ORIGINAL INVESTIGATION

Laboratory Tests to Determine the Cause of Hypokalemia and Paralysis

Shih-Hua Lin, MD; Yuh-Feng Lin, MD; Dung-Tsa Chen, PhD; Pauling Chu, MD, PhD; Chin-Wang Hsu, MD; Mitchell L. Halperin, MD

Background: Hypokalemia and paralysis may be due to a short-term shift of potassium into cells in hypokalemic periodic paralysis (HPP) or due to a large deficit of potassium in non-HPP. Failure to make a distinction between HPP and non-HPP may lead to improper management. Therefore, we evaluated the diagnostic value of spot urine tests in patients with hypokalemia and paralysis during 3 years.

Methods: Before therapy, the urine potassium concentration, potassium-creatinine ratio, and transtubular potassium concentration gradient were determined in a second voided urine sample.

Results: Forty-three patients with hypokalemia and paralysis were identified: 30 had HPP and 13 had non-HPP. There was no significant difference in the plasma potassium or bicarbonate concentrations and in the pH of arterial blood between the 2 groups. All but 2 patients in the non-HPP group had urine potassium concentration values less than 20 mmol/L. Although the potassium concentration was significantly lower in the HPP group, there was some overlap. In contrast, the transtubular potassium concentration gradient and potassium-creatinine ratio differentiated patients with HPP vs non-HPP. Although only a mean±SD of 63±36 mmol of potassium chloride was administered in the patients with HPP, rebound hyperkalemia (>5 mmol/L) occurred in 19 (63%) of these 30 patients.

Conclusions: Calculating the transtubular potassium concentration gradient and potassium-creatinine ratio provided a simple and reliable test to distinguish HPP from non-HPP. Minimal potassium chloride supplementation should be given to avoid rebound hyperkalemia in patients with HPP.

Arch Intern Med. 2004;164:1561-1566

From the Division of Nephrology, Department of Medicine (Drs S. H. Lin, Y. F. Lin, and Chu), and Department of Emergency Medicine (Dr Chen), Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; Biostatistics Unit, UAB Comprehensive Cancer Center, University of Alabama, Birmingham (Dr Hsu); and Renal Division, St Michael's Hospital, University of Toronto, Toronto, Ontario (Dr Halperin). The authors have no relevant financial interest in this article.

HYPOKALEMIA AND PARALYsis (HP) is a potentially reversible medical emergency.[1] Morbidity and mortality are related to complications secondary to hypokalemia such as a cardiac arrhythmia or respiratory failure.[2] Although there are many potential causes of hypokalemia, there are far fewer entities in the differential diagnosis of HP (**Table 1**).[1] Hypokalemia and paralysis can be divided into 2 types, hypokalemic periodic paralysis (HPP) due to a short-term shift of potassium into cells[3-5] and non-HPP resulting from a large deficit of potassium.[6,7]

The differential diagnosis in a patient with HP can be challenging, but it is important to make the diagnosis promptly because different therapies are required for each type. Although some features discerned on patient history such as a positive family history or a recurrent episode can be helpful, the clinical features of HPP and non-HPP are almost indistinguishable.[8] Many patients with non-HPP have been misdiagnosed as having HPP.[9] Because hypokalemia is the primary biochemical abnormality in patients with HP, measurements of the urinary excretion of potassium were the focus of our evaluation. To establish whether renal potassium wasting is present in these medical emergencies, one cannot wait for a prolonged, timed urine collection. Hence, a second voided spot urine collection before initiation of therapy is the optimum sample to examine. In this study, we sought to evaluate the diagnostic value of spot urine tests in patients with HP.

