A Summary Review of the Diagnosis and Pathology of the Primary Familial Periodic Paralyses

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ABSTRACT

This review of the primary familial periodic paralyses (PFPP) summarizes the pertinent clinical and laboratory findings of the three forms of this disorder. The review is intended to highlight diagnostic features of PFPP and to discuss current hypotheses regarding pathogenesis.

Introduction

The skeletal muscle disorders referred to as the “primary familial periodic paralyses” (PFPP) are classified as follows: (1) hypokalemic periodic paralysis (hypoKPP), (2) normokalemic periodic paralysis (normoKPP), (3) hyperkalemic periodic paralysis (hyperKPP) and (4) myotonic periodic paralysis (paramyotonia congenita). Not included in this review are those disorders associated with paralysis, such as thyrotoxicosis and primary aldosteronism; nor are those disorders described that affect potassium metabolism, such as diabetic and renal tubular acidoses resulting in changes in plasma potassium concentration followed by muscle weakness and paralysis.

This paper summarizes those features of PFPP that would aid in making a diagnosis of this disease entity in any of its forms. Early diagnosis is important since permanent muscle damage and weakness are a distinct possibility. In order to minimize this damage, prophylactic measures, such as dietary restrictions and the administration of appropriate drugs, should be instituted.

The exact incidence of PFPP is not known, but it is generally agreed that this disease is uncommon. Individuals with PFPP have episodic attacks of weakness and flaccid paralysis usually involving the skeletal muscles of the extremities and often of an asymmetrical distribution. It is common for the paralysis to abate spontaneously. Although sporadic cases of periodic muscle paralysis have been reported, primary periodic paralysis is usually found in families. A more detailed description of the historical and clinical features of PFPP can be found in the reviews by Graeff and Lameijer, Streeten, McArdle, and most recently by Pearson and Kalyanaraman.

Although much attention has been focused on the levels of potassium in the blood in each of the forms of PFPP, the reports do not include descriptions of the laboratory methods used to determine the
levels of serum potassium. It is assumed that common errors resulting in incorrect determinations have been avoided. The concentration of potassium is reported in mEq per liter in serum and not in plasma, as has been recommended. Since much of the investigation about muscle paralysis centers about ionic concentrations on each side of the sarcolemma and about the dynamics of these ions, it would be well at this point to recall the details of ionic flux through a cell membrane.

The muscle fiber contracts in response to a motor nerve impulse transmitted to the muscle fiber via a motor nerve end-plate. The impulse is carried via the plasma membrane of the sarcolemma. The nature of transmission of an impulse along the plasma membrane of the muscle is believed to be based on the ionic permeability characteristics of the membrane. The plasma membrane of the muscle fiber is permeable to potassium and chloride ions but relatively impermeable to sodium ions. Higher concentrations of sodium are maintained external to the plasma membrane by an active transport mechanism ("sodium pump" theory). There are higher potassium concentrations intracellularly than extracellularly. What results from this ionic arrangement is an electrical potential across the plasma membrane; that is, the interior of the muscle cell is negative to the exterior. An impulse will lower the resting potential across the muscle membrane, permitting a rapid influx of sodium ions. This influx results in a reversal of the resting potential, and the interior of the muscle cell becomes positive to the exterior. This change of polarity is spoken of as the "action potential." The resting potential is restored by a combination of events best summarized as a net return of potassium to the interior of the muscle cell and reestablishment of high extracellular concentrations of sodium by removal of this ion by active transport. With such information at hand about sodium and potassium in muscle, it would not be unreasonable, then, to suspect that muscle disorders associated with abnormal concentrations of plasma potassium might, indeed, reflect abnormalities of potassium within the muscle cell.

**Hypokalemic Periodic Paralysis**

Even though hypoKPP is decidedly uncommon, it has been reported in most areas of the world. Most families affected are Caucasian. It is thought to be inherited as an autosomal dominant, affecting males more often than females. Usually the disease is more fully expressed in males than in females, and the age of onset is during the latter parts of the first and second decades. The attacks tend to diminish in frequency and intensity with increasing age and have been reported to cease spontaneously. Clinically, the episodes of weakness and paralysis generally begin during the night and involve proximal limb and some trunk muscles. Other predisposing conditions include ingesting a meal high in carbohydrates, vigorous exercise followed by a resting phase and exposure to cold temperatures. Facial, glossopharyngeal and intercostal muscles are not affected. The duration of paralysis is variable, lasting a few hours to several days. During paralysis the muscles do not respond to direct electrical or mechanical stimulation.

