Channelopathies: The Nondystrophic Myotonias and Periodic Paralyses

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The term channelopathy does not indicate a new group of neuromuscular conditions, but a re-orientation of well-and long-known muscular conditions, the congenital myotonias, and the periodic paralyses. Although, in the past, they have overlapped clinically here and there, both groups were classified differently, as myotonias and as metabolic myopathies, respectively. The discovery of mutations in several ion channels has rewritten nosography of these disorders and procured a new term, the channelopathy—clinical, electrophysiological, and molecular genetic details of which are discussed in this chapter.

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The predominant symptoms of the myotonias and of the periodic paralyses are transiently occurring muscle stiffness (myotonia) and episodes of muscle weakness, respectively. Both symptoms are caused by closely related disturbances of the excitation of the skeletal musculature and may therefore be present in either group of diseases. The relation is so close that diseases exist that qualify for either classification. Both symptoms are caused by long-lasting depolarisations of the muscle fiber membranes, major differentiations being caused by the time course and degree of membrane polarisation defects. Myotonia may already be present at birth, whereas the spontaneously occurring episodes of weakness usually start in the first or second decade of life.

Electrophysiology has predicted and molecular biology has proven that in the hereditary forms of the diseases, the abnormalities of membrane excitation are caused by specific mutations in genes coding for various ion channels in the muscle fiber membrane. These channels are specific for adult skeletal muscle and thus, all these channelopathies are myopathies as opposed to neurogenic disorders, such as neuromyotonia and chondrodystrophic myotonia (Schwartz-Jampel syndrome). Mutations have been detected in the chloride channel, the sodium channel, or the L-type calcium channel genes.

Point mutations or deletions in the gene encoding the chloride channel lead to diseases with muscle stiffness as the prevailing symptom, i.e., the dominant or recessive forms of myotonia congenita (MC).

Point mutations in the gene coding for the sodium channel result in several diseases of clinically rather different symptomatology. Many of these almost 20 different mutations lead to conditions having myotonia as the key symptom. This is the case in paramyotonia congenita, a disease that may or may not be associated with episodes of paralysis, and in myotonia fluctuans and myotonia permanens where muscle weakness is always absent. The sodium channelopathy with prevailing episodes of long-lasting paralysis is called hyperkalemic periodic paralysis because the weakness is usually associated with an increase of the serum potassium concentration.

Point mutations in the gene encoding the muscle L-type calcium channel are responsible for the most common form of hereditary periodic paralysis. In this disease, the attacks are typically accompanied by a fall in serum potassium, and to stress this contrast to the above-mentioned sodium-channelopathy, it is called hypokalemic periodic paralysis. Myotonia is always absent in this disease.

Although many substances are known that cause "acquired" myotonia when incorporated, and although a number of disorders may be associated with secondary hyper or hypokalemic periodic paralysis only the hereditary (familial) forms of the above diseases will be considered in this report. Myotonic dystrophy, including the important congenital form is hereditary, but it is not a primary channelopathy and therefore not covered here.
MYOTONIA CONGENITA

The first description of MC was given by Asmus Julius Thomsen who had the disease himself. He clearly described the character of myotonic stiffness, pointed out the nonprogressive character of the disease, and correctly noted that the mode of inheritance was dominant. In the 1950s Becker showed that in many families that he diagnosed as having myotonia congenita, the inheritance was recessive, as already discussed by Thomasen. In these families, myotonia was more generalized than in Thomsen's disease. Therefore Becker named this type "recessive generalized myotonia" and henceforth this condition was considered a separate nosological entity.

It is now clear that both the dominant and the recessive form are caused by mutations in the same gene that codes for the major chloride channel of adult human skeletal muscle. The intensive search for mutations that followed this discovery showed that the dominant form is very rare, because less than 10 different families have been identified at the molecular level to date. The recessive form is much more common, and the estimation by Becker of a frequency between 1:23,000 and 1:50,000 might still hold. Males seem to predominate at a ratio of 3:1 when the Becker-type propositi are counted. However, family studies disclose that females are affected at the same frequency though to a much lesser degree.

Clinical Signs of Dominant Myotonia Congenita (Thomsen's Disease)

Usually the myotonia is recognized in early childhood, but the milder cases may go unrecognized until late childhood. The myotonia is generalized; the legs are often most affected, causing the children to fall frequently. The cranial as well as arm and hand muscles can be severely affected, and it may be difficult for the patients to grasp objects. Chewing is sometimes impaired. The myotonic stiffness is most pronounced when a forceful movement is abruptly initiated after the patient has rested for 5 to 10 minutes. For instance, after making a hard fist, the patient may not be able to extend the fingers fully for several seconds. The myotonia decreases or vanishes completely as the same movement is repeated several times, but it always recurs after a few minutes of rest. The patient may experience much difficulty while getting up from a chair or stepping into a bus in a hurry. On rare occasions, a sudden, frightening noise may cause instantaneous generalized stiffness. The patient may then fall to the ground and remain rigid and helpless for some seconds or even minutes. Some patients have hypertrophied muscles and an athletic appearance. Their muscle strength is normal or even greater than normal and they can be quite successful in those sports where strength is more important than speed. A slight contraction of the calves may limit dorsiflexion of the feet. Tapping a muscle produces an indentation that persists for a second or so (percussion myotonia). Lid lag is usually present, and in some patients myotonia of the lid muscles causes blepharospasm after forceful eye closure. The muscle stretch reflexes are normal.

Clinical Signs of Becker-Type Myotonia

The clinical picture of recessive myotonia resembles that of the dominant form. A few special points are worth mentioning. In some patients the myotonia does not manifest until the age of 10 years or even later, but in a few it presents by the age of 2 to 3 years. The severity of the myotonia may slowly increase for a number of years, but usually not after the age of 25 to 30.

