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Hypokalaemia and paralysis

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Summary

It is not uncommon for patients to present to the emergency room with severe weakness and a markedly low plasma potassium concentration. We attempted to identify useful clues to the diagnosis of hypokalaemic periodic paralysis (HPP), because its acute treatment aims are unique. We retrospectively reviewed charts over a 10-year period: HPP was the initial diagnosis in 97 patients. Mean patient age was 29 ± 1.1 and the male : female ratio was 77 : 20. When the final diagnosis was HPP ($n=73$), the acid-base state was normal, the urine K^+ concentration was low, and the transtubular K^+ concentration gradient (TTKG) was <3. In patients with thyrotoxic periodic paralysis (TPP) ($n=39$), hypokalaemia was very commonly accompanied by hypophosphataemia (1.9 ± 0.1 mg/dl). A clinical diagnosis of sporadic periodic paralysis (SPP) was made if hyperthyroidism and a family history of HPP were both absent ($n=29$). One subgroup of patients with HPP had a severe degree of hypernatraemia (167 ± 5.0 mmol/l, $n=3$). There were only two patients with familial periodic paralysis (FPP). In 24 patients, the initial diagnosis was HPP, but subsequent studies failed to confirm this diagnosis. Each of these patients had an acid-base disorder, a high rate of renal K^+ excretion in the presence of hypokalaemia, and a TTKG of close to 7. With respect to therapy, much less K^+ was given to patients with HPP, yet 1 : 3 subsequently had a plasma K^+ concentration that eventually exceeded 5.0 mmol/l. Using plasma acid-base status, phosphate and K^+ excretion parameters allows a presumptive diagnosis of HPP with more confidence in the emergency room.

Introduction

Although there are a large number of potential causes of hypokalaemia in general, there are far fewer entities in the differential diagnosis when hypokalaemia is associated with extreme weakness.[1] In the latter group, hypokalaemic periodic paralysis (HPP) is a major diagnostic entity. In Western countries, most cases are due to familial periodic paralysis (FPP), but in an Asian population, thyrotoxic periodic paralysis (TPP) is most commonly associated with this illness.[2,3] In HPP, hypokalaemia and paralysis are due to an acute shift of potassium (K^+) into cells.[4] In contrast, in cases where HPP is not present, an excessive excretion of K^+ is usually an important aetiological factor.[5]

Failure to differentiate between HPP and other causes of severe hypokalaemia with weakness in the emergency room may lead to errors in management. Accordingly, we reviewed our experience over the past 10 years, seeking clues to the rapid and more accurate diagnosis of HPP. It is important to make a diagnosis of HPP promptly because the initial management will be different: much less K^+ will be needed and rebound hyperkalaemia is a potential threat of therapy.[6]

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Methods

Retrospectively reviewing charts between 1989 and 1999, we identified 97 severely hypokalaemic patients with profound weakness in whom the listed presumptive diagnosis was HPP. Extreme weakness was defined as acute loss of muscle strength with inability to walk. Patients typically had an acute episode of paralysis involving the muscles of the extremities and limb girdle, requiring emergency admission. Hypokalaemia was defined as a plasma K^+ concentration <3.0 mmol/l at the time of presentation. Blood and urine electrolytes as well as acid-base parameters were obtained at the time of presentation before therapy began.

Acid-base balance and electrolytes

Arterial blood gases on admission were done in 72 patients; urine electrolytes and biochemistries were measured in 57. TTKG was calculated in 46 patients as previously described ((urine/plasma $[K^+]$)/(urine/plasma osmolality)).[7] The normal renal response when hypokalaemia is due to non-renal causes is a TTKG <2, whereas a TTKG >5 usually reflects an increased net secretion of K^+ in the cortical collecting ducts (CCD). The quantity of KCl administered and the development of hyperkalaemia during therapy were also recorded.

Statistical analyses

Where possible, all values were expressed as means $\pm$SEM. One-way analysis of variance (ANOVA) was used to compare independent variables among groups. A p value <0.05 was considered statistically significant.

Results

Mean plasma K^+ concentration was 2.2 ± 0.04 mmol/l in this population. The age range was 14–78 (29 ± 1.1); the male : female ratio was 77 : 20. Final diagnosis and patient characteristics are shown in Table 1.

