Hypokalemic periodic paralysis in Emergency Department

DAN MARINESCU M.D. and CONSTANTIN OLTEANU M.D.
Emergency Department, Bucharest Emergency Clinical Hospital

Author for correspondence: DAN MARINESCU M.D., Emergency Department, Bucharest Emergency Clinical Hospital, Calea Floreasca 8, Sector 1, Bucharest, e-mail: danmarinescu@yahoo.com

Abstract: A case of 23 years old man with hypokalemic periodic paralysis in emergency department is presented in this article, followed by a review of pathogeny, clinical features, diagnosis and treatment of the disease.

Key words
hypokalemic periodic paralysis,
emergency treatment, pathogeny, diagnosis,
channelopathies.

A 23 years old man arrives at the emergency department with paralysis of the limbs, trunk and neck, without myotonia. He has a serum concentration of potassium 1,6 meq/l and ECG changes (prolonged PR and flattening of T waves). The patient is admitted at the Neurology department and the paralysis improves, the serum potassium concentration and the ECG changes become normal after intravenous administration of KCl diluted in mannitol.

The onset of the disease was 3 years before with the patient presenting weakness of the limbs and attacks of reversible paralysis more frequent in the morning, when he woke up. The time between attacks was variable and marked by pain and muscle weakness of the limbs.

The patient was the first in his family with those symptoms. After evaluation of thyroid hormonal status (serum T3, T4 and TSH concentration), the diagnosis was hypokalemic periodic paralysis (HOKPP).

Between 2000 and 2004, two more patients came to our emergency department: one with hypokalemic periodic paralysis and the other having paraparesis due to secondary hypokalemia (caused by a prolonged diarrhea).

Since the patients with the afore-mentioned symptoms are coming in the first place to the E.D. and the disease is not frequent, we present the hypokalemic periodic paralysis.

HOKPP is an autosomal dominant disorder characterized by episodic attacks of flaccid paralysis associated with low blood potassium level. If the determination of blood potassium level is not available, myotonia marks the distinction between HOKPP (when myotonia is always absent) and other forms of periodic paralysis (normo- or hyperkalemic).

The attacks are triggered mainly by carbohydrate rich meals and by rest after exercises and they cease after administration of potassium or after exercises.

There are two different forms of HOKPP: the paralytic form which is the most common and the myopatic form.

Genetics and pathogeny

HOKPP is an autosomal dominant transmitted disease. Because the penetrance of some mutations is 100% in males but reduced in females, an X-linked recessive inheritance was initially suggested (based on some pedigree patterns) [1 quoted by 2]. Penetrance: the fraction of individuals with a genotype known to cause a disease who have any signs or symptoms of the disease [3].

The penetrance varies with the disease causing mutations. It is 100% for male and low for female with mutation R672H in the sodium channel [4]. For another mutation (R672G) in same sodium channel, the penetrance is 100% for both women and men [5, 6, 7].

Of the patients with mutations in genes for voltage gated calcium channels, about 45% of the women who have the R528H mutation, and 29% of those with the R1239H are asymptomatic. Of the males having both mutations, 90% of patients are symptomatic [7].

All seven mutations for the gene encoding the channels for calcium and for sodium affect the α-subunit of those channels [8,9,10,11,12,13].

Incidence of HOKPP is about 1:100000 [4].

Structure and function of the voltage-gated cation channels

In all types of cells the most important second messenger for intracellular signal transduction is the calcium ion [14]. The intracellular concentration of calcium (100 nM in resting cells) must be precisely controlled at this low level [15], whereas extracellular concentration is about 1 mM. One of the means by which intra-

cellular calcium concentration is regulated is the influx from the extracellular space through the calcium channels [16].

In the '70 the possible existence of voltage-dependent calcium channels was reported for the first time, those being initially divided in two classes: high-voltage-activated (HVA), and low-voltage-activated (LVA) [17]. Another classification according to their inactivation properties divided the voltage-gated channels into transient (T-type) and long-lasting (L-type). Later HVA were subdivided depending on their tissue expression pattern and toxin sensitivity in other subtypes: B (brain), N (neuronal), P (Purkinje cell) and R (toxin resistant) [18].

L-type is widely distributed in all types of cells except for platelets [16].

Structure and function

L-type calcium channels are best studied because of their abundance in skeletal muscle tissue [19]. L-type channels are sensitive to dyhydropyridines (DHP; e.g. nifedipine) which has lead to the term dihydropyridine receptor (a misnomer because DHP is an antagonist, not an activation ligand) [18].

The calcium channel consists of five different polypeptide subunits: α1, α2, β, γ and δ [20,21]. Voltage-gated calcium, sodium and potassium channels show a varying subunit composition.

The α-subunit is the main structural component of the calcium channel because it determines the main characteristics of the pore. It contents the ion-conducting pore, voltage sensors, gates for the opened and closed channel states and binding sites for ligands [18].

The α1-subunit contains calcium antagonist binding sites [22,23] and has four homologous domains. Each domain has six transmembrane regions (S1 to S6) connected by intracellular and extracellular loops (the interlinkers) [22,24]. The S4 transmembrane segment serves as the voltage sensor of the channel [25] and is present in all voltage-gated channels [26].

The pore region (the S5-S6 regions) contributes to the lining of the channel pore and has negative charges surrounding the external opening of the pore, thus forming the selectivity filter of the channel.

The functions of the L-type calcium channel are related to the generation of the action potentials and the signal of the transduction events at the cell membrane [27], also being involved in the process of neurotransmitter secretion of the central nervous system [28, 29].

Eight different α1 – subunit genes (CACNA to CACNG) are known in vertebrates. Mutations in the genes encoding the α1 – subunit (CACNL1A3) account for most of the cases of HOKPP.

Besides the L-type calcium channel, another important channel is expressed in the adult skeletal muscle: ryanodine receptor (RYR1; sensitive to alkaloid ryanodine) which releases calcium from the sarcoplasmic reticulum (SR) or endoplasmic reticulum (ER). They are located in the triadic junction of the t-tubular system and the SR, respectively, and diseases causing mutations in the genes encoding both channels have been described [18].

In the skeletal muscle, L-type channel is not important as an ion-conducting channel but functions as a voltage sensor of the RYR1 that releases calcium from SR, initiating contraction [30].

Sodium channels

Their basic structure is the same as the one of the calcium channel. Ten different genes that encode α-subunits of the sodium channel are known and they range from SCN1A to SCN10A.

Point mutations in the gene encoding the α-subunit of the adult skeletal muscle sodium channel (SCN4A) are responsible for HOKPP type 2 [7,13,31].

In the SCN4A gene, four mutations for the HOKPP have been identified. They are also responsible for other diseases: hyperkalemic periodic paralysis, normokalemic paralysis, paramyotonia congenitalia and different types of myotonia [4].

Another rare mutation has been described in a family with a rare combination of heat-induced myotonia and cold-induced paralysis [32].