In general, the myotonia is more severe in recessive than in dominant MC. Thus, patients with Becker myotonia are more handicapped in daily life. The disability originates partly from severe myotonic stiffness affecting mainly the leg muscles. Even more disabling is a peculiar transient weakness. This is best shown when the patient makes a tight fist after a period of rest: the force exerted by the finger flexors vanishes almost completely within a few seconds. With repeated muscle contraction, the force returns within 20 to 60 seconds. This transient weakness is often generalized and troublesome, as when a patient attempts to rise from a recumbent position after rest or sleep. The leg and gluteal muscles are often markedly hypertrophied and lordosis is common, whereas the neck, shoulder and arm muscles appear poorly developed,
especially in old age resulting in a characteristic disproportionate figure. Patients with severe recessive MC are limited in their choice of occupation and they are unsuited for military service. Life expectancy is normal. In a few families the heterozygotes can be identified by having repetitive action potentials on electromyograph (EMG).

**Differential Diagnosis**

An experienced physician will usually have no problem recognizing dominant MC, especially when occurrence of the disease is documented among the patient's relatives. The most important task is to rule out myotonic dystrophy, in particular if the patient is young and asking for genetic counseling. Women who have myotonic dystrophy can give birth to severely disabled children (congenital myotonic dystrophy). Usually, in MC, the myotonia is generalized and more severe, as against the distally localized and slight myotonia in myotonic dystrophy. However, exceptions to this pattern exist in some families with myotonic dystrophy, and therefore every patient should be asked whether incidence of cataracts early in life had occurred in the family. Test for a myotonic cataract by slit lamp examination is essential for the diagnostic procedure.

Sometimes an isolated case of recessive MC may be falsely diagnosed as having myotonic dystrophy when transient weakness is mistaken as permanent weakness. A thorough investigation of family members, in particular the patient's parents, if available, as well as clinical and EMG studies are more revealing than muscle biopsy. A muscle biopsy provides little information for the differential diagnosis, particularly at an early stage of the disease. This is because usually the larger proximal muscles are biopsied, while it is the distal muscles that present the morphological changes in early myotonic dystrophy.

The serum creatine kinase (CK) is usually normal. Occasionally there is a borderline elevation in dominant MC and a two or threefold elevation in recessive MC. Needle EMG shows typical myotonic runs in every skeletal muscle. Muscle biopsy does not provide much relevant information for a diagnosis; type II fiber deficiency, hypertrophied fibers, and central nuclei may be found. Isolated tubular aggregates may be shown with the electron microscope. DNA testing is now available for an easy and reliable separation of MC and myotonic dystrophy, if necessary.

Separation of MC from paramyotonia congenita or potassium-aggravated myotonia fluctuans (see below) is only of minor importance because these diseases are basically benign and nonprogressive and respond to the same treatment. In cases of doubt, a search for the mutation should be performed.

**Molecular Pathology**

The muscle stiffness is caused by the fact that, following voluntary excitation, the membranes of individual muscle fibers may continue for some seconds to generate runs of action potentials. This activity prevents immediate muscle relaxation. Experiments with muscles of an animal model, the myotonic goat, showed that the overexcitability is caused by a permanent reduction of the resting Cl⁻ conductance of the muscle fiber membranes. Subsequently, this defect was also shown to exist in human dominant as well as recessive MC.

A big step forward in the understanding of the pathology was made possible by the cloning of the muscle Cl⁻ channel gene and the demonstration of linkage of both dominant and recessive MC to the gene locus at chromosome 7q35. The starting point for this achievement was expression cloning of the Cl⁻ channel in the electric organ of the fish Torpedo marmorata. Human skeletal muscle Cl⁻ channel complementary DNA (cDNA) was then cloned by homology screening.

The gene encoding the chloride channel responsible for the high resting membrane conductance of skeletal muscle cells, is a member of a newly detected multigene family encoding chloride channels that are structurally not related to any other known class of ion channels. It spans at least 40 kb and contains 23 exons whose boundaries have been located. The complete coding sequence consists of 2964 base pairs.

The channel is a protein of 988 amino acids with a predicted molecular weight of 110 kDa. Hydropathy plots of the protein suggest 12 membrane-spanning domains (Fig 1). A 13th, highly conserved domain is located in the cyto-
plasmic segment near the C terminal of the protein. The cDNA was functionally expressed in Xenopus oocytes and human embryonic kidney cells. Structure-function relations of the channel protein are presently being carried out.

More than 15 point mutations and two deletions have been found in the channel gene, and they cause either dominant or recessive MC (Fig 1) by producing change or loss of function of the channel complex. Gene dosage effects of loss-of-function mutations may lead to a recessive or dominant phenotype, depending on whether 50% of the gene product (supplied by the normal allele) is or is not sufficient for normal function. Experiments with myotonia-generating drugs have shown that blockade of 50% of the physiological Cl current is not sufficient to produce myotonic activity. This then explains the existence of recessive transmission in the case of mutations that completely eliminate the gene's coding functions. Dominant effects can be explained by a mutant gene product that can bind to another protein and, in doing so, changes its function. Presuming that chloride channel protein is capable of forming multimers, Steinhmeyer et al co-injected oocytes with constant amounts of normal and increasing amounts of mutant cRNA. The result was interpreted to indicate that the chloride channel complex is a homo-oligomer whose function will be destroyed by the incorporation of mutant subunits.

Therapy

Many MC patients can manage their disease without medication. Should treatment be necessary, myotonic stiffness responds well to drugs that reduce the increased excitability of the cell membrane by interfering with the sodium channels, i.e., local anesthetics, antifibrillar and antiarrhythmic drugs, and related agents. These drugs suppress myotonic runs by decreasing the number of available sodium channels and have no known effect on chloride channels. Of the many drugs tested, mexiletine is the drug of choice.