Patients with established HPP ($n=73$)

Thirty-nine patients were diagnosed with TPP: all were male (Table 1). TPP was established by the presence of hyperthyroidism when hypokalaemic paralysis occurred. The serum T3 and T4 levels were elevated with (4.5 ± 0.2 nmol/l) (normal range 1.2–3.0 nmol/l) and (201 ± 33 nmol/l) (normal range 51–154 nmol/l), respectively, whereas serum TSH levels were markedly depressed (<0.06 mU/l) (normal range 0.5–5.0 mU/l) (Table 2). Blood pressure and heart rate on admission were $142\pm2.0/88\pm1.0$ mmHg and 105 ± 3 bpm, respectively. Of the TPP patients, eight (20.5%) had a family history of hyperthyroidism in one or more family members, 19 (48.6%) gave a prior history of thyrotoxic symptoms before TPP attacks, 24 (61.5%) were clinically thyrotoxic and nine (23%) did not have a suspected hyperthyroid state at the time of presentation. Most of the TPP patients received medical treatment with antithyroid drugs and propranolol (60–240 mg/day); only two patients received I^{131} radiotherapy, and two had subtotal thyroidectomy.

Twenty-nine patients had idiopathic or sporadic periodic paralysis (SPP); they did not have hyperthyroidism or a family history of HPP (Table 2). Their blood pressure ($120\pm2.0/78\pm1.0$ mmHg) and heart rate (76 ± 2 bpm) were significantly lower than those in patients with TPP. Patients with SPP were treated either with oral KCl supplement or with acetazolamide to control recurrent hypokalaemic paralysis.

There was a unique group of patients ($n=3$) who had a severe degree of hypernatraemia (plasma Na^+ concentration 167 ± 5.0 mmol/l) accompanying HPP (two patients had a brain tumour, and one patient had tuberculosis with involvement of the hypothalamus). There were only two patients with familial periodic paralysis (FPP). Thus overall, 24 patients did not have HPP.

The blood and urine acid-base and electrolyte data on admission in patients who had a presumptive diagnosis of HPP are shown in Table 3. Patients eventually diagnosed with HPP ($n=48$) did not have an acid-base disorder (pH 7.40 ± 0.01 (range 7.37–7.43), HCO_3^- 24 ± 0.2 mmol/l (range 20 to 27 mmol/l), and PCO_2 40 ± 0.4 mmHg (range 32–45 mmHg). A clue unique to the diagnosis of HPP was a low urinary K^+ concentration (8 ± 0.6 mmol/l and a low TTKG (2.3 ± 0.1). The serum phosphate (1.9 ± 0.1 mg/dl) and magnesium levels (1.6 ± 0.1 mg/dl) were lower on admission in patients with TPP.

Patients who did not have HPP ($n=24$)

All of these patients had an acid-base disorder. Fifteen had metabolic alkalosis (pH 7.48 ± 0.02, HCO_3^- 33 ± 1.1 mmol/l). The aetiology included six patients with primary hyperaldosteronism (five had an adrenal adenoma, one had bilateral adrenal hyperplasmia); hypertension ($154\pm3/98\pm2$ mmHg) was also present in these patients. In contrast, metabolic alkalosis was seen in six patients with Bartter's or Gitelman's syndromes, and three

others who had taken diuretics (two with furosemide and thiazide, one with furosemide alone). The second subgroup ($n=9$) had hypokalaemia associated with hyperchloraemic metabolic acidosis (pH 7.26 ± 0.06, HCO_3^- 11 ± 4.5 mmol/l). Six had distal renal tubular acidosis (RTA) (three patients had Sjögren's syndrome and three had idiopathic distal RTA) and three were chronic glue-sniffers. In all the patients with an acid-base disorder, there was a relatively high urine K^+ concentration (19 ± 2.3 mmol/l); however, approximately 40% of urinary K^+ concentrations (9/24) were <20 mmol/l when hypokalaemia was present. Nevertheless, the TTKG (7.0 ± 0.4) was consistently high in this subgroup.

There was no significant difference in plasma K^+ and calcium concentrations on admission among all subgroups, nor were plasma creatinine and BUN helpful in discriminating between the patients with or without a final diagnosis of HPP. Serum magnesium concentration was significantly lower in patients with metabolic alkalosis due to Bartter's and/or Gitelman's syndrome and in those using diuretics. Hyponatraemia was present in patients with distal RTA and in the chronic glue-sniffers.