Potassium channels

The pore region of the potassium channel was first studied using the pore blocking agent tetraethylammonium [33].

The under threshold, voltage-gated potassium channel of the skeletal muscle is shown to contain the MinK-related peptide 2 (MiRP2) and the pore-forming subunit Kv3.4. A missense mutation in the gene for MiRP2 (KCNE3) has been identified in two families with periodic paralysis and has been proven to segregate with the disease. Mutant MiRP2-Kv3.4 complexes exhibit reduced current density and have a diminished capacity to set the resting membrane potential [34].

Two further studies invalidate that hypothesis [35,36].

Pathophysiology

During an attack, the sarcolemma becomes depolarised and inexcitable [37].

The basis of this depolarisation remains speculative, although changes in ATP-sensitive potassium channels and in sodium channels have been promoted as direct precipitants [12,38,39].

Another theory involves the adenosine triphosphate sensitive potassium channel (K_{ATP}) in the pathogeny of HOKPP with mutations in the α-subunit of the L-type calcium channels. K_{ATP} is a metabolically regulated potassium channel present in high density in different tissues, including skeletal muscle [40,41,42].

It has been demonstrated in animal models that individuals with chronic hypokalemia have an abnormally reduced activity of the sarcolemal K_{ATP} channels [43].

Insulin promotes the entry of potassium into skeletal muscle and hepatic cells, apparently by increasing the activity of the Na-K-ATPase pump [44].

In humans affected by HOKPP, insulin produces fiber depolarisation and muscle paralysis associated with hypokalemia, while in healthy subjects it produces fiber hyperpolarization [45].

In patients with HOKPP, not only the pore of the muscular KATP channel complex is altered, but also sulfonylurea receptor involved in the activation of the channel [46]. The K_{ATP} channel is functionally coupled to the Na-K-ATP-ase. In healthy subjects, the insulin stimulation of the pump leads to an influx of potassium ions inside the muscle, to a transient hypokalemia and to the activation of the K_{ATP} current that hyperpolarizes the fibers. In subjects with HOKPP (where there is no efflux of potassium ion because of the reduced basal activity of the K_{ATP} channels), insulin aggravates the fiber depolarisation and determines paralysis [47].

In patients with HOKPP, hypokalemia results from the effect of glucose intake and the release of insulin, which stimulates the sodium-potassium pump and shifts potassium ions from the extracellular space into the intracellular one [48]. In normal subjects, the hypokalemia produces hyperpolarization, but in patients with HOKPP it causes sustained depolarization of the fibers which initiates the attack [49].

Cathecolamines promote potassium movement into cells mediated by the β_2-adrenergic receptors which also involves activity of the Na-K-ATP-ase pump. As a result, transient hypokalemia can be induced when adrenaline release is enhanced by hypoglycemia or the stress caused by an acute illness [44] that explains how triggering factors act.

In HOKPP type-2 (caused by mutations in sodium channel), the sustained depolarization causes further inactivation of the mutant sodium channel and through a positive feedback mechanism it inactivates more and more normal sodium channels and renders the cell inexcitable, the patient becoming paralysed. This mechanism is called enhanced inactivation [12, 13].

Clinical manifestation

The clinical polymorphism of HOKPP can be explained by the multiple mutations responsible for the disease, the variable penetrance depending on the mutations, as already mentioned above.

For didactic purposes, two different forms of HOKPP are described: the paralytic form and the myopathic form, with a slowly progressive myopathy. They may occur separately or together. The pure paralytic form is the most common one, the combination of paralytic attacks with progressive myopathy is less common and the pure myopathic form is very rare [4].

The age of onset for the first attack ranges from one to 20 years.The highest frequency of the attacks ranges between 15 and 35 years and it decreases with age [4].

Two patients were described bearing the mutation in the calcium channel (R528H): a 79-year-old man which had no paralysis attacks in his lifetime, and a 65-year-old man which had only two paralysis attacks at 41 and 45 years. The same authors presented four women with R1239H mutation who experienced only one paralysis attack in their lifetime after a trigger event. For two of them, the trigger was a general anaesthesia, for one the flu and for the last one an intoxication [7].

Typically, the attacks occur during the second half of the night or early in the morning. The triggering factors consist of carbohydrate-rich meals, rest after exercises, perfusion with glucose or solutions of NaCl and various conditions of stress (pregnancy, surgical operations) [4,50].

Sometimes prodromes can precede the attacks: excessive hunger or thirst, dry mouth, palpitations, sweating, diarrhoea, nervousness and a sense of weariness or fatigue [50].

The attack evolves over minutes to hours and, once established, the weakness lasts hours or days depending on the severity.

The paralyis is variously distributed and variable. The extremities are earlier and more severely affected than the trunk muscles, usually the legs are more often affected than the arms. The attacks often spare the following muscles: extraocular, facial, tongue, pharynx, larynx and diaphragm.

When the attack is at its peak, tendon reflexes are reduced or abolished and cutaneous reflexes may also disappear, but sensation is preserved [50].

Rarely, death may be caused by a paralysis of the respiratory muscle or by a malignant arrhythmia (especially in the absence of intensive care) [50].

Myotonia is never seen in patients with HOKPP.

Reversible weakness between crisis, postcritic myalgia and cramps have been reported with variable frequency related to the causative mutation [7].

The frequency of attacks is extremely variable: daily, weekly, monthly, yearly or a single attack in a lifetime [4].

The frequency of associated myalgias (paracritic and postcritic) and of permanent muscle weakness are variable, depending on the mutation [7].

Laboratory findings

By definition, the attacks in hipokalemic periodic paralysis are accompanied by a decrease of the potassium level in serum. The level of potassium can reach 1,4 meq/l [7], but is usually almost normal or it has values that do not produce paresis in normal subjects. The decrease in serum potassium is associated with little or no increase in the urinary potassium excretion [50] because Na-K-ATP-ase stimulation leads to the influx of potassium inside the muscle [47].

The amount of potassium excreted in the urine declines during major attacks and can serve as a further diagnostic marker [51].

Normal subjects do not become weak until their blood potassium reaches levels lower than 2,5 meq/l [52 quoted by 51]. Patients with HOKPP are usually very sensitive to decrease of serum potassium. Every normal subject can experience weakness due to an important decrease of serum potassium, but the patients with HOKPP can experience full weakness even after a minimal lowering of potassium level.

The determining factor is not the level of the serum potassium but the condition and response of the patient. It is not the level itself, but the drop that precipitate the paralytic episode [53 quoted by 51].

Transcellular shifts of potassium are more likely to produce symptoms than changes in external balance. The level of the decrease in the plasmatic potassium concentration affects the neuromuscular excitability based on three factors. The mechanism of change (alteration in external balance *versus* transcellular shift), the extracellular concentration of calcium and the extracellular pH [44].

The serum potassium may become normal several hours before the weakness begins to resolve and patients arrive in the emergency department with normal potassium levels.