A simple method for scoring the severity of the myotonia before starting therapy and for evaluating the effect of the treatment is provided by the stair test. The patient should rest for 10 to 15 minutes in a chair at the foot of the stairs, then get up and climb 10 steps as quickly as possible. A healthy person needs about 3 seconds, a patient with severe myotonia needs up to 30 seconds. Immediate repetition of the test shows the "warm-up" phenomenon.

PARAMYOTONIA CONGENITA

The hallmarks of this disease as first described by Eulenburg and later confirmed in many families by Becker are: (1) paradoxical myotonia, defined as myotonia that appears during exercise and increases with continued exercise; (2) severe worsening of the exercise-induced myotonia by cold; (3) a predilection of the myotonia for the face, neck, and distal upper extremity muscles; and (4) weakness after prolonged exercise and exposure to cold in most cases. In some families patients have spontaneous attacks of weakness like those occurring in hyperkalemic periodic paralysis. The condition is transmitted with complete penetrance.

Paramyotonic symptoms are present at birth and remain basically unchanged for the entire lifetime, though the attacks of weakness and hyperkalemia begin to appear in adolescence, if at all. In the cold, the face may appear masklike, and the eyes cannot be opened for several seconds. Working in the cold makes the fingers so stiff that the patient becomes unable to move them within minutes. The stiffness then gives way to weakness. After warming, the hands may not regain strength for several hours. As a rule, the legs are less affected. Under warm conditions many patients have no complaints. Muscle pain, muscle atrophy or hypertrophy are not typical for the disease.

In a number of families the symptoms are clearly different from those found in most cases of paramyotonia: (1) Some patients experience myotonic stiffness during work even under warm conditions. Such patients require long-term medication. (2) In some kinships cold induces stiffness but not weakness. (3) Still other patients are immediately paralyzed by cold. (4) In some kinships the patients have not only paramyotonic symptoms, but also temperature-independent paralytic attacks, resembling those in hyperkalemic periodic paralysis (see below). The attacks usually begin early in the day and can last for several hours. Oral intake of potas-
sium can induce such attacks in these patients distinguished by "paramyotonic hyperkalemic periodic paralysis."

These intermediate forms led to the suggestion that hyperkalemic periodic paralysis and paramyotonia congenita are two facets of the same disease. Although it is now known that the two diseases are indeed allelic, it seems reasonable to retain them as separate entities because in the "pure" forms not only the symptoms but also the treatments are different.

**Diagnosis**

The diagnosis of paramyotonia congenita is suggested by work- and cold-induced muscle stiffness, and by a positive family history. Permanent weakness and muscle atrophy are not signs of paramyotonia congenita. The EMG always shows myotonic discharges in all muscles, even at a normal muscle temperature. The serum CK is often elevated, sometimes 5 to 10 times above normal.

The diagnosis can be verified by the following tests: (1) Cooling reduces the amplitude of the evoked compound muscle action potential. (2) Cooled muscles are slow to relax and generate decreased force on maximal voluntarily contraction. The test is performed by determining the isometric force and relaxation time of the long finger flexor muscles before and after immersing hand and forearm in a water bath at 15°C for 30 minutes. In some patients the test reduces the force of contraction by more than 50% and prolongs the relaxation time from 0.5 seconds up to 50 seconds. In other patients the abnormalities appear after an additional maximal voluntary contraction lasting 1 to 2 minutes. The test is positive when the relaxation is markedly slowed; the isometric force exerted by the finger flexors often decreases to 10% or less of the pretest value. The EMG shows dense fibrillation-like spontaneous activity in the cooled muscles that is different from the myotonic discharges present at normal muscle temperature. In some patients the cooling increases the relaxation time but does not diminish the force. These patients have paramyotonia congenita without cold-induced weakness.

**Pathogenesis**

Electrophysiology on excised muscle specimens revealed normal chloride conductance but a noninactivating component of the Na⁺ current as a specific abnormality. This showed that both stiffness and weakness are caused by the same mechanism, i.e., a long-lasting depolarization of the muscle fiber membranes. When the depolarization is mild (5 to 10 mV), this may fulfill exactly the condition for the voltage-dependent Na⁺ channels to open again spontaneously after an action potential, i.e., for repetitive firing which is the basis for the involuntary muscle activation that the patient experiences as muscle stiffness. When the depolarization is strong (20 to 30 mV) the normally functioning Na⁺ channels adopt the state of inactivation, i.e., the muscle cells become inexcitable which is the basis of the muscle weakness. When all fibers of a muscle are depolarized, the result is incomplete paralysis (fortunately the heart muscle and the diaphragm are always spared).

**The Sodium Channel of Adult Human Skeletal Muscle**

When SCN4A, the gene encoding the α subunit of the adult human skeletal muscle sodium channel, hSkM1, was cloned in 1990, the demonstration of linkage of hyperkalemic periodic paralysis (see below) to its locus on chromosome 17q23 provided the first proof for the existence of a human sodium channel disease. Not much later, three groups showed independently that paramyotonia congenita is also linked to the SCN4A locus.

SCN4A contains 24 exons distributed among approximately 30 kb. As with many genes, the genomic structure becomes more condensed towards the 3' end, with at least 30% of the...
coding sequence appearing in a single exon. Intron-exon boundaries are known; primer sets consisting of intron sequences for amplification of all 24 exons by use of polymerase chain reaction are available. Physiologically, SCN4A is only expressed in skeletal muscle, and its product, the "tetrodotoxin-sensitive" hSkM1, is the only sodium channel detectable in the fully differentiated tissue.

The SCN4A gene product, a 260 kDa glycoprotein containing approximately 2000 amino acids, is distinguished by four domains of internal homology, each encompassing 225 to 325 amino acids (Fig 1B). Each of these so-called repeats (I to IV) consists of six hydrophobic segments ($1 to $6), putative transmembrane helices that are connected with each other by "interlinkers." Between segments $5 and $6 of each repeat, the interlinkers consist of an extracellular part and a sequence that dips into the membrane. These four intramembrane loops are thought to form the lining of the channel pore, similar as in K+ channels. The $4 helices contain a repeating motif with a positively charged amino acid at every third position. The high charge density suggests that it may function as a voltage sensor. The charges could shift, for example, in response to depolarization, thus playing an essential part in voltage-dependent activation and/or inactivation of the channel.

