Original Article

Aetiological, clinical and metabolic profile of hypokalaemic periodic paralysis in adults: A single-centre experience

NARSING RAO, MATHEW JOHN, NIHAL THOMAS, SIMON RAJARATNAM, MANDALAM SUBRAMANIAM SESHADRI

ABSTRACT

Background. Hypokalaemic periodic paralysis constitutes a heterogeneous group of disorders that present with acute muscular weakness. In this analysis, we discuss the aetiological factors that appear to be more common in the Indian population.

Methods. From 1995 to 2001, 31 patients presented with periodic paralysis (mean age 34.5 years, range 11–68 years). Of the 31 patients, 19 were men. The clinical and laboratory data of these patients were analysed. Patients were investigated for possible secondary causes of hypokalaemia.

Results. There were 13 patients (42%) with renal tubular acidosis, 13 with primary hyperaldosteronism (42%), 2 each with thyrotoxic periodic paralysis and sporadic periodic paralysis, and 1 with Gitelman syndrome.

Of the 13 patients with renal tubular acidosis, 10 had proximal and 3 distal renal tubular acidosis. Three of these patients with renal tubular acidosis had Sjogren syndrome. The patients diagnosed to have renal tubular acidosis had significantly lower serum bicarbonate (18.7 [4.6] *v.* 29.6 [5.0] mEq/L; $p<0.05$) and higher levels of chloride (107.5 [6.0] *v.* 99.5 [3.4] mEq/L; $p<0.05$) compared with those who had primary hyperaldosteronism, although the potassium values were similar (2.4 [0.65] *v.* 2.26 [0.48] mEq/L; $p=0.43$). All patients with primary hyperaldosteronism had hypertension at presentation and were proven to have adrenal adenomas.

Conclusion. A significant number of patients in this study had secondary and potentially reversible causes of hypokalaemic periodic paralysis. The common causes were renal tubular acidosis and primary hyperaldosteronism. A detailed work-up for secondary causes should be undertaken in Indian patients with hypokalaemic periodic paralysis.

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INTRODUCTION

Hypokalaemic periodic paralysis (HPP) constitutes a heterogeneous group of disorders that present with acute muscular weakness, and can at times be potentially life-threatening. When recognized and treated appropriately, patients recover without much clinical sequelae. Although a number of these cases may be associated with ion channel mutations, some are due to potentially reversible causes. Since definitive therapy can be offered to some of these patients, identifying causes that are reversible is important.

According to the published literature, familial periodic paralysis is the commonest cause of HPP in Caucasians and thyrotoxic periodic paralysis (TPP) in patients in the Far East.[1,2] We analysed the aetiological factors that appear to be more dominant in the Indian population.

METHODS

Thirty-one patients with HPP were identified over a 6-year period (1995–2001). Their mean age was 34.5 years (range 11–68 years; 19 men). The mean duration of illness before presentation was 23 months (range 1–92 months) and they had had a mean of 4 episodes (median 3, range 1–15 episodes). The data of all patients who presented with HPP were analysed retrospectively (Table I). HPP was defined as acute loss of muscle power with inability to walk and documented plasma potassium levels <3.5 mEq/L during the episode. The clinical data collected included age, sex, ethnic origin, duration of illness, number of episodes of acute muscular weakness, history of renal stones, bone pain, dry mouth, dry eyes, fractures and a family history of HPP. Clinical examination with special emphasis on blood pressure, parotid and lacrimal gland enlargement, and a detailed neurological examination were done.

The following biochemical parameters were estimated: serum sodium, potassium, bicarbonate, chloride, creatinine, fasting serum calcium and phosphate, serum albumin, globulin and alkaline phosphatase. Fasting urinary pH, 24-hour urinary calcium, phosphate and creatinine were also done in all the patients. Spot urinary amino acids (high performance liquid chromatography [HPLC]) and urinary glucose (Diastix, Bayer) were also assessed. The phosphate threshold for renal tubular excretion (TmP/GFR) was calculated using the Bijvoet nomogram. A TmP/GFR level <2.5 mg/dl was taken as confirmatory for phosphaturia.[3]