The major laboratory finding in patients with hypoKPP is a decrease in the plasma potassium concentration during the development of paralysis, often to abnormally low levels. Weakness and paralysis of skeletal muscles may appear at concentrations of approximately 2.5 to 3.0 mEq per l, although this range can vary a good deal. As the paralysis clears, the plasma potassium concentration returns to a nearly normal value and usually remains at that level between attacks.

Other laboratory findings include increases in output of urinary 17-hydroxy-
corticoids, 17-ketosteroids and aldosterone. Although unproven, it may be that these hormonal elevations reflect adrenocortical hyperactivity, possibly instrumental in precipitating attacks of weakness. Similarly, increases in blood pyruvate and lactate have been recorded during both spontaneous and induced attacks. These findings have led to hypotheses, yet unproven, that there may be a disorder of carbohydrate metabolism as an underlying cause for the muscle weakness. Creatinine phosphokinase levels are usually not significantly elevated.

Other pertinent findings include electrocardiographic (ECG) changes consistent with cardiac irregularities often seen in association with hypokalemia; and varying abnormal electromyographic changes. Investigators studying patients with hypoKPP have determined that the intracellular concentration of potassium increases and that concentrations of intracellular potassium are low or decreased between attacks. Theoretically, the increase in intracellular potassium should result in a hyperpolarization of the cell membrane causing a block in transmission of any impulses along the plasma membrane and possibly explaining the weakness or paralysis. However, in vitro analysis of membrane potentials of muscle from patients with hypoKPP showed the membranes to be depolarized rather than hyperpolarized.

Since the reason for the high intracellular concentrations of potassium remains unexplained, one consideration is that it may be due to a structural defect. One consistent structural finding in patients with hypoKPP is the presence of vacuoles within the muscle fiber. Some vacuoles appear transparent and empty, others look granular and contain PAS-positive material. The results of ultrastructural studies lead most investigators to feel that the vacuoles are dilatations of the sarcoplasmic reticulum (SR) owing either to enlargements or fusion of dilated segments of the longitudinally oriented SR. To date, however, there are no other ultrastructural findings to suggest an explanation for the increases in intracellular potassium.

Another feature in patients with hypoKPP is the beneficial response from oral doses of potassium salts. After receiving potassium chloride, patients with hypoKPP generally experience improvement as evidenced by a decrease in severity and frequency of attacks. Diet low in carbohydrates and sodium is also beneficial to these patients. Drugs such as diuretics, aldosterone antagonists, steroids and acetazolamide may be helpful.

In summary, the diagnosis of primary familial hypoKPP is dependent upon the patient's having the following findings:

1. Presenting complaint of periodic episodes of muscle weakness and paralysis usually after exertion followed by rest or during normal sleeping hours, or following ingestion of a heavy carbohydrate meal;
2. A positive family history of periodic muscle weakness and paralysis;
3. Absence of historical and clinical findings suggesting that the muscle weakness is secondary to other disorders, i.e., hyperthyroidism, renal or gastrointestinal diseases, diabetes mellitus, primary aldosteronism or other disorders interfering with normal potassium metabolism;
4. Low or abnormally decreased serum potassium levels during spontaneous or provoked attacks;
5. Morphologic evidence of vacuolization of muscle fibers;
6. Positive response to oral doses of potassium salts.

Normokalemic Periodic Paralysis

It is not clear whether normoKPP represents a third type of PFPP or is a variant of either hypoKPP or hyperKPP. A family reported to have normoKPP had features of the lateral cisterns of the SR or fusion of dilated segments of the longitudinally oriented SR.
that resembled those described in a family with hyperKPP except that serum potassium levels were not abnormally increased.\textsuperscript{18} Clinically, the affected family members had attacks of weakness of paralysis that usually occurred during normal sleeping hours and which lasted longer than those reported in patients with hyperKPP. Like others with PFPP, the inheritance is thought to be autosomal dominant and is expressed in both sexes. The disorder differs from hypoKPP in that administration of potassium chloride may precipitate an attack. Myotonia is evidently not found in patients with normoKPP as it is in patients with hyperKPP. The morphologic changes are similar to those in both hypoKPP and hyperKPP but are of lesser magnitude. Acetazolamide has been beneficial but not in all cases.\textsuperscript{15}

In summary, normoKPP has a number of clinical features in common with both hypoKPP and hyperKPP except for the major laboratory finding or normal serum potassium levels during attacks of weakness and paralysis.