Another part of the protein to which a certain function has been assigned, is the interlinker connecting repeat III S6 with repeat IV S1. Most likely, this part of the protein acts as the inactivation gate of the channel in a way that has been compared with a tethered ball. The intracellular orifice of the pore or its surrounding protein parts may act as acceptor of the ball. In the resting state, the ball is away from the pore and, subsequent to activation, the ball swings into the mouth to block the ion pathway.

**Molecular Genetics**

To date, 16 point mutations have been detected in different parts of SCN4A. The predicted amino-acid substitutions are illustrated in Fig 1B. Six of them lead to paramyotonia congenita. Most of them involve the $4 transmembrane segment thought to act as the voltage sensor for channel gating. Other mutations are situated in the III-IV interlinker supposed to form the inactivation gate of the channel. For almost each of the mutations, several unrelated families were discovered and a strong correlation between genotype and phenotype was noticed.

Electrophysiological experiments with some of these mutant genes expressed in human embryonic kidney and other mammalian cells, designed to study the effect of these mutations on the channel properties, are described at the end of the section on hyperkalemic periodic paralysis later in this report.

**Therapy**

Antiarrhythmic drugs, such as mexiletine, are effective in preventing muscle stiffness and weakness induced by physical activity or exposure to cold. The majority of paramyotonia congenita patients, however, require no treatment and know best how to deal with their symptoms.

In paramyotonic hyperkalemic periodic paralysis, the combined use of mexiletine and hydrochlorothiazide can prevent stiffness and weakness induced by cold, and the spontaneous attacks of hyperkalemic periodic paralysis.

**MYOTONIA FLUCTUANS AND MYOTONIA PERMANENS**

These two diseases have only recently been defined on the basis of existing clinical findings and additional genetic information. Becker had investigated many families with nondystrophic dominant myotonia and proposed many subtypes of what he thought was MC. Molecular biology revealed that these conditions were in fact caused by mutations in SCN4A, the gene encoding the muscle sodium channel. Some of the forms could be classified as special types of paramyotonia, as they did show cold- and exercise-induced stiffness, albeit no cold-induced weakness. Other conditions, however, were too inconsistent with the definition of paramyotonia congenita. As a characteristic finding, afflicted persons experience muscle stiffness that tends to fluctuate from day to day, hence the name "myotonia fluctuans." They never experience muscle weakness and are not substantially sensitive to cold as regards to muscle stiffness. Their muscle stiffness is provoked by exercise, and often it occurs with some delay during rest.
after heavy exercise. The stiffness may then last for 0.5 to 2 hours. On many days or even for weeks, afflicted persons experience no muscle stiffness at all. Another atypical but related disorder is associated with acetazolamide-responsive myotonia, also described as atypical MC.46 In this form the muscle stiffness persists even in a warm environment and, in addition, muscle pain is induced by exercise. Both the stiffness and pain are alleviated by acetazolamide.

The other newly defined disease is characterized by very severe and permanent myotonia; therefore, this form was called "permanent myotonia."36 Continuous myotonic activity is noticeable in the EMG of these patients, and molecular biology revealed that this condition is caused by yet other mutations in SCN4A. Particularly in neck and shoulder, the musculature is markedly hypertrophied, and if the myotonia is aggravated in these patients, ventilation might be impaired because of stiffness of the thoracic muscles. In particular, children can suffer from acute hypoventilation and this may lead to cyanosis and unconsciousness, so that such episodes were occasionally mistaken for an epileptic seizure. In spite of the misdiagnosis, antiepileptic medication, eg, administration of carbamazepine, was successful in these cases because of its antimyotonic effects. The patients could probably not survive without persisting treatment. One of the patients had formerly been misdiagnosed as having the "myogenic type" of Schwartz-Jampel syndrome.47 A further indication of the severity of this disease is that all patients reported to date were sporadic cases having a de novo mutation, ie, their proven biologic parents did not carry the mutation.

In both diseases, depolarizing agents such as potassium or suxamethonium may aggravate the myotonia, but do not induce weakness. It is well known for myotonic disorders that risk of depolarizing relaxants inducing anesthesia-related events is increased. The incidence of such events seems to be highest in myotonia fluctuans families.43,48 There seems to be no other biological reason for this than the frequent absence of clinical myotonia in these patients making the anesthesiologists unaware of the condition. Therefore it is worth mentioning that even during the spells of absence of clinical myotonia, latent myotonia can be consistently recorded in the EMG.

**Molecular Genetics**

Six point mutations at four different positions are responsible for myotonia fluctuans and permanens. Four of the substitutions are located in the inactivation gate (Fig 1B). Three of them affect one and the same nucleotide, resulting in three different amino-acid substitutes for one (Gly-1306) of a pair of glycines (1306/07) supposed to be essential for proper inactivation. The more the substitutes differ from glycine by having side-chains of variable length and charge and/or by ramification, the greater is the degree of membrane hyperexcitability and the more severe are the clinical symptoms. Glutamic acid, having a long side-chain, causes myotonia permanens, the most severe form of sodium channel myotonia.36 Valine, an amino-acid with a side-chain of intermediate size, is the substitute in patients with moderate exercise-induced myotonia,35,36 and alanine, distinguished by a short side-chain, results in benign myotonia fluctuans.36 Electrophysiological experiments with some of these mutant genes expressed in human embryonic kidney cells, designed to study the effect of these mutations on the channel properties, are described at the end of the section on hyperkalemic periodic paralysis later in this report.

