelic disorders: hyperkalemic periodic paralysis, paramyotonia congenita and potassium-aggravated myotonia. Patients with sodium channel hyperPP may also complain of symptoms suggestive of paramyotonia congenita or potassium-aggravated myotonia as these conditions frequently overlap (Sasaki et al., 1999).

The pioneering work on muscle specimens from myotonic goat by Bryant and colleagues (Bryant, 1962, Lipicky and Bryant, 1966) identified the loss of resting chloride conductance as the primary underlying defect, which was later confirmed in myotonia congenita in humans (Lipicky and Bryant, 1973). In the early 1980s Lehmann-Horn and colleagues undertook a series of in-vitro electrophysiological studies on human intercostals muscle fibers to see whether patients with both myotonia and periodic paralysis also had a chloride-channel defect (Lehmann-Horn et al., 1981, 1983). Unlike in muscle with myotonia congenita, chloride conductance was normal but they identified an anomalous persistent inward cation current. This current was blocked by tetrodotoxin which implicated the voltage-gated skeletal-muscle sodium channel. An isoform of the α-subunit of this channel was first cloned from rat by Trimmer et al. (1989). The human gene SCN4A maps to 17q23–q24, spans 35 kb, contains 25 exons and codes for a 1836-amino-acid protein (George et al., 1991, 1992, 1993). Linkage for hyperkalemic periodic paralysis to SCN4A was found in 1990 by Fontaine et al.

(1990). This was confirmed by Ptacek et al. (1991b) and Koch et al. (1991a). Several groups found linkage of paramyotonia congenita to SCN4A establishing the fact that these are allelic disorders (Ebers et al., 1991, Koch et al., 1991b, Ptacek et al., 1991c).

The structure of the channel subunit encoded by SCN4A is analogous to the α-subunit of the skeletal-muscle voltage-gated calcium channel (Fig. 4.3). Four domains each composed of six transmembrane segments form the main channel. The S4 segment acts as a voltage sensor and the S5–S6 loop lines the pore. Channel function is modulated by small β-subunits. All pathogenic changes identified so far have been missense mutations of conserved amino acids of the α-subunit, resulting in periodic paralysis and myotonia. No mutations have been identified in the β_1-subunit associated with neuromuscular disorder but a missense mutation has been found to be a rare cause of generalized epilepsy with febrile seizures (Wallace et al., 1998).

Three main conformations exist for the sodium channel. After membrane depolarization the sodium channels open within a fraction of a millisecond and the resulting inward flux of sodium ions accounts for the rapid upstroke of the action potential. The sodium channels then become rapidly inactivated even if depolarization continues. The linker between domains III and IV is thought to act as a hinged lid, which occludes the channel on fast inactivation. Only membrane repolarization allows sodium channels to change from the inactivated state to the resting state from which further activation is possible.

The majority of mutations in SCN4A lead to a gain-of-function defect. In response to depolarization mutant sodium channels open normally and maintain selectivity
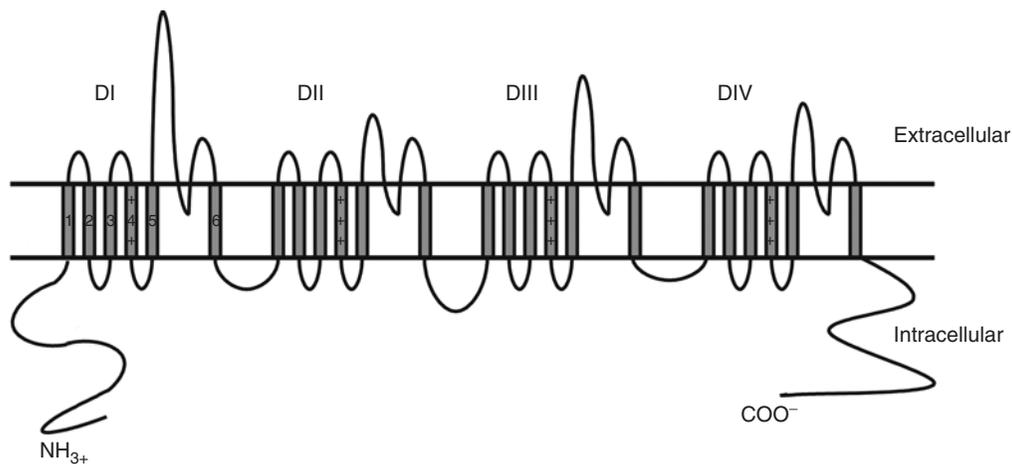
Fig. 4.3. Membrane-spanning topology of the α-subunit of the skeletal muscle sodium channel $Na_v1.4$. Each domain (DI–IV) contains six transmembrane segments (S1–6). The structure of the α-subunit of the L-type skeletal muscle calcium channel $Ca_v1.1$ is homologous.