METHODS

STUDY SUBJECTS

The study protocol was approved by the Ethics Committee on Human Studies at Tri-Service General Hospital, Taiwan. Taipei, Informed consent was obtained from each patient. Forty-three new patients with HP were enrolled in this study between January 1, 2000, and December 31, 2002. *Hypokalemia and pa-*

©2004 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 10/18/2014

Table 1. Patient Characteristics and Final Diagnosis

Patient Group	No. of Patients	Age, Mean ± SD, y	Male-Female
Hypokalemic periodic paralysis (n = 30)			
Thyrotoxic periodic paralysis	20	28 ± 8	20:0
Sporadic periodic paralysis	9	28 ± 7	8:1
Familial periodic paralysis	1	19	1:0
Non–hypokalemic periodic paralysis (n = 13)			
Primary aldosteronism	1	34	1:0
Gitelman syndrome	4	24 ± 2	3:1
Licorice ingestion	1	72	1:0
Distal renal tubular acidosis	5	38 ± 23	2:3
Fanconi syndrome with proximal renal tubular acidosis	1	42	1:0
Profound diarrhea	1	47	1:0

ralysis was defined as an acute loss of muscle power with an inability to ambulate and a plasma potassium concentration that was less than 3 mmol/L on presentation. The paralysis tended to involve the muscles of the extremities and limb girdles.

DEFINITIONS

Hypokalemic Periodic Paralysis

Hypokalemic periodic paralysis must be defined on clinical grounds. There were 4 elements to the diagnosis. First, a positive family history, recurrent clinical pattern, or evidence of hyperthyroidism made HPP a likely diagnosis. The absence of the intake of agents that could cause a shift of potassium into cells was also important in this context. Second, if there was no indication of other diseases known to be associated with potassium wasting, again HPP would be suspected. Third, if the patients required less than 1.5 mmol of potassium chloride per kilogram of body weight to return their plasma potassium concentration to the normal range, this supported the diagnosis of HPP. Fourth, the absence of an acid-base disorder strengthened the diagnosis of HPP.[9]

Non–Hypokalemic Periodic Paralysis

Non–hypokalemic periodic paralysis was suspected if none of the 4 findings in the previous paragraph were present, if there was an explanation for a large deficit of potassium, if more than 3 mmol/kg of potassium was needed to correct the plasma potassium concentration to the normal range, and if an acid-base disorder was present.[9]

PROCEDURES

A spot urine sample was collected before therapy by self-voiding if possible or with a Foley catheter if the patient was unable to urinate. To avoid the possibility of obtaining urine that represented a mixture of urine from before the onset of the attack and at the time of the attack, urine in the bladder on presentation was discarded and a second voided urine specimen was collected during the next hour. An arterial blood sample was collected in all the patients; venous blood samples were collected through an indwelling catheter. All of the patients received intravenous potassium chloride administration at a rate of 10 mmol/h until muscle strength had recovered and the patient could ambulate. The plasma potassium concentration was measured hourly during the attack and for 6 hours after recovery. The *recovery time* was defined as the time required from the initiation of potassium chloride therapy to the recovery of sufficient muscle strength to ambulate. The quantity of potassium chloride administered was recorded.

ANALYTICAL TECHNIQUES

Arterial blood gases were measured by an ABL 510 (Radiometer, Copenhagen, Denmark). Biochemical values, including serum and urine creatinine, urea nitrogen, albumin, total calcium, inorganic phosphate, magnesium, sodium, potassium, and chloride, were determined by automated methods (AU 5000 chemistry analyzer; Olympus, Tokyo, Japan). Plasma osmolality (P_{osm}) and urine osmolality (U_{osm}) were measured by freezing-point depression (Advanced Instruments Inc, Needham Heights, Mass).

CALCULATIONS

The transtubular potassium concentration gradient (TTKG) was calculated as previously described ([urine/plasma potassium]/[urine/P_{osm}]).[10] It is not physiologically valid to calculate the TTKG if the U_{osm} is less than the P_{osm}.[11] The urine potassium-creatinine ratio, an index of the potassium excretion rate, was calculated using their respective concentrations in millimoles per liter.