In patients with hyperchloraemic metabolic acidosis with a normal anion gap (10–12 mEq/L) and in the absence of gastrointestinal losses, a fasting urine pH >5.5 was taken to denote renal tubular acidosis (RTA). In the absence of significant acidosis (HCO_3 <15 mEq/L) an ammonium chloride loading test (0.1 g/kg)

Christian Medical College, Ida Scudder Road, Vellore 632004, Tamil Nadu, India

NARSING RAO, MATHEW JOHN, NIHAL THOMAS, SIMON RAJARATNAM, MANDALAM SUBRAMANIAM SESHADRI
Department of Endocrinology, Diabetes and Metabolism

Correspondence to NIHAL THOMAS, *nihal_thomas@yahoo.com*

was done. When the lowest recorded urine pH was <5.5, a diagnosis of proximal RTA was made and when the urine failed to acidify below 5.5, distal RTA was diagnosed. In patients with proximal RTA a urine aminoacidogram, urine glucose estimations and TmP/GFR were done to rule out Fanconi syndrome. The diagnosis of distal RTA was supported by nephrocalcinosis on ultrasonography. Further investigations were done in patients with RTA to identify the causes. These investigations included serum electrophoresis and urinary Bence–Jones proteins to rule out multiple myeloma, and serum lead and caeruloplasmin levels to rule out heavy metal poisoning and Wilson disease. In patients with a history of the sicca syndrome or unexplained hyperglobulinaemia, the Schirmer test and lower lip biopsy for focal sialadenitis was done to diagnose Sjogren syndrome. All the patients underwent thyroid function tests including free thyroid hormone concentration (FT4) and TSH to rule out thyrotoxicosis. Whenever there was a clinical suspicion of primary hyperaldosteronism (hypertension with hypokalaemia and alkalosis), serum aldosterone, plasma renin levels and computerized tomography of the adrenal glands were done to rule it out.

Statistics

Data analysis was done with SPSS ver. 9.0. Where possible, all values were expressed as means (SD). Independent *t* test was used to compare means assuming unequal variance. A p value <0.05 was considered statistically significant.

RESULTS

Thirteen of the 31 patients who presented with HPP had RTA (42%), 13 had primary hyperaldosteronism (42%), 2 TPP, 2 sporadic periodic paralysis and 1 Gitelman syndrome (Table II). Of the 13 patients with RTA, 10 had proximal RTA and 3 distal RTA. All the patients had severe hypokalaemia, hyperchloraemic metabolic acidosis and phosphaturia (mean TmP/GFR 1.4 mg/dl).

TABLE I. Serum biochemistry of patients with hypokalaemic periodic paralysis (n=31)

Age (years)	Sex	Duration (months)	Number of paralytic attacks	Potassium mEq/L	Sodium mEq/L	Bicarbonate mEq/L	Chloride mEq/L	Phosphate mEq/L	Fasting urine pH	TmP/GFR	Diagnosis
42	M	24	3	1.3	139	18	108	2.1	6.0	1.0	pRTA
30	M	12	2	2.0	142	17.5	100	1.3	6.0	1.0	p RTA
55	M	6	3	3.4	137	20	102	2.9	7.1	1.8	pRTA. Sjogren
20	M	60	6	2.2	140	18	103	2.9	7.2	1.8	p RTA
44	F	1	1	2.0	138	13.6	115	2.9	6.6	1.2	pRTA
39	M	36	3	2.0	141	23	101	2.6	5.3	1.7	pRTA
21	F	12	3	2.0	136	10	110	2.4	7.2	1.3	pRTA
30	F	8	3	2.2	141	17	113	3.1	7.0	2.3	pRTA
28	F	5	3	2.6	136	15	114	2.4	7.1	0.5	pRTA Sjogren
32	M	36	3	3.2	145	19	112	3.7	5.1	1.5	pRTA
30	M	12	15	3.3	141	23	114	2.7	6.8	2.8	dRTA
29	M	72	15	2.0	130	21	98	2.2	7.1	1.8	dRTA, Sjogren
30	M	1	4	3.3	143	28	108	2.6	5.6	2.6	dRTA
38	M	4	2	3.4	143	23	103	3.9	5.9	3.0	Thyrotoxic PP
35	M	6	3	3.3	142	23	100	4.2	5.1	4.0	Thyrotoxic PP
24	M	48	2	3.4	137	22	101	2.8	5.2	2.6	Idiopathic PP
11	M	36	4	2.0	140	25	101	6.2	5.9	6.0	Idiopathic PP
68	M	1	1	1.4	128	23	102	1.0	7.0	–	Gitelman syndrome
39	F	48	3	2.6	141	27	104	3.7	–	–	Conn syndrome
32	F	2	2	2.5	137	28	103	3.4	–	–	Conn syndrome
23	F	18	4	1.6	140	28	103	3.2	–	–	Conn syndrome
54	M	36	15	1.7	140	29	92	3.4	–	–	Conn syndrome
30	M	36	5	2.0	141	26	97	2.6	–	–	Conn syndrome
42	F	48	3	2.9	143	25	98	3.5	–	–	Conn syndrome
38	F	56	2	2.2	139	31	100	4.0	–	–	Conn syndrome
37	F	92	4	2.2	136	36	97	3.8	–	–	Conn syndrome
47	M	48	2	2.0	139	34	98	4.0	–	–	Conn syndrome
35	F	56	1	2.3	143	32	97	3.7	–	–	Conn syndrome
43	F	60	2	2.8	137	24	103	3.0	–	–	Conn syndrome
44	M	1	2	1.6	150	41	102	3.4	–	–	Conn syndrome
43	M	12	5	3.0	142	24	99	3.5	–	–	Conn syndrome