for sodium ions, but they inactivate less completely, too slowly, recover too quickly or have a shifted voltage dependence. Some mutations (including the most common hyperPP mutation T704M) shift the activation to more hyperpolarized potentials (Cummins et al., 1993). Both inactivation and activation defects result in an increase in sodium current conducted by the mutant channels compared to the wild-type.

p0760 The question arises how gain-of-function mutations in the sodium channel gene can lead to seemingly opposite clinical presentations with increase in excitability (myotonia) on the one hand and loss of excitability (paralysis) on the other. In-vitro experiments and computer modeling have provided an answer to this problem. A toxin-based subtle disruption of sodium channel inactivation of about 2% in rat muscle in vitro can cause myotonia (Cannon and Corey, 1993). A computer simulation of a model fiber confirmed that a small defect of inactivation produces repetitive discharges following a single pulse stimulation (Cannon and Corey al., 1993). An increase of failed inactivation to only about 3% induces a susceptibility for a depolarizing shift of the resting membrane potential after stimulation. This depolarized membrane potential of -40mV is maintained by the sodium channels which have failed to inactivate while at the same time the majority of sodium channels (both mutant and wild type) are inactivated, which leads to inexcitability and paralysis. In keeping with these findings expression studies have shown that paralysis-associated mutations tend to cause a more severe disruption of gating compared to those leading to myotonia (Cannon, 2000). The toxin-based model also demonstrated a common mechanism between chloride- and sodium-channel myotonia. Each action potential in skeletal muscle leads to outward flow of potassium into the extracellular space. In skeletal muscle this includes the T-tubule system which consists of long narrow invaginations of the cell membrane and allows propagation of action potentials into the core of the fiber. Although these T-tubules communicate with the extracellular space they also present a significant diffusion barrier. During sustained contraction activity-dependent potassium accumulation occurs and in the presence of reduced chloride conductance or sodium-channel inactivation defect this increase in potassium is sufficient to trigger myotonic discharges.

p0770 Another feature of sodium-channel function is the presence of fast inactivation (milliseconds) and slow inactivation (seconds to minutes) mechanisms which are operated through different molecular gates. Ruff (1994) suggested that a defect in slow inactivation must be present for paralysis-associated mutations as the slow inactivation mechanism would otherwise lead to a shutdown of the mutant sodium channels which have failed to close down and thus allow repolarization of the membrane. This has been confirmed in in-vitro expression systems for the two most common mutations that lead to hyperkalemic periodic paralysis (T704M and M1592V) and a mutation associated with cold-induced weakness (I693T; Hayward et al., 1999). Some rare mutations exist that cause periodic paralysis without impairment of slow inactivation.

p0780 In contrast to the above, SCN4A loss-of-function defects have been identified in a subset of patients with hypokalemic periodic paralysis (Bulman et al., 1999, Jurkat-Rott et al., 2000b, Bendahhou et al., 2001). All of the mutations are located in the voltage-sensing segment S4 of domain II and all neutralize positively charged arginines in analogy to the hypoPP calcium-channel mutations. The phenotype of patients with calcium-channel compared to sodium-channel hypokalemic periodic paralysis is identical (Jurkat-Rott et al., 2000b). Electrophysiologically, these mutations attenuate sodium current due to excess fast and slow inactivation and reduced density of sodium channels (Struyk et al., 2000, Jurkat-Rott et al., 2000b, Bendahhou et al., 2001, Kuzmenkin et al., 2002). The production and insertion of normal sodium channels did not compensate for the reduced sodium current, which raises the question of how skeletal muscle fibers regulate the expression of sodium channels to control membrane excitability. Interestingly, muscle fibers with a calcium-channel mutation associated with hypoPP have also been shown to have a reduction in sodium current (Ruff and Al-Mudallal, 2000).