During therapy in patients with HPP, the dose of intravenous and/or oral K^+ prior to recovery ranged from 20 to 230 mmol (mean 57 ± 5 mmol). A paradoxical fall in serum K^+ concentration from 2.2 ± 0.4 mmol/l to 1.9 ± 0.2 mmol/l was observed in 11 patients with HPP (seven patients with TPP and four patients with SPP). One patient with SPP developed acute respiratory failure, with a documented plasma K^+ concentration of 1.2 mmol/l during KCl therapy. There was no fall in the plasma K^+ concentration in all but one hypokalaemic patient with an acid-base disorder; this patient had distal RTA and developed acute respiratory failure with a plasma K^+ concentration of 1.4 mmol/l because alkali therapy was too aggressive.

Upon recovery, peak plasma K^+ concentrations ranged from 3.6 to 7.2 mmol/l (mean 4.7 ± 0.12 mmol/l) in HPP patients. A plasma K^+ concentration >5 mmol/l occurred in almost 1 : 3 patients with HPP ($n=22$). Among these 22 patients, there were seven with a plasma K^+ concentration >6 mmol/l. Interestingly, there was also mild rebound hyperphosphataemia (plasma phosphate concentration >4.5 mg/dl) in 21 patients with TPP when paralysis resolved; none of these patients were given phosphate supplements.

The quantity of K^+ given was much greater in patients with an acid-base disorder (185 ± 12 mmol), ranging from 140 to 320 mmol. There was no rebound hyperkalaemia in these patients. Intravenous magnesium sulphate (400–1200 mg elemental magnesium) was infused in two patients with Gitelman's syndrome and in two cases of diuretic use.

Table 1 Characteristics and final diagnosis for patients initially diagnosed with HPP

	n	Age	M : F
Patients with HPP			
Thyrotoxic periodic paralysis (TPP)	39	28 ± 1.3	39 : 0
Sporadic periodic paralysis (SPP)	29	26 ± 1.5	23 : 6
Hypernatraemic hypokalaemic paralysis (HHP)	3	18 ± 2.1	3 : 0
Familial periodic paralysis (FPP)	2	16 ± 1.0	2 : 0
Patients who did not have HPP			
Metabolic alkalosis			
Primary aldosteronism (PA)	6	39 ± 2.1	2 : 4
Bartter or Gitelman's syndrome (BS/GS)	6	21 ± 0.7	4 : 2
Diuretics	3	40 ± 6.0	0 : 3
Hyperchloraemic acidosis			
Distal renal tubular acidosis (dRTA)	6	47 ± 8.1	3 : 3
Toluene abuse	3	28 ± 5.6	1 : 2

Table 2 Diagnostic criteria in patients with periodic paralysis

	TPP	SPP
History		
Acute episodes	Yes	Yes
Episodic	Yes	Yes
Family history of paralysis	No	No*
Family history of hyperthyroidism	Some	No*
Provoking factor		
Large carbohydrate meal	Often	Rare
Adrenergic stress	Often	Rare
Physical findings		
High pulse rate	Yes*	No
Blood pressure	Relatively high	Normal
ECF volume contraction	No	No
Signs of hyperthyroidism	May be absent	No
Laboratory findings		
T3 (nmol/l)	4.5 ± 0.2* (2.3–8.4)	1.9 ± 0.1
T4 (nmol/l)	201 ± 33* (154–299)	104 ± 5
TSH (mU/l)	<0.06* (<0.6–0.32)	1.8 ± 0.1

The range of laboratory values is shown in parentheses.
*Critical finding.

Table 3 Acid-base and electrolytes on admission in patients with initial presumptive HPP