Because the serum potassium is usually normal between the crises, provocative tests may be helpful for diagnosis but they must be performed very carefully especially since other reliable tests are available which are less aggressive for the patients.

Provocative tests must be avoided in patients with any possibility of cardiac involvement [54].

A type of provocative test described by Gamstorp consists in giving 50 g glucose in 150 ml water orally per hour until the weakness commences. Serum potassium, oxygen levels and cardiac activity must be monitored and the patient must be kept under continuous observation from the beginning of the test period. A transient attack of weakness combined with a reversible decrease in serum potassium and/or transient hypopotassemic ECG abnormalities confirm the diagnosis [55].

A drop in serum potassium may be also be induced by an insulin provocation test in which the oral administration of 100 g glucose is combined with 25 IU insulin given subcutaneously. The glucose/insulin test may also be performed by giving the glucose and the insulin intravenously. Since weakness induced by this test may occasionally be severe, it is wise to begin only with glucose, since this is a less potent stimulus and the combined administration of insulin and glucose may produce life-threatening arrhythmias if the serum potassium drops to very low levels [52].

For a correct determination of serum potassium, the following clues are useful:

Hemolysis when drawing the blood sample has to be avoided: it will give false-to-high results. The sample must be delivered to the laboratory and examined at once to separate cells from serum. Potassium moves out of the cell and will be falsely high after four hours [55].

After a tourniquet is applied to obtain a blood sample, the patient is often instructed to repeatedly clench and unclench his fist to increase local blood flow and to make the veins more prominent. This can result in extracellular potassium shift and an elevation in the plasma potassium concentration with 1 to 2 meq/l, leading to errors [56]. For this reason, it is recommended to draw the blood sample without a tourniquet, or to release the tourniquet after the needle has entered the vein and wait for two minutes before drawing the sample [55].

ECG changes

PR and QT intervals are prolonged.

QRS complex begins widening at a serum potassium level of about 3 mEq/l.

ST segment may become depressed by 1 mm or more.

T waves begin to flatten at a potassium level of about 3 meq/l and continue to be smaller as the U waves that increase in size and the T/U ratio may be inverted.

At a serum potassium level of about 3 meq/l the U waves may have the same amplitude as the T waves and at around 2 meq/l they become higher than T waves. The U waves get to a "giant" amplitude and fuse with the T waves at 1 meq/l.

Ventricular arrhythmia (torsade de pointes) may occur in hypokalemia especially in the presence of digitalis [50, 51, 57].

Electromyogram

During the attack, the electromyogram (EMG) findings are not specific. EMG demonstrates a reduced number of motor units (myopathic abnormalities) [4]. Between the attacks, EMG may exhibit myopathic abnormalities in patients with fixed myopathy. Between the attacks, a standardised test elaborated by Mc Manis is performed. The test is performed on the *abductor digiti minimi* muscle, with stimulation of the ulnar nerve at wrist. Compound muscle action potentials (CMAP) are recorded after supramaximal stimulation and maximal voluntary isometric exercise. A decrement of CAMP more than 40% is highly suggestive for periodic paralysis, but does not differentiate between the primary and secondary forms of periodic paralysis [58].

Histopathology

Pathology is very useful in the patients with the myopathic form. Optic or electron microscopy show some abnormalities on muscle biopsy material.

Vacuoles are predominant in the muscles of patients carrying calcium channel mutations. The patients with sodium channel mutations have a myopathy characterised by tubular aggregates in type II fiber. Tubular aggregates consist of densely packed double-walled reticulum [59 quoted by 7]. Those lesions are found as a minor feature in the skeletal muscle of normal patients, but also in subacute alcoholic myopathy, drug myopathy, malignant hypertermia and metabolic or inflammatory myopathies [60].

The vacuoles remain the morphological hallmark of the HOKPP in the myopathic stage and may be present in patients with no clinical permanent muscle weakness. Rarely electron microscopy detected tubular aggregates among the predominant vacuoles as well. Electron microscopy can also detect mitochondrial changes [7], without being necessary for diagnosis of the disease.

Molecular genetic testing

Disease causing mutations are localised in genes encoding the calcium channel (70%), the sodium channel (12%) and (controversial) the potassium channel. Molecular genetic testing is clinically available for the most common seven mutations described for the calcium channel (chromosomal locus 1q32, gene CACNA-1S, exon11 and 30) and for the sodium channel (chromosomal *loci* 17q23.1; 17q25.3, gene SCN4A, exon 12).

Molecular genetic testing identifies disease-causing mutations in the afore-mentioned genes in 80% of individuals with clinical diagnostic criteria. In 20% of the patients with clinically diagnosed HOKPP none of seven most common mutations are found, indicating possible further allelic heterogeneity and/or genetic heterogeneity of the disorder [4].

Besides the mutations causing HOKPP, other mutations in the same genes expand the spectrum of diseases of this genes. For the gene of calcium channel (CACNA1S) the mutation in exon 26 causes malignant hypertermia susceptibility in an autosomal dominant manner. For the gene of sodium channel (SCN4A) to the date more than 20 mutations in other exons have been shown to cause disease inherited in an autosomal dominant manner, characterised by hyperexcitability of the sarcoplasmic membrane, which include: normokalemic or hyperkalemic periodic paralysis, paramiotonia congenita, potassium-aggravated myotonia, myotonia fluctuans, myotonia permanens, acetazolamide-responsive myotonia, hyperkalemic periodic paralysis with or without malignant hypertermia susceptibility and succinylcoline-induced masseter muscle rigidity, a complication of anaesthesia closely related with malignant hypertermia [4,7,50].

Until now, a positive genetic test can prove that a patient has HOKPP, but a negative result does not rule out the possibility of the disease.

Differential diagnosis

The main differential diagnosis is mainly considered with: normokalemic- and hyperkalemic periodic paralysis, thyrotoxic periodic paralysis, Andersen syndrome and secondary hypokalemia (Figure 1).

Normokalemic – and hyperkalemic periodic paralysis

In some patients with hyperkalemic paralysis the serum concentration of potassium decreases at the end of the attack to a level patognomonic for HOKPP. For this reason, is is important to measure the serum potassium early in the attack.

The triggering factors of the HOKPP are not found.

The age of paralytic attacks onset is lower and the duration of the attacks is shorter [61].

Myotonic symptoms e.g. ocular muscle myotonia (slow opening of the lids after forced active closure of the eyes) and myotonic discharges on EMG between attacks are specific [11].

Hyperkalemic periodic paralysis can be provoked by administration of potassium.

The progressive myopathy may be as common as it is in HOKPP [62].

Patients were presented with hyperkalemic periodic paralysis who had paralytic episodes in adoles-

cence precipitated by rest after exercise, cold, alcohol intake and fasting, the attacks worsening over the years, occurring daily and spontaneously [63].

Thyrotoxic periodic paralysis

Periodic paralysis with hypokalemia and thyrotoxicosis have an identical clinical picture with the hereditary form without hyperthyroidism, but the thyrotoxicosis may be mild. Same as HOKPP, the attacks can be triggered by meals rich in carbohydrates [64].

