

HYPOKALEMIC PERIODIC PARALYSIS: AGE OF ONSET IN A RETROSPECTIVE STUDY

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Abstract- Primary hypokalemic periodic paralysis is a familial channelopathy inherited as an autosomal dominant trait. The first attack of paralysis may be evolved at any age, but has been reported to be most common in the second decade, so that some authorities believe that an episodic weakness beginning after age 25 is almost never due to primary periodic paralysis. In this retrospective study, we reviewed 50 patients admitted in two hospitals of Tehran University of Medical Sciences during 1992-2001 with acute flaccid weakness and hypokalemia, twenty-three of whom fulfilled our inclusion and exclusion criteria. Two patients showed first attack below age 15, 8 in 15-20, 4 in 20-25, 3 in 25-35, 4 in 35-45, and 2 beyond age 45. In our study, in contrast to previous ones, the first attack was beyond age 20 in 13 patients (56.5%) and beyond 25 in 9 (39 %). Age at first attack is more than other studies, which seems to be due to a difference between our epidemiological characteristics compared to that in the West. In other words, in our epidemiological condition, periodic weakness, although started beyond second decade of age, could be due to primary periodic paralysis if secondary hypokalemia had been ruled out.

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INTRODUCTION

Primary hypokalemic periodic paralysis is a familial autosomal dominant disease. It is one of several neurological disorders known to be due to impaired voltage gated ion channels such as myotonia congenita, paramyotonia congenita, hyperkalemic periodic paralysis, malignant hyperthermia, Lambert – Eaton myastenic syndrome, nocturnal frontal lobe epilepsy, benign nocturnal convulsion, episodic ataxia, and hemiplegic migraine (1-3). In the majority of familial hypokalemic periodic paralysis cases the responsible gene is on chromosome 1q 31-32 that encodes for the α -1-subunit of the S4 segment of domains 2 and 4 of dihydropyridine voltage sensitive calcium channel (4). The related receptor is located in transverse tubular system of skeletal muscle fibers (5). Two common mutations are substitution of histidine for arginine at 528 and 1239 positions (4,6), and one less common is glycine for arginine at 1239 (7). Arg 528 His mutation has an incomplete penetration in women that causes male predominance of the disease (4). Male to female ratio is 3-4 to one (5). Voltage

sensor sodium channel mutations have been reported to cause hypokalemic periodic paralysis as well, which is known as hypokalemic periodic paralysis type 2. Two mutations are substitution of histidine and glycine for arginine at 672 position (8). The disease can be sporadic in 33% of the patients (9). Studies indicate that the resting membrane potential of the muscle fibers in patients with the calcium channelopathy is depolarised by approximately 5-15 mv compared to the normal value of -85 mv (4,10). The relation of this depolarization to calcium channelopathy is obscure. The possible mechanism seems to be involvement of the muscular adenosine triphosphate (ATP) sensitive K⁺ (KATP) channel that is the most abundant K⁺ channel active in the skeletal muscle fibers. Abnormally low activity of this channel has been demonstrated in familial hypokalemic periodic paralysis. The low activity of KATP channel is enhanced with insulin in these patients, a fact that describes why the attacks of paralysis are triggered by causes of increased insulin secretion (11-13). Hypokalemia and insulin hypersecretion depolarizes more the fibers to -50 mv and in this situation muscle fibers are inexcitable (4,10). Involvement of KATP channels is also supported by the observations that the K⁺ channel openers, like cromakalim and pinacidil are capable of repolarizing the skeletal muscle fibers of patients and restoring the muscle strength. On the other hand application of calcium to weak muscle