Hyperkalemic Periodic Paralysis (Adynamia Episodica Hereditaria)

Gamstorp\textsuperscript{4} and Tyler et al\textsuperscript{23} described families with periodic paralysis where it was noted that the serum potassium level increased during episodes of weakness and paralysis rather than decreased as in patients with hypoKPP. Another feature that was noted was that patients with hyperKPP did not respond beneficially to oral doses of potassium chloride as did patients with hypoKPP; instead, muscle weakness increased or paralysis developed. As in the other forms of PFPP, hyperKPP has an inheritance pattern of an autosomal dominant.\textsuperscript{4} The age of onset can be the first or second decades. The attacks in patients with hyperKPP seem to occur more frequently than in patients with the other forms of PFPP. Attacks of weakness and paralysis often occur after exercise followed by rest as in hypoKPP and normoKPP; however, the attacks usually are more rapid in onset and do not last as long as those described in the other forms of PFPP. Patients discover that they can abort an attack by continuing the exercise. Neck muscles and even nasopharyngeal muscles can be affected during severe attacks. Other factors predisposing patients to weakness include exposure to cold, emotional upheaval and, in some cases, agents used for general anesthesia.

In addition to the physical findings of proximal muscle weakness, usually of the muscles of the upper and lower girdle and trunk, evidence of myotonia is generally present. Myotonia is found in most patients with hyperKPP, and this feature sets this form of PFPP apart from hypoKPP and normoKPP. It is the presence of myotonia in patients with hyperKPP that suggests that this form of periodic paralysis may have some defect in common with that of paramyotonia congenita (PC). Patients with PC also have episodes of muscle weakness. One report\textsuperscript{10} presents evidence suggesting that PC is a form of hyperKPP rather than being a variant of myotonia congenita. A summary describing the evidence for the relationship between hyperKPP and PC points out that additional clarification of this relationship is in order.\textsuperscript{17}

The major laboratory finding is the increase in serum potassium level which can vary quantitatively in some patients with hyperKPP. Weakness or paralysis may be associated with levels of plasma potassium of 7 to 8 mEq per l. In other patients, the levels may stay normal or may include a few readings slightly below normal levels. Determination of other blood constituents (including the other electrolytes, calcium, phosphorus, and some enzymes) are generally normal. Electromyocardiograph studies reveal electrical activity characteristics of myotonia. ECG's obtained during at-
tacks have changes characteristic of hyperkalemia.

 Routinely stained paraffin sections of skeletal muscle from patients with hyperKPP do not have the same degree of vacuolization as those found in muscle from patients with hypoKPP. If vacuolization is present, it may have only a perinuclear location, and the vacuoles can contain PAS-positive material.\textsuperscript{16} Aside from a few focal nonspecific myopathic changes, there is not much histologic change. Ultrastructurally, the major change is that of dilatation of the sarcoplasmic reticulum similar to that described in both hypoKPP and normoKPP.\textsuperscript{4}

 As might be suspected, the concentration of intracellular potassium is believed to be decreased and the resting membrane potential to be reduced.\textsuperscript{5,9} However, the role of sodium ions should be considered since it is believed that not only is there a change in the concentration of intracellular potassium ion but also the muscle membrane becomes increasingly permeable to the sodium ion.\textsuperscript{14} The increased concentration of sodium within the muscle cell would also contribute to the low membrane potential. In accordance with this concept of increased concentration of intracellular sodium, investigators have urged creation of a negative sodium balance for patients with hyperKPP so as to stabilize the muscle resting membrane potential.\textsuperscript{2} Treatment with carbonic anhydrase inhibitors, such as acetazolamide and dichlorphenamide, have had beneficial effects in relieving muscle weakness;\textsuperscript{12} others have demonstrated improvement by using chlorothiazide.\textsuperscript{20} The beneficial results of diuretics are believed to be due to some effect these drugs have on the muscle membrane rather than being due solely to effects on the kidney. Diets high in carbohydrates and low in potassium are recommended.

 In summary, the two main diagnostic features characteristic of this form of PFPP and distinguishing it from the other forms, are that of periodic episodes of muscle weakness or paralysis associated with myotonia and elevated levels of plasma potassium.

 Finally, the three forms of PFPP may or may not have a common underlying defect. The elucidation of any defect in PFPP will, no doubt, add greatly to the understanding of the physiology of muscle. It is hoped that one of the dividends from any new knowledge of the uncommon forms of PFPP will be to offer insight into the more common, crippling forms of neuromuscular disease.

References