Spontaneous or induced attacks do not occur in persons with corrected hyperthyroidism.

The disease is more frequent in men, especially of Asian origin and possibly people of Latin American and Afro-American origin [4,65].

It is likely that the Oriental periodic paralysis is precipitated by one of many factors: abuse of thyroid hormone [66], primary aldosteronism [67], barium poisoning (barium blocks the potassium channels in the cell membrane that normally allow potassium to diffuse into the extracellular fluid) [44] – a side effect of gosypol (a fertility regulating agent used in China) –, "hashitoxicosis" (Graves disease and Hashimoto thyroiditis) [66].

The assessment of thyroid hormonal status (serum T3, T4 and TSH concentration) is diagnostic.

The hypothesis that HOKPP and thyrotoxic periodic paralysis are caused by the same mutation was infirmed. A mutation in KCNE3 gene was identified in one sporadic case: a patient who experienced episodic paralysis for two years before developing thyrotoxicosis caused by Graves disease [68].

Andersen syndrome

It is a distinct form of periodic paralysis characterised by the triad of periodic weakness, a large QT interval predisposing to ventricular tachyarrhythmias and dismorphism (short stature, scoliosis, tapered/curved fingers, hypertelorism, micrognathia, cleft palate and missing teeth) [69].

The possibility of Andersen syndrome is suggested by episodic periodic paralysis in patients with characteristic clinical features and family history of sudden death.

To eliminate the suspicion of Andersen syndrome an ECG or a Holter-ECG recording is necessary between attacks of weakness. The causative mutation is situated on the chromosomal locus 17q23, the gene for potassium channel KCNJ2 [70].

Secondary hypokalemia may be caused by reduced potassium intake, enhanced renal excretion or digestive loss (for details see references 4 and 44)

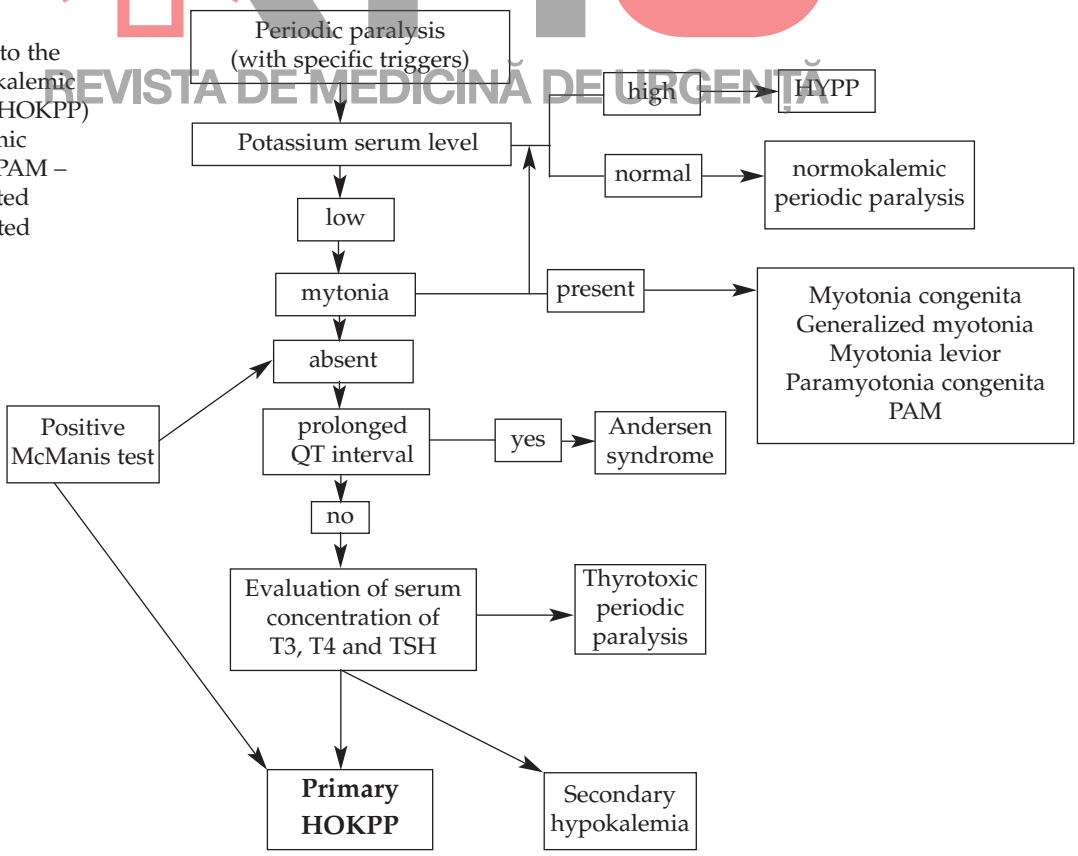

Figure 1
Stepwise approach to the evaluation of hypokalemic periodic paralysis (HOKPP)
HYPP – hyperkalemic periodic paralysis; PAM – potassium-aggravated myotonias and related disorders

Treatment

The two aims of the treatment are: 1) treatment of the paralytic crisis and 2) prevention of the attacks.

Treatment of the paralytic crisis Emergency management

In severe paralysis, swallowing may be compromised and the gag reflex lost. In that case, place the patient in the recovery position to avoid aspiration. Monitor ECG and assess the respiration. In patients with total paralysis of the extremities without difficulties in deglutition and respiration, oral KCl solution can be administered. If no improvement occurs after 4 to 5 oral doses, or if nausea or diarrhoea occurs after the oral KCl intake, the i.v. administration is necessary. I.v. administration is preferable in patients with attacks, difficulties in swallowing and impaired breathing [71].

On one hand, the treatment of an attack normalises the serum concentration of potassium and, on the other hand, shortens the paralytic episode. The inaccuracy of the treatment is the consequence of the incomplete knowledge of the disease mechanism: the administration of the potassium treats hypokalemia directly, but the weakness only indirectly. This is why weakness improves sooner than the serum concentration normalises. Once the muscular weakness ameliorated, the serum concentration of potassium may normalise several hours later.

The electrocardiogram monitoring is very important because both hypokalemia and the subsequent changes in potassium concentration determined by the treatment may induce cardiac arrhythmia. The patients must be ECG monitored before, during and after the treatment and they must have repeated determinations of serum potassium concentration.

A prominent increase in the amplitude of U wave on ECG (because of the hypokalemia) is an alarm signal, because it is associated with a higher susceptibility to the particular form of ventricular arrhythmia – torsade de pointes [4,50,71].

Potassium can be administrated orally or intravenously.

Oral administration is easy, safe and inexpensive. Is the preferred route for patients with mild hypokalemia and minimal symptoms [72].

Oral administration consist of doses of 0,2-0,4 mmol/kg repeated every 15 to 30 minutes over one to three hours [73].