**HYPERKALEMIC PERIODIC PARALYSIS**

The disease was first described by Tyler et al49 and Helweg-Larsen et al,50 and was extensively investigated by Gamstorp51 who clearly differentiated it from "paroxysmal familial paralysis" and named it "adynamia episodica hereditaria." Clinically, the most striking difference of the two diseases is that, during the paralytic episode, serum potassium decreases in the former and increases in the latter. To stress this distinction, the names hypokalemic periodic paralysis and hyperkalemic periodic paralysis, respectively, are now preferred for these two nosological entities. Hyperkalemic periodic paralysis is transmitted as an autosomal dominant trait with complete penetrance in both sexes: however, incomplete penetrance was reported for a family with a rare mutation.52 Sporadic cases have also been
reported, and a de novo mutation was proven in a patient whose genetically confirmed father and mother did not carry the defective gene. The disease has three clinically distinct variants. It can occur (1) without myotonia, (2) with clinical or electromyographic myotonia, or (3) with paramyotonia. In some patients, a chronic progressive myopathy may develop, which seems to be genetically determined.

Clinical Features

The attacks usually begin in the first decade of life. Initially they are infrequent but then increase in frequency and, in severe cases, may recur daily. The attack commonly starts in the morning before breakfast and lasts 15 minutes to an hour, and then spontaneously disappears. Often rest provokes the attack, and prior strenuous work usually aggravates it. Potassium loading, as during a provocative test, usually precipitates an attack. Cold environment, emotional stress, glucocorticoids, and pregnancy provoke or worsen the attacks. After strenuous exercise, weakness can follow within a few minutes of rest. In some patients paraesthesia or the sensation of muscle tension herald the attack. Sustained mild exercise after a period of strenuous exercise may postpone or prevent weakness in the exercising muscle groups while the resting muscles become weak.

The generalized weakness is usually accompanied by significant increase of serum potassium (up to 5 to 6 mmol/L). Sometimes the serum potassium level remains within the upper normal range and only seldom reaches cardiotoxic levels. Yet, in very rare cases it may become life-threatening. As the serum potassium increases, the precordial T waves in the electrocardiogram increase in amplitude. When the serum potassium level begins to rise, the serum sodium level falls 3 to 9 mmol/L. This fall is caused by sodium entry into muscle; this, in turn, causes movement of water into muscle that causes hemoconcentration and increases the serum potassium level. During attacks the urinary potassium excretion increases and this may terminate the attack. Moderate exercise also hastens recovery. Slight weakness, however, may persist for days. Sometimes transient hypokalemia occurs at the end of an attack. Between attacks the serum potassium is normal. The frequency of attacks declines in the second half of life.

The course of the paralytic attacks is the same in all three forms of hyperkalemic periodic paralysis. Cooling can induce weakness, but not stiffness, and reheating restores contractile force quickly (except for the paramyotonic form). EMG studies are required to determine the presence or absence of myotonia. In the nonmyotonic form, clinical and electrical myotonia are both absent. In families with the myotonic variant, the myotonic phenomena are present in all affected members. The clinical myotonia is usually very mild and never impedes voluntary movements. It is most readily observed in the facial, lingual, thenar, and finger extensor muscles. In the attack-free interval, the EMG shows typical myotonic discharges in almost every muscle. At the beginning of an attack the EMG may show bursts of fibrillation potentials which may explain the sensation of muscle tension. Cooling may provoke weakness but does not cause substantial myotonia. Paramyotonic hyperkalemic periodic paralysis is characterized by attacks of generalized muscle weakness associated with hyperkalemia and by paradoxical myotonia (for details see previous section on Paramyotonia Congenita).

Normokalemic Periodic Paralysis: A Variant of the Hyperkalemic Form

This rare disorder resembles hyperkalemic periodic paralysis in many respects but differs from it in that the serum potassium does not increase even during serious attacks. The existence of normokalemic periodic paralysis as a nosological entity has been questioned because some patients with this condition are sensitive to oral potassium salts. The disorder is transmitted as an autosomal dominant trait with high penetrance in both sexes. The attacks begin in the first decade of life and are provoked or worsened by rest after exercise, exposure to cold, and by potassium loading. Large doses of sodium improve the weakness but glucose loading has no effect. There are no consistent changes in the serum electrolytes but increased sodium excretion and potassium retention occur during the attacks. The urinary potassium
retention, the lack of a beneficial effect of glucose, and failure of the serum potassium to increase in attacks distinguish this disease from primary hyperkalemic periodic paralysis. However, in at least one such family, the condition is caused by the common Val-704-Met mutation in SCN4A normally associated with hyperkalemic periodic paralysis.

**Diagnosis of Hyperkalemic Periodic Paralysis**

The diagnosis is based on the presence of typical attacks of weakness or paralysis, the positive family history, and the myotonic or paramyotonic phenomena, if present. Except for some older patients with progressive myopathy, the muscles are well developed. Calf hypertrophy has been reported. The serum CK is sometimes elevated up to 200 to 300 U/L. When the diagnosis is unclear, a provocative test can be performed. This consists of the administration of 2 to 10 g of potassium chloride (40 to 120 mmol) in an unsweetened solution in the fasting state, just after exercise, and preferably in the morning. The test is contraindicated in subjects already hyperkalemic and in those who do not have adequate renal or adrenal reserve. An abnormally high serum potassium level between attacks suggests secondary rather than primary hyperkalemic periodic paralysis. The provocative test usually induces an attack within the next 1 to 2 hours.

An elegant alternative test consists of exercise on a bicycle ergometer for 30 minutes, so that the pulse increases to 120 to 160 beats/min followed by absolute rest in bed. The serum potassium rises during exercise and then declines to almost the preexercise level, as in healthy individuals. Ten to 20 minutes after the onset of rest, a second hyperkalemic period occurs in the patients in contrast to normal subjects, and during this period the patients become paralyzed. Recordings of the evoked compound muscle action potential during rest and exercise are also helpful in confirming the diagnosis of periodic paralysis and paramyotonia congenita.