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dose not relieve weakness. The mechanism (s) responsible for the appearance of the subconductance states in the KATP channels and its relation to calcium channelopathy are obscure (11-13). Although serum potassium may fall as low as 1.5 mEq/Lit during an attack, paralysis usually occur at much higher levels, even lower limits of normal value. So hypokalemia itself has limited role in pathophysiology of disease. The attacks may be evolved at any age, as early as age 4 years or be delayed until the sixth decade (14), but several studies indicate that its onset is most common in second decade and is earlier in Arg 1239 His mutation (10). In Talbott's study in 152 cases, onset was before the 10th year of life in 40 and before 16th year in 92 patients (15). Early onset is so important that some authorities believe that episodic weakness beginning after age 25 is almost never due to periodic paralysis (9). The attacks commonly begin in second half of the night or early morning probably because sleep is associated with the movement of the ions, such as potassium, across the muscle membrane. Heavy exercise, carbohydrate or salt rich diet, coldness and stress or any other cause of increased insulin secretion could be provoking factors (16). Alcohol can induce an attack as well (16). Epinephrin, norepinephrin and corticosteroids may have a role in weakness (4). Attacks are more common in pregnancy (4). Weakness does not occur in midst of vigorous activity, although antecedent exercise could provoke weakness (9). In fact an attack could be relieved with exercise (warm up or warm off phenomenon) (9,14). Weakness usually begins in lower limbs and is more severe in proximal muscles. Respiratory, bulbar, ocular and sphincter muscles are not usually severely involved. Deep tendon reflexes may be lost. Sensory signs or symptoms are not found, although decreased amplitude of sensory action potential during paralytic attacks has been reported. It could be a consequent of possible inactivation of the sodium-potassium pump by the low conductance of extracellular potassium (17). Weakness lasts for several hours, even up to several days (4) (average 2-12 hours [9]) and returns as suddenly as had left, first to the muscles last to be affected (5). A mild residual weakness may last for a longer time.

MATERIALS AND METHODS

This retrospective study includes patients admitted in two university hospitals in Tehran during 1992-2000. We reviewed the medical documents of 50

patients with flaccid weakness and hypokalemia. Twenty-seven patients were excluded due to deficits in data and inclusion and exclusion criteria. Inclusion criteria comprised of at least one episode of acute flaccid weakness without sensory symptoms and signs that lasted a few to 36 hours, associated with serum potassium level of 1-3.5mEq/Lit. Serum potassium should return to normal value after cessation of attack. Causes of secondary hypokalemia should be ruled out as well. Exclusion criteria were incomplete data from observation, neurological exam or laboratory tests as well as any suspicion of secondary hypokalemia. Causes of secondary hypokalemia were considered for each patient according to the list mentioned below.

Causes of secondary hypokalemia (18,19):

A. Decreased intake: Starvation.

B. Increased loss:

a. Gastrointestinal: Diarrhea, frequent vomiting, fistula, and nasogastric suction.

b. Sweating.

c. Urinary loss:

1. Mineralocorticoid excess:

Hyperaldosteronism, Cushing's disease, 17 α hydroxylase deficiency, Bartter's syndrome, renin secreting tumors, renal artery stenosis, licorice and carbenoxolone.

2. Loop and thiazid-type diuretics, carbonic anhydrase inhibitors.

3. Salt wasting nephropathies.

4. Hypomagnesemia.

5. Due to drugs: Amphotericin B, Levodopa.

6. Polyuria.

7. Metabolic acidosis (such as DKA and RTA type2).

C. Redistribution into cells:

a. Metabolic alkalosis.

b. Increased availability of insulin.

c. Elevated beta-adrenergic activity: Stress, drugs (beta 2 antagonists, alpha 1 agonists, abuse of thyroid hormone), and delirium tremens.

d. Anabolic states, treatment with vitamin B12 or foliate.

e. Hypothermia.

f. Barium toxicity.

D. Dialysis.

RESULTS

Twenty-three patients fulfilled the above criteria. Twenty were male (87%). The ratio is 3-4 to one in other studies (5). There was obvious familial history

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in 10 patients (43%). In other studies the disease can be sporadic in 33% of patients (9). First attack was beyond age 20 in 13 patients (56.5%) and beyond 25 in 9 patients (39%). Two patients were below age 15, 8 in 15-20, 4 in 20-25, 3 in 25-35, 4 in 35-45, and 2 were older than 45. Onset was in 9, 16, 17, 21, 24, 26, 27, 36, 41 and 43 years old in patients with obvious familial history. Serum potassium was 2.5-3.5

mEq/Lit in 10 patients (43.5%), 1.8-2.5 in 10 (43.5%), and 1-1.8 in 3(13%). Attacks began early morning after awakening in 15 patients (65.2%) and weakness occurred first in lower limbs in 18 patients (78.3%), upper limbs in 3 patients (13%), and simultaneously in 2 patients (8.7%). Most of our patients (17cases, 73.9%) had weakness for more than 20 hours (20-36 hours).