	Na^+	K^+	Cl^-	HCO_3^-	pH	Ca^{++}	Mg^{++}	Inorg P	UK^+	TTKG
Normal acid-base										
TPP ($n=39$)	141 ± 0.3	2.2 ± 0.1	104 ± 0.4	24 ± 0.2	7.40 ± 0.01	9.5 ± 0.1	1.6 ± 0.1	1.9 ± 0.1[a]	7.3 ± 0.8	2.3 ± 0.3
SPP ($n=29$)	141 ± 0.5	2.3 ± 0.1	103 ± 0.6	24 ± 0.3	7.41 ± 0.01	9.4 ± 0.1	2.0 ± 0.1	3.1 ± 0.1	8.3 ± 0.9	2.3 ± 0.2
HHP ($n=3$)	167 ± 5.0[ab]	2.4 ± 0.2	130 ± 2.5	22 ± 1.6	7.39 ± 0.01	9.3 ± 0.2	2.4 ± 0.2	3.2 ± 0.9	6.7 ± 2.3	2.1 ± 0.1
FPP ($n=2$)	141 ± 0.5	2.0 ± 0.1	105 ± 0.5	25 ± 0.7	7.41 ± 0.01	9.5 ± 0.1	2.1 ± 0.1	3.6 ± 0.3	9.8 ± 0.9	2.5 ± 0.1
Metabolic alkalosis										
PA ($n=6$)	145 ± 0.7	2.1 ± 0.1	99 ± 0.9[a]	33 ± 2.0[a]	7.47 ± 0.01[a]	9.2 ± 0.1	2.0 ± 0.1	3.5 ± 0.1	21 ± 2.3[a]	6.6 ± 0.6[a]
BS/GS ($n=6$)	142 ± 0.5	1.9 ± 0.1	99 ± 0.9[a]	31 ± 1.4[a]	7.46 ± 0.01[a]	9.7 ± 0.3	1.4 ± 0.1[a]	3.9 ± 0.3	18 ± 2.3[a]	6.5 ± 0.8[a]
Diuretics ($n=3$)	139 ± 0.9	1.9 ± 0.1	97 ± 0.3[a]	33 ± 0.5[a]	7.48 ± 0.01[a]	9.4 ± 0.1	1.3 ± 0.1[ac]	3.4 ± 0.1	18 ± 1.8[a]	7.1 ± 0.6[a]
Metabolic acidosis										
dRTA ($n=6$)	132 ± 1.6[bc]	2.0 ± 0.1	112 ± 1.7[bc]	11 ± 1.7[bc]	7.19 ± 0.03[bc]	9.2 ± 0.3	1.8 ± 0.1	2.3 ± 0.1[c]	21 ± 2.5[b]	7.3 ± 0.5[b]
Toluene ($n=3$)	130 ± 1.1[bc]	2.1 ± 0.1	112 ± 0.9[bc]	11 ± 2.3[bc]	7.22 ± 0.03[bc]	9.4 ± 0.2	1.9 ± 0.1	2.1 ± 0.2[c]	23 ± 2.4[b]	7.2 ± 0.3[b]

[a] $p<0.05$ normal acid-base vs. metabolic alkalosis; [b] $p<0.05$ normal acid-base vs. metabolic acidosis; [c] $p<0.05$ metabolic alkalosis vs. metabolic acidosis.

Discussion

In this retrospective study in an Asian population, HPP was the cause of hypokalaemia and extreme weakness in approximately 75% of our patients.[2,3,6] Non-familial TPP was our most common subgroup of HPP in particular, as it is in Asians in general. The events that lead to paralysis with hypokalaemia and hypophosphataemia in TPP are complex,[6] including a genetic and racial predisposition, a putative exaggerated response to insulin, and a hyperadrenergic state.[8–10] In one previous study from Taiwan, SPP was much more common than TPP;[11] the reason for this discrepancy remains obscure.

One of our objectives was to find abnormalities that would help distinguish between HPP and other causes of muscle weakness in hypokalaemic patients. Acid-base abnormalities were absent on admission in all HPP patients. The rate of excretion of K^+, the urine K^+ concentration, and especially the TTKG were all very low in these patients. When a diagnosis of TPP was thought to be likely, a very useful clinical finding was the presence of a higher heart rate (~105 beats/min) even in the absence of obvious overt hyperthyroidism. At the biochemical level, hypophosphataemia and possibly hypomagnesaemia were helpful clues, but the latter ion concentration was also low in patients with Gitelman's syndrome (Table 3).

We found a new association with respect to HPP: the presence of a severe degree of hypernatraemia in three patients with brain lesions involving the hypothalamus. It is well known that control of osmoregulation, including thirst, resides in the hypothalamus and this region is also important for regulation of adrenergic activity. We speculate that involvement of this region of the brain by a tumour or infiltrative disease impaired thirst and led to hypernatraemia; and resulted in hypokalaemia via a hyperadrenergic state that activated the Na-K ATPase, causing a transcellular shift of K^+ into cells. In addition, hypernatraemia has been implicated to some extent in the aetiology of muscle weakness or paralysis.[12–14]