STATISTICAL ANALYSIS

The mean±SD was calculated for patient characteristics and diagnostic measures. A 2-sample *t* test was used to compare the differences in diagnostic measures, recovery times, and amount of potassium chloride that was administered in the HPP and non-HPP groups. Scatterplots were used for data visualization to explore the cutoff values for diagnostic measures.

RESULTS

Forty-three patients with a severe degree of hypokalemia (range, 1.5-2.6 mmol/L) and paralysis were included in the study. The male-female ratio was 38:5; their ages ranged from 18 to 78 years. Of the 43 patients, 30 were in the HPP group and 13 in the non-HPP group. The mean age (28±8 vs 37±18 years) and body mass index (calculated as weight in kilograms divided by the square of height in meters) (22.0±2.3 vs 21.5±2.1) were not significantly different between the 2 groups. In the HPP group, 20 patients had thyrotoxic periodic paralysis (TPP) (Table 1). Three known dihydropyridine-sensitive calcium channel α1 subunit (*CACNA1S*) gene mutations (R528H, R1239H, and R1239G) were analyzed in the patients with TPP, sporadic periodic paralysis (SPP), and familial periodic paralysis (FPP). The pa-

©2004 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 10/18/2014

Table 2. Biochemical Study Results on Admission in Patient Groups*

Study	Reference Range	Hypokalemic Periodic Paralysis	Non–Hypokalemic Periodic Paralysis
Plasma			
pH	7.35-7.45	7.39 ± 0.03	7.39 ± 0.12
Sodium, mmol/L	135-142	142 ± 2	141 ± 3
Potassium, mmol/L	3.5-5.0	2.0 ± 0.3	1.9 ± 0.2
Chloride, mmol/L	98-106	106 ± 2	105 ± 6
Bicarbonate, mmol/L	22.0-26.0	24.0 ± 1.6	25.0 ± 8.8
Phosphate, mmol/L	0.8-1.5	0.7 ± 0.2	0.8 ± 0.2
Magnesium, mmol/L	0.7-1.0	0.8 ± 0.1	0.7 ± 0.2
Glucose, mmol/L	4.0-7.0	8.2 ± 0.9	7.7 ± 1.2
Urea nitrogen, mmol/L	3.0-7.0	5.0 ± 1.4	6.1 ± 1.8†
Creatinine, mmol/L	0.06-0.10	0.08 ± 0.02	0.09 ± 0.02†
Urine			
Potassium, mmol/L	NA	9 ± 3	15 ± 4‡
Creatinine, mmol/L	NA	6.8 ± 2.8	3.7 ± 1.2‡
Urine osmolality, mOsm/kg	NA	598 ± 165	363 ± 105‡
Urine osmolality-creatinine ratio, mOsm/mmol	NA	94 ± 20	100 ± 16
Potassium-creatinine ratio, mmol/mmol	NA	1.3 ± 0.1	4.1 ± 0.2‡
Transtubular potassium concentration gradient	NA	2.1 ± 0.5	6.0 ± 1.2‡

Abbreviation: NA, not applicable.
Conventional conversion factors: To convert to milligrams per deciliter, divide creatinine by 88.4, glucose by 0.0555, magnesium by 0.411, and urea nitrogen by 0.357.
*Data are given as mean ± SD.
†$P<.05$.
‡$P<.001$.

tient with FPP had an R528H point mutation. Only one patient with SPP had a de novo mutation (R528H). None of the patients with TPP had mutations in the 3 hot spots.

The major causes of disease in the non-HPP group were Gitelman syndrome (GS) (n=4) and distal renal tubular acidosis (n=5). The diagnosis of GS was based on the following criteria: hypokalemia of renal origin with renal potassium wasting, hypomagnesemia of renal origin, and hypocalciuria with a urine calcium-creatinine ratio less than 0.1 mmol/mmol. Mutations in the thiazide-sensitive sodium chloride cotransporter (*NCC*) gene were found in 3 of 4 patients. These included a homozygous mutation with H90M in the first patient, compound heterogeneous mutations with T60M and R642C in the second patient, and compound heterogeneous mutations with T163M and N426K in the third patient.[12] The diagnosis of distal renal tubular acidosis was based on the findings of normal anion gap metabolic acidosis associated with minimal ammonium excretion and a urine pH greater than 6.0. Sjögren syndrome was present in 4 of the 5 patients with distal renal tubular acidosis.