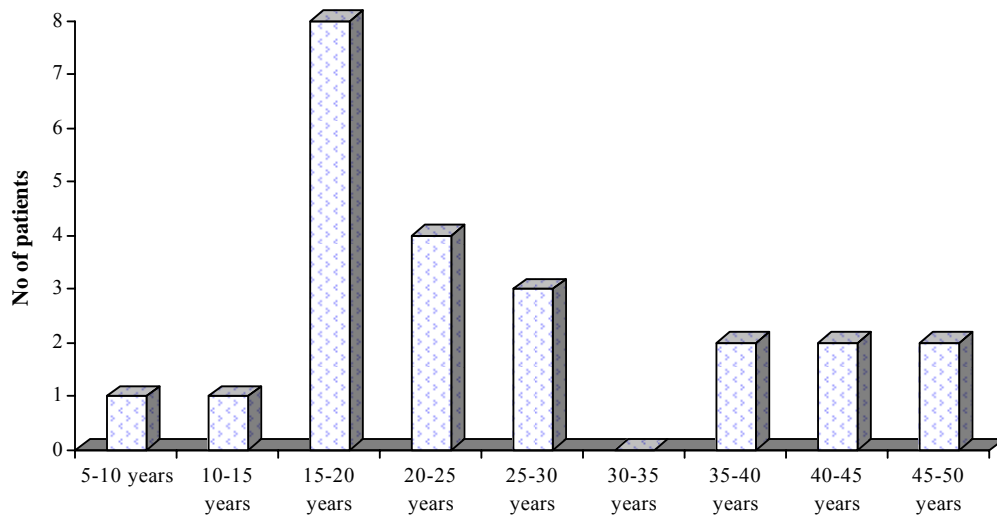


Fig. 1. Age (years) of onset (first attack) of hypokalemic periodic paralysis in patients

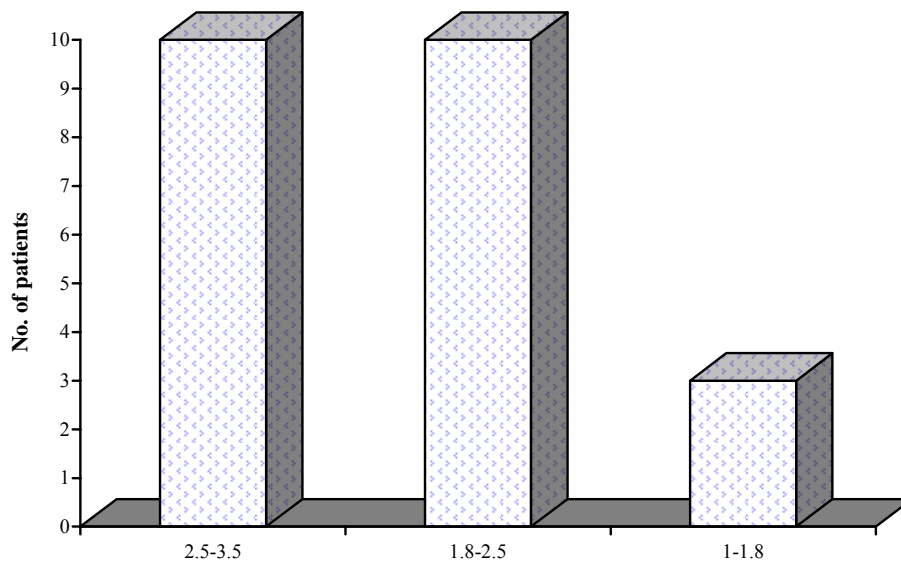


Fig. 2. Serum potassium level of patients during the attack

DISCUSSION

Age of first attack is much more than other studies and it seems to be a difference between our epidemiological characteristics and that in the Western countries. We concluded that in our epidemiological condition, periodic weakness, even when began beyond second decade of age, could be due to primary periodic paralysis if secondary hypokalemia had been ruled out. It may be however mild attacks in early ages that were not noticed by patients. Male predominance is similar to other studies. Lack of familial history which is reported in about 33% of patients in other studies, was more in ours (57%). This could be due to a gene mutation, incomplete penetration of gene or mild weakness in parents that was not noted. Duration of attacks was more than other studies (20-30 hours compared to 2-12).

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