**Pathogenesis**

*In vitro* electrophysiological studies on muscle strips from patients with hyperkalemic periodic paralysis revealed abnormal inactivation of the sarcolemmal sodium channels. As in the other sodium channelopathies, also in hyperkalemic periodic paralysis two types of sodium channels are expressed in the muscle fibers: one that inactivates (ie, closes) normally, and another that fails to inactivate normally. Hyperkalemia induced by potassium intake or by activity causes slight membrane depolarization even in normal muscle. In hyperkalemic periodic paralysis muscle, this small depolarization opens abnormally inactivating sodium channels. This allows a greater than normal influx of sodium, which prolongs and augments the depolarization. This, in turn, causes complete inactivation of the normally functioning sodium channels (ie, those expressed by the normal gene), and renders the fiber membrane unexcitable. These studies explain both the mechanism of the membrane inexcitability and the cause of the paralysis in the disease. The sodium influx also causes a shift of water into the muscle fibers which causes hemoconcentration and thus a further increase of serum potassium. This in turn causes additional muscle fibers to become depolarized and thus may result in paralysis of the entire muscle. The vicious cycle is probably terminated when the hyperkalemia is relieved by kaliuresis. An increased activity of the sodium-potassium pump, stimulated by the increased concentration of intracellular sodium and extracellular potassium, may also help terminating the attack. When the serum potassium returns to normal, the defective sodium channels are likely to close and a normal resting membrane potential is again attained.

Interestingly, patients never become weak during activity despite an increase of the extracellular potassium level. This seems to be connected to the work-related decrease in intracellular pH because lowering the pH of the high-potassium bathing solution normalizes the contractile force exerted by muscle bundles obtained from hyperkalemic periodic paralysis patients. Also, physical activity is associated with enhanced adrenalin release; adrenalin stimulates the sodium-potassium pump which, in turn, helps to compensate for the abnormal sodium influx into the muscle fibers.
Molecular Genetics

Five mutations in SCN4A, the gene encoding the α subunit of the adult skeletal muscle sodium channel, were found to cause hyperkalemic periodic paralysis (Fig 1).52,55,57,58,70 Thr-704-Met is the most frequent SCN4A mutation and, in addition to hyperkalemic periodic paralysis with or without myotonia, it often causes chronic progressive myopathy.57 All other mutations cause myotonic hyperkalemic periodic paralysis without permanent weakness. Two rare mutations (Ala-1156-Thr, Met-1360-Val) are of interest because they were discovered in families showing incomplete penetrance in females, and another rare mutation (Val-783-Ile) was found in a patient also suffering from cardiac abnormalities. Finally, in one family with hyperkalemic periodic paralysis no mutation was found when the cDNA coding for the α subunit of the sodium channel was sequenced and, therefore, genetic heterogeneity was proposed for the disease.71

Therapy

Preventive therapy consists of frequent meals rich in carbohydrates, a low potassium diet, and avoidance of fasting, strenuous work, and exposure to cold. Many patients are able to prevent or abort attacks by continuing slight exercise and/or the oral ingestion of carbohydrates at the onset of weakness (eg, 2 g glucose per kg body weight). However, severe attacks may fail to respond to these measures.51 Interestingly, attacks occur more frequently on holidays and weekends when patients rest in bed longer than usual. Thus, patients are advised to rise early and have a full breakfast.

Some patients can abort or attenuate attacks by the prompt oral intake of a thiazide diuretic or acetazolamide, or by inhalation of a β-adrenergic agent. The beneficial effect of the diuretics is probably because of their capacity to lower the serum potassium level. The effects of the β-adrenergic agents is probably mediated via stimulation of the sodium-potassium pump.69 The inhalation of three puffs of 1.3 mg metaproterenol (repeatable after 15 minutes) or of two puffs of 0.18 mg albuterol,72 or of two puffs of 0.1 mg salbutamol59,73 has aborted acute attacks. Calcium gluconate, 0.5 to 2 g given intrave-}

nously, has also terminated attacks in some patients but not in others.

It is often advisable to prevent attacks by the continuous use of a thiazide diuretic51 or acetazolamide.54,74 Diuretics that lower serum potassium are very effective in mild cases. The diuretics are used in modest dosages at intervals from twice daily to twice weekly.74 Thiazide diuretics are preferable because of the possible complications of acetazolamide therapy.75 The dosage should be kept as low as possible, eg, 25 mg of hydrochlorothiazide daily, or every other day. The drug should not lower the serum potassium less than 3.3 mmol/L or the serum sodium less than 135 mmol/L.74 In severe cases, 50 mg or 75 mg of hydrochlorothiazide should be taken daily very early in the morning.

Normal and Mutated SCN4A Expressed in Human Embryonic Kidney Cells

Studies of the sodium currents in this expression system, performed with patch-clamp methods, revealed that the various mutant channels have impaired inactivation. Contrary to expectation, however, mutations leading to clinically very different phenotypes of paramyotonia congenita, myotonia fluctuans, myotonia permanens, or hyperkalemic periodic paralysis yield results that resemble each other. Under the experimental conditions of voltage-clamped membrane patches, neither extracellular potassium nor low temperature had a direct effect on any of the mutant channels investigated in the heterologous expression system. Therefore, these triggering factors probably exert their effects indirectly, eg, they may increase a persistent sodium current by causing membrane depolarization according to physiological mechanisms.