The biochemical values in plasma and urine are shown in **Table 2**. There were no significant differences in the mean plasma potassium concentrations between the 2 groups (2.0±0.3 [range, 1.5-2.6] vs 1.9±0.2 [range, 1.5-2.3] mmol/L). The plasma creatinine and urea nitrogen concentrations were lower in patients with HPP ($P<.05$), but these differences were small. Although abnormal acid-base values were helpful to identify patients with non-HPP, at times the results of this initial blood test were equivocal. For example, the lowest plasma bicarbonate concentration at the time of admission was 25 mmol/L (pH 7.43) in the metabolic alkalosis subgroup, and the highest plasma bicarbonate concentration was 18 mmol/L (pH 7.35) in this subgroup. Hence, there was a need for other supportive evidence to confirm that non-HPP was the likely diagnosis.

When examining the spot urine samples, the U_{osm} and creatinine concentration were significantly higher in the HPP group compared with the non-HPP group ($P<.001$) (Table 2). These were likely to be unreliable indexes because there was no significant difference in the U_{osm}-creatinine ratio, indicating comparable daily osmole excretion rates but higher water intakes in the non-HPP group. Although the mean urine potassium concentration was significantly lower in patients with HPP vs non-HPP (9±3 [range, 3-15] vs 15±4 [range, 11-21] mmol/L; $P<.001$), all but 2 patients in the non-HPP group had values less than 20 mmol/L. Furthermore, there were overlapping urine potassium concentration values in the HPP and non-HPP groups (**Figure 1**). Hence, the urine potassium concentration is not reliable to discriminate between these 2 entities. One patient with HPP and 2 patients with non-HPP had a U_{osm} that was less than the P_{osm}, invaliding the TTKG calculation.[11] Nevertheless, the mean TTKGs (2.1 ± 0.5 [range, 1.2-3.0] vs 6.0 ± 1.2 [range, 4.5-8.5]; $P<.001$) were sufficiently different in every other case to help differentiate between HPP and non-HPP categories (**Figure 2**). The urine potassium-creatinine ratio (mean, 1.3±0.1 [range, 0.6-2.3] vs 4.1±0.2 [range, 2.6-5.8] mmol/mmol; $P<.001$) was helpful in differentiating between HPP and non-HPP in every case (**Figure 3**). The diagnostic cutoff values for the TTKG and the potassium-creatinine ratio were 3.0 mmol/mmol and 2.5 mmol/mmol, respectively.

The mean quantities of potassium chloride administered up to the time of recovery were 63±36 mmol (range, 20-180 mmol) in the HPP group vs 171±44 mmol (range, 90-260 mmol) in the non-HPP group. Rebound hyperkalemia (plasma potassium concentration, >5

©2004 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 10/18/2014

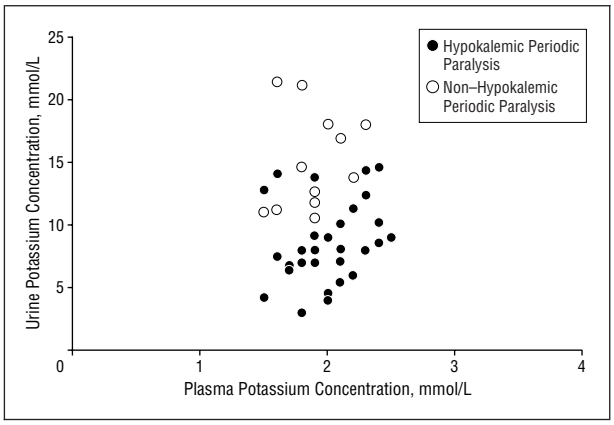

Figure 1. Plasma and urine potassium concentrations in the patient cohort.