p0790 The distinction between SCN4A mutations associated with hyper- or hypoPP may not always be so clear. Vicart et al. (2004) reported four kindreds with three new SCN4A mutations affecting an arginine at position 675, located in the S4 voltage sensor of domain II adjacent to residues R669 and R672 where mutations causing hypoPP have been identified. Administration of corticosteroids resulted in severe weakness associated with hypokalemia in two affected individuals from different families, in one of them in the presence of thyrotoxicosis. Repeated ictal testing however did not reveal consistent potassium abnormalities in a number of affected subjects during attacks. The presence of EMG myotonia in one individual together with symptoms of muscle cramps and stiffness and provocation by cold and fasting may point towards a defect similar to hyperPP mutations but functional expression data is awaited.

p0800 The P1158S mutation located in the linking loop between segments 4 and 5 of domain III was identified in a single kindred with cold-induced hypoPP and myotonia (Sugiura et al., 2000). This is the only mutation where a true combination of hypoPP and myotonia exists. Functional expression identified a slowing of

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inactivation and cold-induced shift of activation and inactivation to more hyperpolarized potentials (Sugiura et al., 2003). In a computer model these abnormalities accounted fully for myotonia regardless of the temperature. Taking hypokalemia into account the electrical activities of P1158S cells in the computer model ceased at a depolarized potential at 22°C, reproducing cold-induced paralysis. This might be related to a general reduction in membrane potassium conductance associated with low temperature as well as specifically reduced potassium current through inward-rectifying potassium channels due to low extracellular potassium.

p0810   In a unique case with congenital myasthenic syndrome including fatigable generalized weakness, recurrent attacks of respiratory and bulbar paralysis since birth and rapid decrement of compound muscle action potential on high frequency repetitive stimulation, Tsujino et al. (2003) identified a loss-of-function *SCN4A* mutation which caused a left-shift in the voltage dependence of fast inactivation. This defect is compounded by enhanced cumulative use-dependent inactivation. A conclusion on the inheritance pattern could not be drawn due to lack of data from other family members. However, in the same subject a second mutation was identified on the other allele of *SCN4A* which also had detectable changes in biophysical properties when tested in the heterologous expression system. This mutation caused no clinical manifestation when found alone in the patient's mother and sister and thus may indicate a recessive inheritance, but this is by no means proven. Interestingly, the patient responded both to pyridostigmine as well as acetazolamide therapy.

p0820   Cardiac arrhythmias are not thought to be a major part of this form of periodic paralysis. Baquero et al. (1995) reported a patient with periodic paralysis in whom the *SCN4A* mutation V781I was identified. He was later investigated for presyncope attacks and found to have ventricular tachycardia and multiform ventricular ectopy on electrocardiography. This particular mutation has only been reported in one other paper (Miller et al., 2004) without any details of the patient's characteristics. Functional expression suggests that this might be a benign polymorphism (Green et al., 1997). A mutation in *KCNJ2* was not excluded in Baquero's subject. The main voltage-gated sodium channel in cardiac tissue is an isoform of $Na_v1.5$. However, Nav1.4 RNA is detectable in human cardiac tissue at about 30% compared to skeletal muscle (Pereon et al., 2003). Cardiac expression of $Na_v1.4$ has also been demonstrated in mice (Zimmer et al., 2002, Haufe et al., 2005).   Au20