Familial Hypokalemic Periodic Paralysis

The clinical symptoms of the disease were already described in the 19th century. An early review summarizes what was known about the disease before 1941.76 Interestingly, it was not until 1934 that hypokalemia was recognized to occur during the paralytic attacks.77 The prevalence is estimated to be 1:100,000 and thus the disease is the most common of the familial periodic paralyses. It is transmitted as an autosomal dominant trait with reduced penetrance in women (the male to female ratio is 3 to 4:1).78
In a systematic genome analysis, it was shown that the disease is linked to chromosome 1q31-32 and cosegregates with the gene encoding the α1 subunit of the L-type calcium channel of the skeletal muscle, also called dihydropyridine receptor. Only for one family, linkage of the disease to this locus was excluded, suggesting genetic heterogeneity. Sporadic cases also occur and are more frequent in men than in women. The severity of the symptoms may vary greatly within a family. Mild episodes often go unrecognized. Occasionally a carrier is asymptomatic and the disease appears to skip a generation.

**Clinical Features**

The disease is very homogeneous both clinically and electrophysiologically. Severe cases present in early childhood, mild cases as late as the third decade of life, and about 60% present before age 16. Initially the attacks are infrequent but after a few months or years they increase in frequency and eventually may recur daily. An attack may range in severity from slight temporary weakness of an isolated muscle group to generalized paralysis. Paralytic attacks usually occur in the second half of the night or the early morning hours and on awakening the patient is unable to move his arms, legs or trunk. In most cases, the cranial muscles are spared. The vital capacity is reduced in severe attacks and death can occur from ventilatory failure. Usually strength gradually increases as the day passes. Occasionally the weakness lasts two to three days.

The trigger for a nocturnal attack is often strenuous physical activity or a carbohydrate-rich meal on the preceding day. During the day, attacks can be provoked or worsened by high carbohydrate and high sodium intake, and by excitement. Injection of a mixture of antiphlogistics and local anesthetics can trigger a severe attack after a few hours. Exposure to cold can induce local weakness. Slight physical activity can sometimes prevent or delay mild attacks. During major attacks, the serum potassium decreases, though not always below the normal range, and there is urinary retention of sodium, potassium, chloride, and water. The serum potassium decrease is accompanied by a parallel decrease in serum phosphorus. Oliguria, obstipation, and diaphoresis can occur during major attacks. Sinus bradycardia and electrocardiogram signs of hypokalemia (U waves in leads II, V-2, V-3 and V-4, progressive flattening of T waves and depression of ST segment) appear when the serum potassium falls below the normal range. Clinical or histopathologic signs of cardiomyopathy are absent.

Patients with mild forms of the disease may experience only a few attacks in their lifetime. Those with moderately severe disease experience fewer attacks after age 30 and may become attack-free in their 40s and 50s. Those with severe disease have attacks nearly daily, may not recover fully between the attacks and show diurnal fluctuations of strength. These patients are usually weakest during the night and in the morning and become stronger as the day goes by.

Independently of the severity and frequency of the paralytic attacks, many patients develop a myopathy with permanent residual weakness. In some families all affected members develop a permanent myopathy. This myopathy is chronically progressive and affects especially pelvic girdle and proximal and distal lower limbs muscles. The computed tomography scan shows hypodense areas in the core of the muscles and replacement of muscle by fat.

**Diagnosis**

The diagnosis of familial hypokalemic periodic paralysis is suggested by a decrease of the serum potassium level during a major attack and by a positive family history. The serum CK level is usually normal or slightly increased between the attacks and may increase transiently a few days after a major attack. Abnormally low serum potassium levels between attacks suggest secondary rather than primary periodic paralysis. In these cases appropriate tests are needed to search for renal or gastrointestinal potassium wastage. Another secondary form is thyrotoxic periodic paralysis which resembles the familial form with respect to changes in serum and urinary electrolytes during attacks and its response to glucose, insulin, potassium, and rest after exertion. The attacks cease when the euthyroid state is restored. Approximately 75% of the thyrotoxic cases occur in Orientals. Since 95% of them are sporadic, this form will not be discussed in this report.

EMG evidence of myotonia usually excludes
the diagnosis of hypokalemic periodic paralysis. In the absence of myotonia, one must still exclude the diagnosis of nonmyotonic hyperkalemic periodic paralysis. Lid lag, without electromyographic evidence of myotonia, has been noted in a few patients, but may also be observed in healthy subjects. When there is no permanent weakness, the motor unit potentials are normal between the attacks; patients presenting permanent weakness show myopathic changes and fibrillation potentials or sometimes a peculiar pattern resembling neurogenic alterations. During a severe attack no activity can be detected upon insertion of the EMG needle, voluntary effort elicits few, if any, motor unit potentials, and the evoked compound muscle action potential is either abnormally small or absent.

When the serum potassium of a patient cannot be investigated during a spontaneous attack, further tests are required to establish the diagnosis of periodic paralysis and to determine its type. The systemic provocative tests carry the risk of inducing a severe attack. Therefore they must be performed by an experienced physician, and the serum potassium and glucose levels and the ECG must be closely monitored. Provocative tests with glucose with or without the additional use of insulin must never be done in patients who are already hypokalemic, and potassium chloride must not be given to patients unless they have adequate renal and adrenal function.

The simplest systemic provocative test exploits the physiological potency of glucose, or of glucose plus insulin, to cause hypokalemia. The oral administration of glucose, 2 g/kg body weight, in the early morning combined with 10 to 20 units of crystalline insulin, given subcutaneously, may provoke a paralytic attack within 2 to 3 hours. Exercise and intake of carbohydrates the evening before increases the potency of the test. If the test is equivocal, intravenous administration of 1.5 to 3 g glucose per kg body weight over 60 minutes may provoke an attack. In cases difficult to diagnose, intravenous insulin in doses not exceeding 0.1 U/kg at 30 and 60 minutes during the glucose infusion may precipitate an attack. Another form of the test uses prolonged glucose loading, 50 g glucose in 150 mL water administered hourly for up to 15 hours. Paresis normally appears within 7 to 15 hours and paralysis within 12 to 16 hours. If these tests fail to induce an attack, they may be repeated after exercise and combined with salt loading (2 g of sodium chloride given orally every hour for a total of 4 doses). In general, a serum potassium level of 3.0 mmol/L or less should be achieved. The test is positive when weakness ensues. A negative test does not exclude the diagnosis of primary hypokalemic periodic paralysis because at times patients may be refractory.