For children, the dose is 1 to 4 mmol/kg/24 hours divided bid or qid [72].

Oral potassium is better tolerated when added to food. If the KCl solution is not tolerated, another K salt can be used.

If oral potassium administration is not possible or if there is no improvement in 1 or 2 hours, KCl may be given intravenously.

A bolus of 0,05 to 0,1 mmol/kg can be given, followed by infusion *via* peripheral intravenous line or *via* central intravenous line.

For the peripheral intravenous line the concentration should be 20 to 40 mmol/l, 60 mmol/l in exceptional circumstances, but local pain and phlebitis can occur [73]. The dose per hour should be between 0,25 to 0,5 mmol/kg.

Serum potassium concentration must be checked every 4 hours at 0,25 mmol/kg/hour, every 2 hours at 0,5 mmol/kg/hour and frequently during aggressive diuresis and correction of acidosis. A cardiac monitor is required for administration rates higher than 0,25 mmol/kg/hour.

For the central intravenous line the concentration can be between 0,02 and 0,16 mol/l [74].

For children, the dose is 0,25 mmol/kg and must not exceed 0,5 mmol/kg/hour to a maximum of 30 mmol/h and 200-250 mmol/day [72].

Hypokalemia may be refractory to treatment until hypomagnesemia is corrected [75].

In patient with HOKPP, the overcorrecting of potassium must be avoided, because this condition is a transcellular maldistribution, not a true deficit.

Prevention of the attacks

At first the identification and, if it is possible, the avoidance of triggering factors is necessary.

Preventive therapy consists of low sodium diet (2 g per day, but 1 g is better if it is possible) and a diet poor in simple carbohydrates (85 g per day) [76].

The oral intake of potassium salts (10 to 20 mmol/dose, 3 dose per day) can prevent the attacks, especially if the dose is taken a few hours before the usual time of the attack (nocturnal dose if crises occur at awakening) [4].

The potassium citrate or bicarbonate formulas are better tolerated and absorbed than potassium chloride.

Acetazolamide is highly effective in most patients, depending on the causative mutation. Acetazolamide can be ineffective or even have deleterious consequence in patients having some mutations (rare for calcium channel, but frequent for sodium channel) [7,77]. Thus, in some patients with a mutation for the sodium channel, acetazolamide increases the frequency and severity of attacks [7,77].

Therefore it is desirable to know precisely the mutation before starting the therapy with acetazolamide.

Acetazolamide is most successful when the therapy is started at a low dose (125 mg daily) then grad-

ually increased over a period of a few weeks up to 1000 mg per day divided qid to bid.

Acetazolamide may act by diminishing potassium uptake by skeletal muscle, an effect that may be mediated by the inhibition of carbonic anhydrase in the muscle cells [44].

The patients who respond poorly to acetazolamide or who have adapted to the drug after a long usage may respond to dichlorphenamide, a more potent but more expensive inhibitor of carbonic anhydrase. The dosage is 25 to 200 mg per day.

The patients who fail to respond to carbonic anhydrase inhibitors often respond well to the potassium sparing diuretics: triamterene 50 to 150 mg daily or spironolactone 25 to 100 mg daily. Both can be used in addition to acetazolamide or dichlorphenamide [71].

Risks and precautions

The risks in medical practice are related especially to the triggers of the paralytic attacks, which must be avoided during the treatment of the other associated disease or conditions.

For the surgical interventions, there are, on one hand, the surgical stress (that can trigger the attack by itself *via* adrenaline) and, on the other hand, the local or general anaesthesia which have special risks.

Local anaesthesia

The use of local anaesthetics on patients with periodic paralysis involves some unusual challenges. Many patients report that these agents trigger weakness or paralysis and some of the patients also report that these drugs do not produce the desired anaesthesia.

Adrenaline can cause hypokalemia even in normal subjects and also explains the acute hypokalemia during a stress (plasmatic level of potassium with 0,5-0,6 mmol/l lower).When adrenaline is combined with a local anaesthetic agent, the potassium level falls another 1 mmol/l. In this condition in a patient with HOKPP a paralytic attack can occur. For this reason, adrenaline must be avoided in those patients.

At first, adrenaline increases the serum potassium. Subsequently, combined alpha and beta adrenergic receptor stimulation enhances potassium uptake by muscles and liver and the serum potassium level decreases [44,47,78].

After an epidural anaesthesia with 2% mepivacaine with adrenaline the average decrease in serum potassium is 0,4 mmol/l [79].

An axially block, with 1% lidocaine and adrenaline 1:100000, decreases the serum potassium level to 2,9 mMol/l, 30 minutes after the blockade, but insignificant decrease of the serum level occurs if the patient receives propranolol 2 mg intravenously, before the blockade [80].

General anaesthesia

Patients with HOKPP have an increased risk of malignant hyperthermia, but not as high as those with true autosomal dominant malignant hyperthermia susceptibility (MHS) [4].

Malignant hyperthermia is not a disease, but a genetic predisposition of individuals to respond abnormally when exposed to volatile anaesthetics or depolarising muscle relaxants (succynilcholine). When exposed to those triggering agents, a pathologically high increase of the myoplasmic calcium concentration occurs, leading to increased muscle metabolism and heat production. The symptoms consist in muscle rigidity (masseter or generalised), hyperthermia, acidosis, rhabdomyolysis, hyperkalemia and hypoxia [81, 82]. The susceptibility of a patient is determined by an invasive *in vitro* contracture test which assesses the response of the viable muscle tissue at the exposure to halothan and caffeine [81].

This test differentiates between clearly MH susceptibility, MH normal individuals, and the group of MH equivocal, and showed a sensitivity of 99% and a specificity of 93,6% [82].

The metabolic alteration usually progresses rapidly and, without treatment, up to 70% of the patients may die, but early administration of dantrolene [83] (an inhibitor of calcium release from the sarcoplasmic reticulum) has reduced the mortality to 10% [18].

The initial dosage of dantrolene is 2,5 mg/kg, with a total dose of 10 mg/kg, although this dose can be exceeded safely [84].

MHS is caused by several mutations. The most frequent are in the gene encoding the calcium release channel (also called ryanodine receptor). Additional mutations are in the α1-subunit of the DHP receptor [85], the voltage sensor of the ryanodine receptor [18], in SCNA4, gene encoding alpha subunit of the muscle sodium channel [86] and maybe in CACNA2, gene encoding α2/δ – subunit of DHP receptor [87,88]. In conclusion, MHS is genetically heterogeneous and it was proven to be allelic to HOKPP (alleles being different forms of the same gene).

The incidence of MH is estimated at 1:50000 anesthetis and 1:5000 to 1:10000 anesthetics for children [90]. When succinilcholine is used, incidence can reach 1:4500 anesthetics [91].

Only two cases of malignant hyperthermia in patients with HOKPP have been reported to date [92, 93].

Therefore, the general anaesthesia in patients with HOKPP needs an assessment, a multidisciplinary ap-

proach and precautions during the drug administration [94,95].