4.5.3. Potassium-channel periodic paralysis (Andersen–Tawil syndrome)   s0240

Plaster et al. (2001) showed that mutations in *KCNJ2*, a   p0830
gene encoding a voltage-independent potassium channel (Kir2.1) located on chromosome 17q23, are causative in the majority of patients with Andersen–Tawil syndrome. All potassium channels belonging to the Kir family consist of an intracellular N- and C-terminal domain, two α-helical transmembrane segments (M1 and M2) and the loop connecting M1 and M2 (H5 or P-loop) which contains the pore-forming elements and the Gly-Tyr-Gly signature sequence conferring potassium selectivity (Fig. 4.4). A complete channel is formed by assembly of four homo- or heteromeric subunits (Yang et al., 1995). The recently resolved crystallographic structure of the prokaryotic Kir channel KirBac1.1 has helped to refine the structural model of the channel (Kuo et al., 2003). Kir2.1 is an inward-rectifying channel highly expressed in heart, skeletal muscle and brain (Kubo et al., 1993, Raab-Graham et al., 1994). It is known to be important for stabilizing
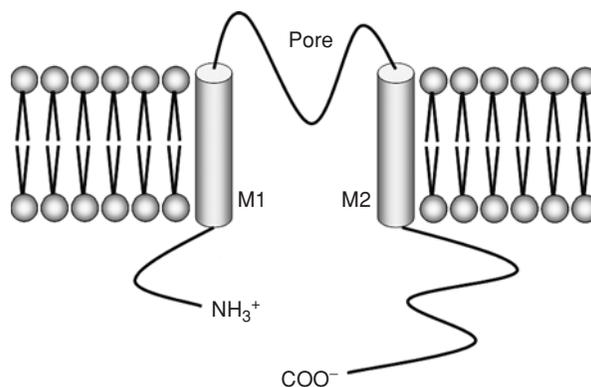
Fig. 4.4. Structure of a Kir2.1 subunit encoded by the *KCNJ2* gene. It contains two transmembrane segments (M1 and M2).   f0040
The majority of mutations causing ATS are located in the C- and N-terminal regions. Four subunits are required to assemble to form a complete channel.

the resting potential in cardiac muscle and thought to contribute to the late-repolarization phase in both skeletal and cardiac muscle. Inward rectification refers to the fact that the channel permits inward flux of potassium at membrane potentials negative to the potassium reversal potential more easily compared to outward flux at more positive potentials. This prevents excess potassium loss during the plateau phase of the cardiac action potential but allows participation in the late repolarization. The closure of Kir2 channels occurs due to binding of intracellular magnesium or cationic polyamines at potentials positive to the potassium reversal potential (Lopatin and Nichols, 2001). The open state of Kir2.1 and other inward-rectifying channels is facilitated by phosphatidylinositol 4,5-bisphosphate (PIP$_2$; Huang et al., 1998). PIP$_2$ is a membrane-bound phospholipid which acts as a precursor for secondary messengers. It binds directly to Kir channels through interaction between positively charged amino acids of the Kir channel and negatively charged phosphate groups of the lipid. Three putative PIP$_2$ binding sites exist within the C-terminal domain of Kir2.1 (Soom et al., 2001).

p0840   In rat embryos mRNA is detectable in cardiac and skeletal muscle, brain, metanephrons and developing bony structures of the cranium, extremities and vertebrae (Karschin and Karschin, 1997). This closely mirrors the organ systems affected in ATS. A Kir2.1 knockout mouse showed developmental craniofacial abnormalities in analogy with ATS (Zaritsky et al., 2000). Functional expression of the majority of mutations so far has demonstrated a dominant-negative effect on wild-type subunits in the tetrameric channel. The clinical severity of symptoms does not seem to be correlated with the degree of dominant negative effect in expression studies (Tristani-Firouzi et al., 2002). At least half of the mutations impair interaction with PIP$_2$ (Tristani-Firouzi et al., 2002, Lopes et al., 2002, Donaldson et al., 2003). The delS314–Y315 mutation has been shown to interfere with protein trafficking leading to intracellular trapping of the channel containing one or more mutant subunit (Bendahhou et al., 2003). The same study suggested that the mutation V302M disrupts both channel trafficking or folding as well as assembly trapping only mutant subunits in the cell and causing ATS through a haploinsufficiency mechanism.