**Pathogenesis**

The pathogenesis of the attacks is not understood. Forearm arterio-venous blood studies revealed that hypokalemia is generated by an insulin-dependent uptake of potassium from the extracellular space into the muscle fibers. Increased insulin binding by muscle was found in one patient, but it was not clear whether the number or affinity of the insulin receptors was increased. Another possibility tested was that the attacks are caused by episodic overactivity of the sarcolemmal sodium-potassium ATPase. Although the basal pumping activity of the enzyme was normal, insulin or epinephrine could abnormally enhance pumping activity in an intermittent manner.

In situ, muscle fiber inexcitability in hypokalemic periodic paralysis is caused by a depolarized sarcolemma. In vitro, a lowered extracellular potassium concentration causes membrane depolarization of hypokalemic periodic paralysis muscle but hyperpolarization of normal muscles. The contractile apparatus is unaffected because direct application of calcium to electrically excitable skinned muscle fibers produces a focal contraction. The well-known enhancing effect of glucose and insulin on potassium uptake by muscle is likely to lower the serum potassium level; this induces an abnormal depolarization of the muscle fibers, and initiates the attack. Cromakalim, a substance that activates sarcolemmal potassium channels, is able to repolarize hypokalemic periodic paralysis fibers in vitro so that they regain their contractile force.
**Therapy and Preventive Measures**

Mild paralytic attacks need no treatment. Attacks of generalized paralysis should be treated with 2 to 10 g potassium chloride orally in an unsweetened 10% to 25% aqueous solution. In most cases this causes muscle strength to recover considerably within 0.5 to 1 hours, especially when the patient uses every opportunity for physical activity as strength returns. If the patient shows no signs of recovery after 3 to 4 hours, the dose may be repeated. Intravenous potassium administration, however, is not recommended to terminate an acute attack as it may produce life-threatening hyperkalemia. Some patients like to take potassium at the beginning of an attack. At first they take small doses but with time they tend to increase the dose to relieve an attack more quickly, or even to prevent one. This can lead to potassium “dependency” and the disease becomes more difficult to control. In these patients the daily paralytic attacks do not improve until the potassium is discontinued and other preventive measures are used. Nevertheless, occasional smaller doses of potassium are often unavoidable.

In some families with mild disease even simple therapy is effective; in other families all forms of therapy fail. The basic recommendations are to avoid the ingestion of carbohydrate-rich meals and to avoid strenuous exertion. The medication of choice is acetazolamide. The dosage should be as low as possible, eg, 125 mg every other day. If the paralytic attacks continue, the dose can be increased up to a maximum of 250 mg twice daily. Adverse reactions to the drug include paresthesia, anorexia, transient myopia and an increased incidence of nephrolithiasis. Few patients have developed renal failure during protracted acetazolamide therapy. In two families, one with the typical form and the other with a variant form of hypokalemic periodic paralysis, the drug precipitated muscle weakness. Like ammonium chloride, acetazolamide may act by inducing mild metabolic acidosis, which may prevent an intracellular shift of potassium. Interestingly, the medication is also effective in preventing attacks in primary hyperkalemic periodic paralysis. Patients refractory to acetazolamide may respond favorably to dichlophenamide, an other carbonic anhydrase inhibitor, at doses of 25 mg three times daily. Other medications also have been shown to be useful.

**Molecular Pathology**

A systematic genome-wide search in members of three families showed that the disease is linked to chromosome 1q31-32 and cosegregates with the gene encoding the L-type calcium channel (DHP-receptor) α1 subunit (CACLN1A3), which is located in this region. This subunit is part of the dihydropyridine (DHP) receptor/calcium channel complex located in the transverse tubular system and, altogether, consists of 5 subunits: α1, α2δ, β, and γ. The α1 subunit (Fig 1C) contains the receptor for dihydropyridines and other calcium channel antagonists, and a pore. It is assumed to possess a dual function as calcium channel and as voltage sensor for excitation-contraction coupling, as it generates a voltage-dependent calcium release from the sarcoplasmic reticulum, mediating contraction.

Sequencing of cDNA derived from muscle biopsy specimens of patients revealed so far three mutations. Two of these are analogous predicting arginine to histidine substitutions within the highly-conserved S4 regions of repeats II and IV (Arg-528-His and Arg-1239-His, respectively), the third predicts an arginine to glycine substitution in IV-S4 (Arg-1239-Gly). The substitutions have corresponding counterparts in the α subunit of the sodium channel and those cause paramyotonia congenita by uncoupling activation from inactivation. The majority of families carry either the Arg-528-His or the Arg-1239-His substitution.

Expression of cDNA of CACLN1A3 results in functional channels only when (1) the cell system has a sarcoplasmic reticulum and triads necessary for excitation-contraction coupling and contraction and (2) the other four subunits of the pentameric L-type calcium channel are co-expressed. Thus, for the study of the dysfunction of mutant CACLN1A3, myotubes cultured from muscle specimens of patients are the preparation of choice although they contain also normal channels. In such myotubes, both arginine-to-histidine exchanges enhanced inac-
tivation of the channel.\textsuperscript{113,114} How inactivation of the L-type calcium current is related to hypokalemia-induced attacks of muscle weakness that characterize familial hypokalemic periodic paralysis can only be speculated upon. The hypokalemia-induced membrane depolarisation observed in excised muscle fibres\textsuperscript{35} might reduce calcium release by inactivating sodium channels as well as by a direct effect on its voltage control. Such potential effects of the mutation on the dual function of the L-type calcium channel will be further investigated by studying the transmembrane calcium currents using patch-clamp techniques as well as the transient changes of the intracellular calcium concentration using fluorescent indicators.

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