Conclusions

HOKPP is a rare but potentially life threatening disease.

The diagnosis can be difficult, often needing an interdisciplinary assessment.

The treatment depends on the disease causing mutation and it is not always effective. An aggressive therapy in the Emergency Department is rarely necessary.

All these patients need genetic counseling.

Acknowledgments. We are indebted to Dr. Horia Stănescu for helpful discutions, and to Dr. Laura Balica and Violeta Vintilescu PhD for translation of the manuscript.

References

1. Sagild U. Hereditary Transient Paralysis**.** Copenhagen: Munksgaard, 1959.
2. Online Mendelian Inheritance in Man.[homepage on the Internet]. Hypokalemic periodic paralysis.[created 2 June 1986 by Mc Kusick V A, last updated 23 January 2004, cited 25 June 2004]. Available from:
http:// www.ncbi.nlm.nih.gov/Omim
3. Nussbaum RL, McInnes RR, Willard HF. Thompson & Thompson Genetics in Medicine.(glossary). Philadelphia: W B Saunders, 6th edition, 2001.
4. Gene Reviews [homepage on the Internet] Sternberg D., Nacera Tabti N., HainqueB. , Fontaine B Hypokalemic Periodic Paralysis. [created 30 April 2002, last updated 19 May 2004, cited 20 May 2004]. Available from:
http://www.geneclinics.org/,
5. Elbaz A, Vale-Santos J, Jurkat-Rott K et al. Hypokalemic periodic paralysis and the dihydropyridine receptor (CACNL1A3): genotype/phenotype correlations for two predominant mutations and evidence for the absence of a founder effect in 16 caucasian families. Am J Hum Genet , 1995, 56: 374-80.
6. Fouad G, Dalakas M, Servidei S, et al. Genotype-phenotype correlations of DHP receptor alpha 1-subunit gene mutations causing hypokalemic periodic paralysis**.** Neuromuscul Disord. 1997, 7(1):33-8.
7. Sternberg D, Maisonobe T, Jurkat-Rott K et al. Hypokalaemic periodic paralysis type 2 caused by mutations at codon 672 in the muscle sodium channel gene SCN4A. Brain, 2001, 124, 6, 1091-1099.
8. Ptacek LJ, George AL Jr, Griggs RC et al. Identification of a mutation in the gene causing hyperkalemic periodic paralysis. Cell. 1991, 67(5):1021-7.
9. Ptacek LJ, Tawil R, Griggs RC et al. Dihydropyridine receptor mutations cause hypokalemic periodic paralysis. Cell. 1994 , 77(6):863-868.
10. Fontaine B, Trofatter J, Rouleau GA et al Different gene loci for hyperkalemic and hypokalemic periodic paralysis Neuromuscul Disord 1991, 1(4): 235-8.
11. Jurkat-Rott Karin, Mitrovic N, Hang C et al. Voltage-sensor sodium channel mutations cause hypokalemic periodic paralysis type 2 by enhanced inactivation and reduced current. Proc Natl Acad Sci U S A. 2000, 97 (17): 9549–9554.
12. Kuzmenkin A, Muncan V, Jurkat-Rott Karin Enhanced inactivation and pH sensitivity of Na^+ channel mutations causing hypokalaemic periodic paralysis type II. Brain, 2002,125, 4:835-843.
13. Bulman DE, Scoggan KA, van Oene MD et al. A novel sodium channel mutation in a family with hypokalemic periodic paralysis. Neurology. 1999, 53(9):1932-6.
14. Somlyo AP, Somlyo AV. Signal transduction and regulation in smooth muscle. Nature. 1994, 372(6503):231-6.
15. Ghosh A, Greenberg ME.Calcium signaling in neurons: molecular mechanisms and cellular consequences. Science. 1995, 268(5208):239-47.
16. Yamakage M, Namiki A. Calcium channels – basic aspects of their structure, function and gene encoding; anesthetic action on the channels – a review. Canadian Journal of Anesthesia 2002, 49:151-164.
17. Hagiwara S, Ozawa S and Sand O. Voltage clamp analysis of two inward current mechanisms in the egg cell membrane of a starfish. The Journal of General Physiology, 65: 617-644.
18. Lehmann-Horn F and Jurkat-Rott Karin. Voltage-Gated Ion Channels and Hereditary Disease. Physiological Reviews, 1999, 79, 4 :1317-1372.
19. Fosset M, Jaimovich E, Delpont E [3H]nitrendipine receptors in skeletal muscle J. Biol. Chem., 1983, 258,10: 6086-6092.
20. Ruth P, Rohrkasten A, Biel M et al. Primary structure of the beta subunit of the DHP-sensitive calcium channel from skeletal muscle. Science. 1989, 245(4922):1115-8.
21. Jay SD, Ellis SB, McCue AF Primary structure of the gamma subunit of the DHP-sensitive calcium channel from skeletal muscle. Science.1990, 248(4954): 490-2.
22. Tanabe T, Takeshima H, Mikami A Primary structure of the receptor for calcium channel blockers from skeletal muscle. Nature. 1987, 23-29;328(6128):313-318.
23. Ellis SB, Williams ME, Ways NR et al. Sequence and expression of mRNAs encoding the alpha 1 and alpha 2 subunits of a DHP-sensitive calcium channel.[Abstract] Science. 1988, 241(4873):1661-1664.
24. Catterall WA. Structure and function of voltage-sensitive ion channels. [Abstract] Science,1988 ;242(4875):50-61.
25. McCleskey EW, Womack MD, Fieber LA. Structural properties of voltage-dependent calcium channels. Int Rev Cytol 1993; 137C: 39–54.
26. Stuhmer W, Conti F, Suzuki H et al Structural parts involved in activation and inactivation of the sodium channel. [Abstract] Nature. 1989, 22339(6226):597-603.
27. Kostyuk PG Diversity of calcium ion channels in cellular membranes. [Abstract] Neuroscience, 1989, 28, (2): 253-61.
28. Bonci A, Grillner P, Mercuri NB et al. L-Type Calcium Channels Mediate a Slow Excitatory Synaptic Transmission in Rat Midbrain Dopaminergic Neurons. The Journal of Neuroscience, 1998, 18(17):6693-6703.
29. Protti D and Llano I. Calcium Currents and Calcium Signaling in Rod Bipolar Cells of Rat Retinal Slices The Journal of Neuroscience, 1998, 18(10):3715-3724.