p0850   Preisig-Muller et al. (2002) demonstrated the ability of Ki2.1 to form heteromeric channels with potassium channel subunits from the Kir2 subfamily (Kir 2.2 and 2.3). The also showed a dominant-negative effect of mutant Kir2.1 subunits on these heteromers. This finding may provide a possible explanation of the phenotypic variation within and between families with ATS.

p0860   Of interest also is the recent discovery of two gain-of-function mutations in *KCNJ2* underlying familial atrial fibrillation in a Chinese kindred (Xia et al., 2005) and short QT syndrome in another family (Priori et al., 2005). Neither of the two families had any dysmorphic features or skeletal muscle symptoms.

4.5.4. Thyrotoxic periodic paralysis s0250

p0870   Although TPP typically occurs sporadically, the heavily skewed ethnic distribution suggests a genetic component. It is suspected that in thyrotoxic periodic paralysis a genetically determined susceptibility to abnormal membrane excitability exists that is only unmasked in the presence of hyperthyroidism. It is not clear whether the primary abnormality is associated with one of the voltage-gated skeletal muscle ion channel genes or a gene that has a secondary effect. Screening for mutations in *CACNA1S* and *SCN4A* known to be associated with hypokalemic periodic paralysis has been negative (Dias da Silva et al., 2002b, Kung et al., 2004).

p0880   The associated hypokalemia in TPP is to be due to a rapid influx of potassium into cells similarly to the familial periodic paralyses (Feely, 1981). The sodium–potassium ATPase is an important transporter that allows potassium to be pumped into the cells. Thyrotoxicosis causes an increase in number and activity of the sodium-potassium ATPase per se, but this effect is more pronounced in patients with TPP (Oh et al., 1990, Chan et al., 1991). The difference between thyrotoxic patients with and without TPP disappears after restoration of the euthyroid status.

p0890   Many recent genetic studies in TPP have concentrated on detection of polymorphisms with potential functional effects in membrane channel or transporter genes. Dias da Silva et al. (2002a) discovered two polymorphisms in *CACNA1S* at nucleotides 1551 and 1564 at higher frequency in 13 cases of sporadic thyrotoxic periodic paralysis compared to normal controls (77% and 31% vs 18% and 8.6%). This was not confirmed in a larger study including 97 male Chinese patients with TPP who were screened for polymorphisms in the coding and promoter region of *CACNA1S* in addition to microsatellite markers in the region of the Na/K-ATPase subunits α1, α2 and β1 (Kung et al., 2004). However, the latter study identified two intronic and one 5′-flanking region single nuclear polymorphisms (SNPs) in *CACNA1S* which occurred with significantly different frequencies compared to groups of normal controls and thyrotoxic patients without periodic paralysis. All three SNPs are located at or near putative thyroid hormone response elements but whether they have any functional effect remains to be seen. The authors hypothesized that these SNPs may modulate the effect of thyroid hormones on the expression of *CACNA1S*. Polymorphisms in the β2-adrenergic receptor

gene were not found to be associated with TPP (Kim et al., 2005).

p0900   Dias da Silva et al. (2002b) also described the mutation R83H in *KCNE3* in a patient with TPP. *KCNE3* encodes the MinK-related peptide 2 (MiRP2) which coassembles with Kv3.4 to form the human skeletal-muscle voltage-gated potassium channel. This change had been reported previously in a case of familial HypoPP (Abbott et al., 2001). However more detailed studies later showed that it was in fact a polymorphism (Sternberg et al., 2003, Jurkat-Rott and Lehmann-Horn, 2004).

p0910   Human leukocyte antigen (HLA) markers have been extensively studied. Various associations with TPP have been reported which differ according to the population studied (Yeo et al., 1978, Hawkins et al., 1985, Tamai et al., 1987, Cavan et al., 1994), but no consistent marker has emerged.

s0260 ## Acknowledgements

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