TmP/GFR tubular maximum for phosphate PP periodic paralysis pRTA proximal renal tubular acidosis dRTA distal renal tubular acidosis

TABLE II. Demographic and biochemical characteristics of patients with hypokalaemic periodic paralysis

Diagnosis	n	Men	Mean (SD) age (years)	Duration (months)	No. of episodes	Potassium (mEq/L)	Bicarbonate (mEq/L)	Chloride (mEq/L)
Renal tubular acidosis (RTA)	13	9	33 (9.6)	21.9 (22.8)	4.9 (4.6)	2.4 (0.65)*	18.7 (4.57)†	107.5 (6.03)‡
Primary hyperaldosteronism	13	5	39 (7.9)	39.4 (25.9)	3.8 (3.5)	2.26 (0.48)	29.6 (5.0)	99.5 (3.45)
Miscellaneous§	5	5	34.8 (21.6)	19 (21.5)	2.4 (1.1)	2.6 (0.87)	23.2 (1.09)	101.4 (1.1)

All values are mean (SD) * There was no significant difference in serum potassium values between patients with RTA and primary hyperaldosteronism (p=0.43)
† Patients with RTA had significantly lower bicarbonate values compared to those with primary hyperaldosteronism (p<0.05)
‡ Patients with RTA had significantly higher values of serum chloride compared to those with primary hyperaldosteronism (p<0.05)
§ This includes 2 cases of TPP, 2 cases of sporadic HPP and 1 case of Gitelman syndrome

These patients could not be distinguished from those with primary hyperaldosteronism based on their sodium (139.1 [3.8]) *v.* 140.6 [3.5] mEq/L; p=0.327) or potassium levels (2.4 [0.65] *v.* 2.26 [0.48] mEq/L; p=0.43). The patients diagnosed to have RTA had significantly lower serum bicarbonate (18.7 [4.6] *v.* 29.6 [5.0] mEq/L; p <0.05) and higher levels of chloride (107.5 [6.0] *v.* 99.5 [3.4] mEq/L; p<0.05) compared with those who had primary hyperaldosteronism. Two patients with proximal and 1 with distal RTA had Sjogren syndrome. No definite cause of RTA could be found in the others.

Among the 13 patients with primary hyperaldosteronism, all had severe hypertension (>110 mmHg diastolic blood pressure) at the time of presentation. These subjects were proven to have adrenal adenomas by imaging and underwent successful adrenalectomy as definitive therapy.

Two patients had subtle clinical symptoms and signs of TPP. Both were natives of West Bengal. Two patients were diagnosed to have sporadic periodic paralysis based on the age of onset (<25 years), with no family history of similar illness and normal thyroid and renal tubular functions. The patient with Gitelman syndrome was a 68-year-old man who presented with severe hypokalaemia, hypomagnesaemia, hypophosphataemia and hypocalciuria. Two of his children were screened and found to have similar biochemical abnormalities, though they were asymptomatic.