In contrast to the patients with HPP, an acid-base disorder was present in the non-HPP patients in our study group (Table 3). Almost 60% of them had metabolic alkalosis. In none of these patients was liquorice abuse a cause of renal K^+ wasting. Primary aldosteronism, diuretic use, and hereditary tubular disorders causing renal K^+ wasting such as Bartter's and/or Gitelman's syndrome were the usual clinical diagnoses. A myopathy associated with hypokalaemia occurs more frequently in Asians than in Western populations who have primary aldosteronism.[15] Hypokalaemic paralysis occurred in 10–15% of primary aldosteronism in

our series and others,[16] whereas in Huang's study, half of their patients (21/43) with a diagnosis of primary aldosteronism presented with muscle paralysis and hypokalaemia.[17] In Bartter's or Gitelman's syndrome, tetany and muscle cramps are common clinical symptoms. Nevertheless, extreme weakness or paralysis may be the common presenting features and they can be quite incapacitating in adults.[18,19] In some patients, this may be associated with hypomagnesaemia due to renal magnesium wasting. Hypokalaemia and metabolic alkalosis were common electrolyte and acid-base imbalances in patients using diuretics, but hypokalaemic paralysis is rarely seen in this setting.[20] In our study, only two patients taking loop diuretics and thiazide for control of body weight, and one patient taking loop diuretics for oedema, developed hypokalaemic paralysis.

Another subgroup had hyperchloraemic metabolic acidosis. Distal RTA caused by Sjögren's syndrome was the clinical diagnosis in half of this subgroup. Hypokalaemic paralysis in Sjögren's syndrome may precede the more classic clinical findings, and serves as a clinical marker for this diagnosis.[21–23] The others had idiopathic distal RTA. Toluene abuse (glue-sniffing) was also a cause of hypokalemia and weakness in our subgroup with metabolic acidosis. Renal K^+ wasting is secondary to hippuric acid formation and the eventual urinary excretion of hippurate with the cation K^+.[24] When ECF volume decreases as a result of the excretion of hippurate with Na^+, aldosterone is released, and this leads to a high rate of excretion of K^+, with subsequent K^+ depletion, hypokalaemia, and possibly muscular paralysis.[25,26] Other causes of hypokalaemia associated with metabolic acidosis, such as profound diarrhoea of gastrointestinal disorders, were not present in our population.

Measurements of renin, angiotensin II and aldosterone are helpful in the differential diagnosis of hypokalemia.[1,15] In HPP, one would anticipate that there might be lower levels of aldosterone if hypokalaemia was present for a period of time. Renin levels on the other hand might be quite variable. In contrast, patients with hypokalaemia due to Bartter's syndrome, Gitelman's syndrome, glue sniffing, or diuretic use usually have high renin values and possibly higher aldosterone levels than expected for their degree of hypokalaemia. In patients with primary hyperaldosteronism, aldosterone levels are high and renin levels are very low. In our retrospective chart review, only a small proportion of the patients had these measurements performed. Moreover, even if blood was drawn for these measurements, the results would not be available in time for clinical decision-making in this emergency setting.

To establish whether renal K^+ wasting is present, one cannot wait for a 24-h urine collection. Hence a spot urine collection must be used. If creatinine was also measured in the urine, the K^+/creatinine ratio will reflect the K^+ excretion rate at that time.[27] Determination of the urinary K^+ concentration alone might be misleading, because K^+ depletion can cause polyuria, and a relatively low K^+ concentration (<20 mmol/l) could still represent substantial urinary K^+ loss. The TTKG provides a better way to evaluate the K^+ excretory process. In our patients with HPP, very low urine K^+ concentration and appropriately low TTKG suggested that hypokalaemia was due to a transcellular shift of K^+. In the subgroups with an acid-base disorder, there was a high mean urine K^+ concentration, but in approximately 40% of these patients, its concentration was <20 mmol/l when hypokalaemia was present. Nevertheless, their TTKG was high (~ 7).

The therapy for all forms of HPP will differ from therapy for the other causes of a severe degree of hypokalaemia and profound muscular weakness. Since the latter are due primarily to negative total body K^+ balance, whereas the hypokalemia of HPP is due to a shift of K^+ into cells, the amount of K^+ to be administered should be much less in HPP. Even though the cause of hypokalaemia in HPP is an intracellular shift of K^+, vigorous K^+ replacement has been advocated for the treatment of paralysis and prevention of fatal arrhythmias.[1,3,6] However, the efficacy of this therapeutic therapy is questionable, because there is no correlation between the dose of potassium chloride administered and recovery time.[6] Furthermore, spontaneous recovery from paralytic attacks with subsequent normalization of serum K^+ levels occurs in many patients who do not receive K^+ replacement. Failure to reveal the underlying cause for hypokalaemia and excessive weakness may lead to overly aggressive treatment of an apparent K^+ deficiency that places the patient at risk of rebound hyperkalaemia. In this study, rebound hyperkalaemia occurred in close to 1 : 3 patients with HPP, although the quantity of K^+ given was much less than in those with an acid-base disorder.