30. Melzer W, Herrmann-Frank A, Luttgau HC. The role of Ca^{2+} ions in excitation-contraction coupling of skeletal muscle fibres. Biochim Biophys Acta. 1995;1241(1):59-116.
31. Davies NP, Eunson LH, Samuel M. et al. Sodium channel gene mutations in hypokalemic periodic paralysis: an uncommon cause in the UK. Neurology. 2001, 57(7):1323-5.
32. Sugiura Y, Aoki T, Sugiyama Y et al. Temperature-sensitive sodium channelopathy with heat-induced myotonia and cold-induced paralysis. Neurology, 2000, 54(11): 2179-81.
33. Kavanaugh MP, Varnum MD, Osborne P.B.et al. Interaction between tetraethylammonium and amino acid residues in the pore of cloned voltage-dependent potassium channels. J. Biol. Chem.,1991, 266, 12, 7583-7587.
34. Abbott GW, Butler MH, Bendahhou S, et al. MiRP2 forms potassium channels in skeletal muscle with Kv3.4 and is associated with periodic paralysis. Cell., 2001,104(2):217-31.
35. Sternberg D, Tabti N, Fournier E, et al. Lack of association of the potassium channel- associated peptide MiRP2-R83H variant with periodic paralysis. Neurology. 2003, 61(6): 857-859.
36. Jurkat-Rott K, Lehmann-Horn F. Periodic paralysis mutation MiRP2-R83H in controls: Interpretations and general recommendation Neurology. 2004, 62 (6):1012-5.
37. Rudel R, Lehmann-Horn F, Ricker K. Hypokalemic periodic paralysis: in vitro investigation of muscle fiber membrane parameters. Muscle Nerve. 1984;7(2):110-120.
38. Ruff RL. Insulin acts in hypokalemic periodic paralysis by reducing inward rectifier K+ current. Neurology. 1999, 22;53(7):1556-63.
39. Tricarico D, Servidei S, Tonali P et al.Impairment of skeletal muscle adenosine triphosphate–sensitive K^+ channels in patients with hypokalemic periodic paralysis J Clin Invest, 1999, 103, 5: 675-682.
40. Noma A. ATP-regulated K+ channels in cardiac muscle.[Abstract] Nature. 1983, 305(5930):147.
41. Sakura H.C., Bond M., Warren-Perry S. et al. Characterization and variation of a human inwardly-rectifying-K-channel gene (KCNJ6): a putative ATP-sensitive K-channel subunit. FEBS Lett. 1995,367: 193-197.
42. Tricarico D, Camerino DC. ATP-sensitive K+ channels of skeletal muscle fibers from young adult and aged rats: possible involvement of thiol-dependent redox mechanisms in the age-related modifications of their biophysical and pharmacological properties. Mol Pharmacol. 1994. 46(4):754-761.
43. Tricarico D, Mallamaci R, Barbieri M et al. Modulation of ATP-sensitive K+ channel by insulin in rat skeletal muscle fibers. Biochem Biophys Res Commun. 1997, 17;232(2):536-9.
44. Burton DR. Clinical physiology of acid-base and electrolyte disorder, fourth edition, New York: McGraw-Hill, 1994: 753-822.
45. Iannaccone ST, Li KX, Sperelakis N et al. Insulin-induced hyperpolarization in mammalian skeletal muscle. AJP – Cell Physiology, 1989, 256, 2 C368-C374.
46. Aguilar-Bryan L, Nichols CG, Wechsler SW Cloning of the beta cell high-affinity sulfonylurea receptor: a regulator of insulin. secretion Science. 1995; 268(5209):423-426.
47. Tricarico D, Pierno S, Mallamaci R et al. The Biophysical and Pharmacological Characteristics of Skeletal Muscle ATP-Sensitive K^+ Channels Are Modified in K^+-Depleted Rat, an Animal Model of Hypokalemic Periodic Paralysis. Mol. Pharm. 1998, 54, 1, 197-206.
48. Minaker KL, Meneilly GS, Flier JS et al. Insulin-mediated hypokalemia and paralysis in familial hypokalemic periodic paralysis. Am J Med., 1988, 84(6):1001-6.
49. Ruff RL. Insulin acts in hypokalemic periodic paralysis by reducing inward rectifier K+ current. Neurology. 1999, 22;53(7):1556-63.
50. Victor M and Ropper AH. The hereditary myotonias and periodic paralysis (channelopathies). In Victor M, Ropper AH editors: Adams' and Victor's principles of Neurology. 2001, 7th edition, New York: Mc Graw-Hill: 1553-1565.
51. The Periodic Paralysis News Desk. [homepage on the Internet] Diagnosis in Hypokalemic Periodic Paralysis.[last updated 8 January 2004, cited 13 May 2004]. Available from: http://www.hkpp.org
52. Swash M, Schwartz MS. The Periodic Paralyses. In: Neuromuscular Diseases: A practical approach to diagnosis and management ; 2nd ed. London: Springer-Verlag 1988: 344-348.
53. Johnsen T. Familial Periodic Paralysis with Hypokalaemia; Danish Medical Bulletin, 1981 Vol. 28 No. 1.
54. Mendell J R, Griggs R C, Ptacek J L. Diseases of muscle. In: Isselbacher K J editor Harrison's Principles of Internal Medicine [CD-ROM]. 14-th edition, New York: Mc Graw Hill
55. The Periodic Paralysis News Desk. [homepage on the Internet] The Potassium Draw: Special Measures [last updated 15 February 2002, cited 26 Mars 2004]. Available from: http://www.hkpp.org
56. Don BR, Sebastian A, Cheitlin M et al. Pseudohyperkalemia caused by fist clenching during phlebotomy. N Engl J Med , 1990, 322 : 1290-1292.
57. Periodic Paralysis Association [homepage on the Internet]Emergency information for hypokalemic periodic paralysis c.1997-2004 [last updated 25 January 2004, cited 30 Mars 2004]. Available from: http://www.periodicparalysis.org/PPA
58. McManis PG, Lambert EH, Daube JR. The exercise test in periodic paralysis. Muscle Nerve. 1986, 9(8):704-710.
59. van Engelen BG, Ter Laak HJ. Images in neurology. Tubular aggregates: their continuity with sarcoplasmic reticulum. Arch Neurol 1999; 56: 1410–1411.
60. Morgan-Hughes JA. Tubular aggregates in skeletal muscle: their functional significance and mechanisms of pathogenesis. Curr Opin Neurol. 1998, (5):439-42.
61. Online Mendelian Inheritance in Man.[homepage on the Internet] Hyperkalemic periodic paralysis. [created 2 June 1986 by Mc Kusick V A, last updated 23 January 2004, cited 25 June 2004]. Available from: http:// www.ncbi.nlm.nih.gov/Omim
62. Bradley WG, Taylor R, Rice DR. et al Progressive myopathy in hyperkalemic periodic paralysis. Arch Neurol. 1990 Sep;47(9):1013-1017.
63. Brancati F, Valente EM, Davies NP. Severe infantile hyperkalaemic periodic paralysis and paramyotonia congenita: broadening the clinical spectrum associated with the T704M mutation in SCN4A. Journal of Neurology Neurosurgery and Psychiatry, 2003, 74:1339-1341.
64. Online Mendelian Inheritance in Man.[homepage on the Internet].Thyrotoxic periodic paralysis. [created 2 June 1986 by Mc Kusick V A, last updated 10 November 2003, cited 18 December 2003]. Available from: http:// www.ncbi.nlm.nih.gov/Omim