DISCUSSION

Periodic paralysis is a group of disorders with varied aetiologies characterized by episodic, short-lived and hyporeflexic skeletal muscle weakness with or without myotonia, but without sensory deficit and without loss of consciousness. HPP is the best-known form of periodic paralysis and is characterized by hypokalaemia occurring during the episode of muscle weakness.[4] HPP has been conventionally divided into two forms: primary and secondary. Primary (familial) HPP is a group of disorders associated with single-gene mutations in the ion channels. Secondary HPP is associated with demonstrably known causes (Table III).[5]

The aetiology of HPP varies in different series, depending primarily on the ethnicity of the patients in whom it was studied. In a large series of 97 patients with HPP from Taiwan, 39 (40%) had TPP and 29 (21%) had sporadic periodic paralysis. Overall, 66 (68%) of the patients had a secondary cause of HPP.[7] In the previous largest published series from India, of the 22 patients with HPP, 12 had the secondary variety. The causes of hypokalaemia in this subgroup were gastroenteritis, thyrotoxicosis and diuretic use.[3]

The aim of early treatment of HPP is to increase the potassium level by supplementation so that the muscle weakness can be reversed, and respiratory paralysis and cardiac arrhythmias prevented. The aim of potassium supplementation in TPP and familial HPP is to normalize K^+ concentrations instead of repairing the potassium deficit. The danger of exogenous K^+ administration is that K^+ is rapidly released from the cells when the paralysis subsides, leading to the development of rebound hyperkalaemia.[8] In patients with renal K^+ wasting in the presence of hyperchloraemic metabolic acidosis, correction of hypokalaemia should precede alkali therapy, since it may shift the K^+ into the cells.[2] This can even result in acute respiratory failure due to severe hypokalaemia. Hypomagnesaemia should be simultaneously corrected in these patients.[2] Therapy with the non-selective β-adrenergic blocker propranolol can rapidly eliminate paralytic symptoms in patients with TPP refractory to potassium supplementation.[6]

Familial HPP occurs as an autosomal dominant condition in two-thirds of the cases and is sporadic in one-third. Symptoms begin in late childhood or adolescence and rarely after the age of 25 years. There is a male preponderance (3–4:1) and the condition is typically seen in Caucasians.[4,7] Episodes can last from 3–4 hours to as long as a day or more. They are frequently precipitated by rest or sleep and almost never during vigorous physical activity. A meal rich in carbohydrates favours its development. The limb muscles are affected earlier and often more severely than the trunk muscles, and the proximal muscles are more susceptible than distal ones.[4] The fall in serum potassium level is associated with little or no increase in urinary potassium levels, favouring a transcellular shift of potassium into the muscle during an attack.[4] Prophylaxis has been successful against acute episodes of familial HPP with a wide variety of treatment modalities including spironolactone, triamterene and acetazolamide.[7] Acetazolamide may block the flux of potassium from the blood into the muscle and is probably related to metabolic acidosis.[7] It may be associated with a reduced potassium level and may need potassium supplementation.[3] Two patients in our series had sporadic HPP. Both were treated with acetazolamide with no recurrence of symptoms.

The incidence of TPP is highest among Asians from the Far East. Approximately 2% of patients with thyrotoxicosis in China and Japan reportedly have TPP.[9] Cases have been reported from India as well.[8,9] It occurs in the summer and autumn months and is related to the increased consumption of sweet drinks, outdoor activities and exercise. It is also associated with an increase of potassium in the sweat.[8] TPP can occur in association with any of the causes of hyperthyroidism although the most common cause is Graves disease. Increased activity of the Na^+–K^+–ATP-ase pump due to a hyperadrenergic state induced by thyrotoxicosis; direct stimulation by thyroid hormone and hyperinsulinaemia due to carbohydrates are postulated factors.[8] Kung *et al.* reported that 3 novel single-nucleotide polymorphisms in Ca (V) 1.1 found in patients with TPP have significant differences in genotype distribution compared with controls with Graves disease and healthy controls.[10] Initial treatment of TPP should be followed by definitive therapy with antithyroid drugs or radioactive iodine. Acetazolamide can precipitate recurrent attacks of TPP and should not be used.[8] As classically seen in the literature, only subtle signs of thyrotoxicosis were present in both our patients with TTP, although both had biochemical evidence of thyrotoxicosis. Both the patients became euthyroid with radioactive ablation. They had no recurrence of paralytic episodes during the 1-year follow up, without potassium supplementation.