It is especially important to distinguish between the two major subtypes of HPP, TPP and SPP. Unless special laboratory tests for thyroid gland function are available in this emergency setting, one must rely on clinical suspicion. We place great emphasis on the family history, past episodes, history of symptoms compatible with hyperthyroidism, and the presence of a more rapid heart rate and a somewhat higher blood pressure to diagnose TPP (Table 2). If TPP is strongly suspected, we now prefer to treat initially with propranolol,

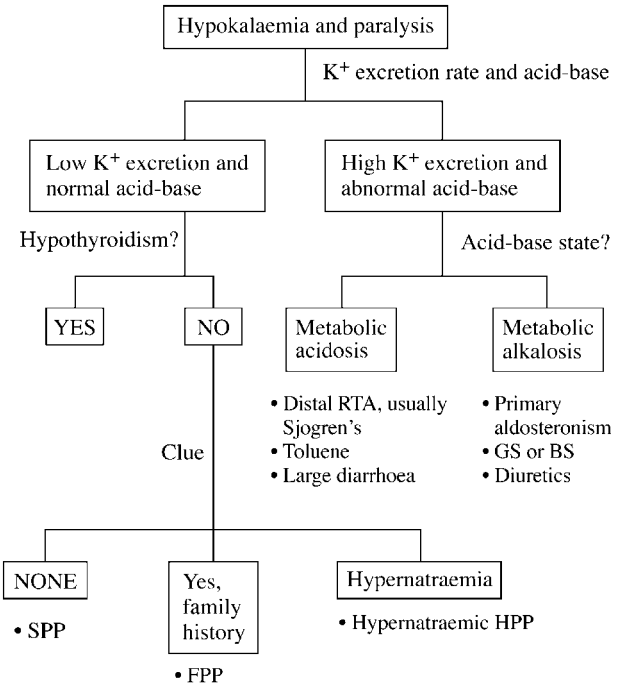

Figure 1. Diagnostic approach in patients presenting with hypokalaemic paralysis.

a non-selective beta-blocker.[28] Our experience so far is to administer a relatively higher oral propanolol (3 mg/kg) without KCl supplement, using heart rate as an index to block beta adrenergic activity. When the heart rate is markedly reduced, muscle paralysis and plasma potassium concentration may be rapidly reversed. The administration of a beta-blocker has been shown to prevent future acute paralytic attacks;[29] it also rapidly reversed acute attacks of TPP when K^+ supplements failed to terminate symptoms.[30] In patients where TPP cannot be substantiated, we try to give as little KCl as possible initially (5–10 mmol/h) and careful follow-up is mandatory to avoid a serious degree of rebound hyperkalaemia. There is little information with regard to adrenergic abnormalities in the non-thyrotoxic form of HPP, and propranolol appears to have little if any therapeutic effect on this group of patients.[31] To date, acetazolamide is the most effective long-term therapy for non-thyrotoxic form of HPP, but its mechanisms of action are not yet clear.[32–33]

As regards therapy for the hypokalaemia associated with renal K^+ wasting, two points must be stressed. Firstly, hypokalaemia in the presence of hyperchloraemic metabolic acidosis should be corrected before giving $NaHCO_3$, because alkali therapy might aggravate the degree of hypokalaemia by enhancing a shift of K^+ into cells. In fact, acute respiratory failure, due to a further fall in the plasma K^+ concentration during aggressive alkali therapy, developed in one patient with distal RTA in our population. Secondly, hypomagnesaemia may accompany hypokalaemia and metabolic alkalosis. Correction of hypomagnesaemia may help in the treatment of hypokalaemia and prevention of a cardiac arrhythmia.

In conclusion, HPP is a common disorder in Taiwan. Measurement of blood and urinary electrolyte and acid-base parameters may provide potentially very valuable clues to help make a diagnosis of HPP and lead to its prompt therapy on admission. A simple diagnostic approach in patients presenting with hypokalaemic paralyses is shown in Figure 1. Low urinary K^+ concentration with low TTKG, and the absence of an acid-base disorder on admission, are both very useful clues to suggest the diagnosis of HPP. The diagnosis of TPP must usually be suspected initially on clinical grounds. While much less KCl is needed during therapy of HPP, there is still a danger of rebound hyperkalaemia. Other options for therapy, such as non-selective beta-blockers, should be formally evaluated in patients with TPP.

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