65. Kilpatrick RE, Seiler-Smith S, Levine SN. Thyrotoxic hypokalemic periodic paralysis: report of four cases in black American males. Thyroid, 1994; 4(4):441-445.
66. Leung AKC. Familial 'hashitoxic' periodic paralysis. [Abstract] J. Roy. Soc. Med..1985, 78: 638-640.
67. Ma JT, Wang C, Lam K. et al Fifty cases of primary hyperaldosteronism in Hong Kong Chinese with a high frequency of periodic paralysis. Evaluation of techniques for tumour localisation. Q J Med. 1986; 61(235):1021-37.
68. Dias Da Silva MR, Cerutti JM, Arnaldi LA. A mutation in the KCNE3 potassium channel gene is associated with susceptibility to thyrotoxic hypokalemic periodic paralysis. J Clin Endocrinol Metab. 2002 ;87(11):4881-4884.
69. The Periodic Paralysis News Desk. [homepage on the Internet] Physician's Sheet: Andersen's Syndrome c. 2001-2002 [last updated 15 February 2003, cited 20 May 2004]. Available from: http://www.hkpp.org
70. Plaster NM, Tawil R, Tristani-Firouzi M et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. Cell. 2001, 105(4):511-519.
71. The Periodic Paralysis News Desk.[homepage on the Internet] Physician's Information Sheet on Hypokalemic Periodic Paralysis. c.2001-2002[last updated 15 February 2003, cited 20 May 2004]. Available from:
http://www.hkpp.org http://www.hkpp.org
72. e-MEDICINE [homepage on the internet] Garth D. Hypokalemia. In e-Medicine Journal . [last updated 21 July 2001,cited 27 may 2004] Available from: http://www.emedicine.com/emerg/topic.htm
73. Periodic Paralysis Association [homepage on the Internet]Therapeutic Guidelines. c. 1997-2004 [last updated 25 January 2004, cited 5 April 2004]. Available from:
http://www.periodicparalysis.org/PPA
74. Periodic Paralysis Association [homepage on the Internet]Guidelines for Potassium Administration c.1994-2004 [last updated 25 January 2004, cited 18 May 2004] Available from:
http://www.periodicparalysis.org/PPA
75. Whang R, Hampton EM, Whang DD Magnesium homeostasis and clinical disorders of magnesium deficiency. Journal Ann Pharmacother , 1994, 28:220-226.
76. The Periodic Paralysis News Desk.[homepage on the Internet] Physician's Information Sheet on Hypokalemic Periodic Paralysis. C. 2001-2002 [last updated 22 July 2003, cited 20 May 2004] Available from: http://www.hkpp.org
77. Bendahhou S, Cummins TR, Griggs RC et al. Sodium channel inactivation defects are associated with acetazolamide-exacerbated hypokalemic periodic paralysis. Ann Neurol. 2001, 50(3):417-420.
78. The Periodic Paralysis News Desk [homepage on the Internet].Physician's Information Sheet on Local Anaesthesia. C. 2001-2002 [last updated 8 September 2003, cited 14 February 2004] Available from:
http://www.hkpp.org
79. Hahn RG. Decrease in Serum potassium concentration during epidural anaesthesia.[Abstract] Acta Anaesthesiol Scand 1987; 31(8):680-683.
80. Toyoda Y, Kubota Y, Kubota H, Murakawa M, Ishida H, Asada A, Fujimori M. Prevention of hypokalemia during axillary nerve block with 1% lidocaine and epinephrine 1:100,000. Anesthesiology 1988; 69:109-111.
81. Robinson RL, Monnier N, Wolz W. A genome wide search for susceptibility loci in three European malignant hyperthermia pedigrees Human Molecular Genetics, 1997, 6 : 953-961.
82. Brandt A, Schleithoff L, Jurkat-Rott K. Screening of the ryanodine receptor gene in 105 malignant hyperthermia families: novel mutations and concordance with the in vitro contracture test. Hum Mol Genet. 1999, 8(11):2055-62.
83. Kolb ME, Horne ML, Martz R. Dantrolene in human malignant hyperthermia. Anesthesiology. 1982; 56:254-262.
84. DeRuyter ML, Wedel DJ, Berge KH. Delayed malignant hyperthermia requiring prolonged administration of high dose dantrolene in the postoperative period. Anesth Analg. 1995; 80:834-836.
85. Monnier N, Procaccio V, Stieglitz P et al. Malignant-hyperthermia susceptibility is associated with a mutation of the alpha 1-subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor in skeletal muscle. Am J Hum Genet. 1997, 60(6):1316-1325.
86. The Periodic Paralysis News Desk.[homepage on the Internet]. Malignant Hyperthermia in Hypokalemic Periodic Paralysis. C.2001-2002 [last updated 15 February 2002, cited 15 May 2004]. Available from: http://www.hkpp.org
87. Schleithoff L, Mehrke G, Reutlinger B, Lehmann-Horn F. Genomic structure and functional expression of a human alpha(2)/delta calcium channel subunit gene (CACNA2). Genomics. 1999, 15;61(2):201-209.
88. Iles DE, Lehmann-Horn F, Scherer SW et al. Localization of the gene encoding the alpha 2/delta-subunits of the L-type voltage-dependent calcium channel to chromosome 7q and analysis of the segregation of flanking markers in malignant hyperthermia susceptible families. Human Molecular Genetics, 1994, Vol 3, 969-975.
89. Online Mendelian Inheritance in Man.[homepage on the Internet].Hypokalemic periodic paralysis.[created 22 June 1997 by Mc Kusick V A, updated 27 October 1997, cited 7 January 2004]. Available from:
www.ncbi.nlm.nih.gov/Omim
90. Hogan K. To fire the train: a second malignant-hyperthermia gene. Am J Hum Genet. 1997 Jun;60(6):1303-8.
91. Wedel DJ. Malignant hyperthermia – prevention and treatment. ASA Newsletter [serial on the Internet], April 1997 [cited 11 May 2004], 51, 4. Available from:
www.asahq.org/Newsletters/**1997**/04_97/Prevention.html
92. Lambert C, Blanloeil Y, Horber RK et al. Malignant hyperthermia in a patient with hypokalemic periodic paralysis. Anesth Analg. 1994, 79(5):1012-4.
93. Rajabally YA and El Lahawi M Hypokalemic periodic paralysis associated with malignant hyperthermia. Muscle Nerve , 2002, 25:453-455.
94. Robinson JE, Morin VI, Douglas MJ et al. Familial hypokalemic periodic paralysis and Wolff-Parkinson-White syndrome in pregnancy. Canadian Journal of Anesthesia 2000, 47: 160-164.
95. Hofer C, Zalunardo MP, Zollinger A. Total intravenous anaesthesia in a patient with familial hypokalaemic periodic paralysis. Anaesthesia 2001, 56:1082-5