The cause of HPP in 13 patients (42%) in our series was RTA. Three of them had evidence of Sjogren syndrome. Besides HPP, patients with RTA can have myopathy related to chronic

TABLE III. Aetiology of hypokalaemic periodic paralysis (modified from reference 5)

Familial (primary) periodic paralysis

- Hypokalaemic periodic paralysis (HPP)

Secondary periodic paralysis

- Thyrotoxic periodic paralysis (TPP)
- Thiazide/loop diuretic-induced
- Drug-induced: Gentamicin, carbenicillin, amphotericin B, degraded tetracycline, vitamin B_{12}, alcohol, carbenoxolone
- Primary hyperaldosteronism
- Acute barium toxicity
- Gastrointestinal potassium loss: Acute gastroenteritis, short bowel syndrome, gastrointestinal fistula
- Renal potassium loss: Tubulointerstitial disorder, Gitelman syndrome, Barrter syndrome, renal tubular acidosis (RTA)

hypokalaemia which may not be responsive to therapy.[11] In addition, patients with Sjogren syndrome may have a chronic inflammatory myopathy.[11] In the series of HPP from Taiwan, 6 patients had RTA, of whom 3 had Sjogren syndrome.[2] Sjogren syndrome is complicated by RTA in 40% of patients.[12] In a case series, Pun *et al*. described 3 patients with Sjogren syndrome in which HPP and distal RTA preceded the diagnosis of Sjogren syndrome by 2–8 years. In this series, HPP was the presenting symptom in 3 of 26 patients with Sjogren syndrome.[12] In a western series of 16 patients with Sjogren syndrome, only 2 had RTA, but none presented with HPP.[13] Sjogren syndrome presenting with hypokalaemic paralysis has also been reported from India.[14,15]

Periodic paralysis as a presentation of primary hyperaldosteronism is commonly reported among the oriental races.[7,16] In a series of 50 patients with primary hyperaldosteronism from Taiwan, 42% presented with periodic paralysis, although all 50 had hypokalaemia.[16] In another oriental series, 21 of 43 cases (49%) of primary hyperaldosteronism presented with muscular paralysis as the initial symptom. The serum potassium level of patients with muscular paralysis was significantly lower than that of patients without it.[17] In a series of 97 patients with HPP, 6 (6%) had primary hyperaldosteronism.[2] In our series, 13 patients (42%) had primary hyperaldosteronism. In our series of patients with primary hyperaldosteronism who were seen during the same time-frame as those with periodic paralysis, 13 of 25 patients (52%) presented with HPP.

One patient in our series had biochemical evidence of Gitelman syndrome. Gitelman syndrome is an autosomal recessive disorder due to a defective thiazide-sensitive sodium chloride co-transporter in the renal tubules. Spontaneous hypokalaemia, hypomagnesaemia and hypocalciuria are the key features.[18] Treatment of patients with Gitelman syndrome includes magnesium and potassium supplementation. Potassium-sparing diuretics and indomethacin have also been advocated.[18] In Lin's series, 6 patients had Barrter/ Gitelman syndrome.[2] The prominent feature in our series was the high percentage of patients with secondary causes of periodic paralysis. Even though a large series from Taiwan had reported a higher percentage of secondary RTA, a majority of these patients had thyrotoxicosis. To our knowledge, this is the largest series of periodic paralysis from India.

Since this study is from a single tertiary referral centre, only those patients with repetitive and severe episodes may have been seen by us. Patients with transient causes such as gastroenteritis and diuretic use may not have been referred to our centre. This may be a limitation of our study.

In summary, among our patients a high proportion had secondary causes of HPP. Primary hyperaldosteronism was common, which is a totally reversible condition. RTA is an important, medically treatable cause and should be looked for in a proactive manner. Identifying the cause of HPP can help in optimizing management protocols.

It may be worthwhile collating multicentric data prospectively with a standardized protocol to further establish the magnitude and nature of periodic paralysis in India.

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