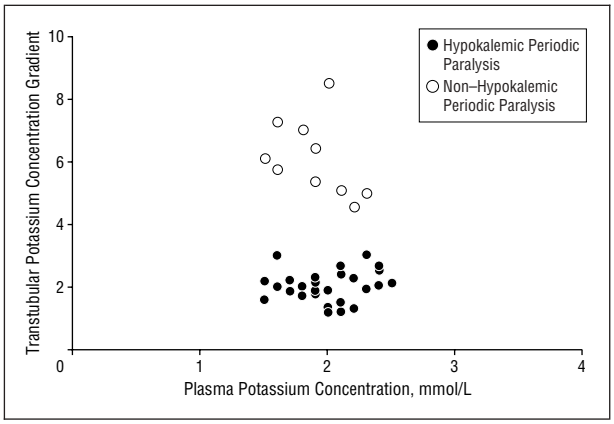

Figure 2. Transtubular potassium concentration gradients in the patient cohort.

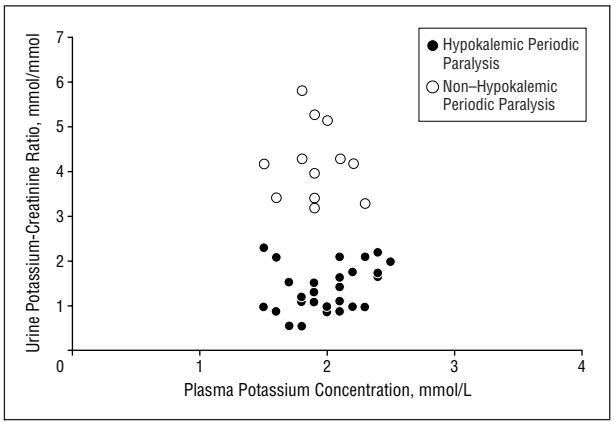

Figure 3. Urine potassium-creatinine ratios in the patient cohort.

mmol/L) after recovery developed in 19 of 30 patients in the HPP group, with a mean peak plasma potassium concentration of 5.6±0.4 mmol/L; hypokalemia persisted in the patients with non-HPP (mean, 2.7±0.2 mmol/L).

COMMENT

The traditional approach to distinguishing between extrarenal and renal causes of hypokalemia is based on spot urine potassium concentration values or urine potassium excretion rates measured in 24-hour urine samples.[13] A urine potassium concentration that is less than 15 to 20 mmol/L or less than 15 to 20 mmol/d suggests that there is an extrarenal cause for potassium depletion. Hypokalemia in the setting of levels exceeding these values indicates that there is a renal cause for potassium wasting.[14,15] Obtaining a 24-hour potassium excretion rate is not practical in a medical emergency because therapy with potassium chloride must be given promptly. A spot urine collection before potassium chloride therapy is the specimen that should be used to help establish the diagnosis.

Three urinary indexes of renal response to hypokalemia were studied: spot urine potassium concentration, TTKG, and potassium-creatinine ratio. Although all 3 indexes have been used previously, their ability to distinguish between HPP and non-HPP has never been evaluated in an emergency department setting, to our knowledge. In this study, the spot urine potassium concentration was significantly lower in the HPP group than the non-HPP group; however, there were many overlapping values because polyuria is common in patients with hypokalemia (Figure 1). The polyuria may be due to thirst or defective renal concentration in patients with chronic hypokalemia; this leads to a low value for the urine potassium concentration even if significant renal potassium wasting is present.[16,17] This is likely part of the explanation why 11 (85%) of the 13 patients in this study with non-HPP had spot urine potassium concentration values that were less than 20 mmol/L in the presence of excessive renal potassium wasting. Therefore, a more reliable test is required.

The TTKG is a semiquantitative index for events in the lumen of the cortical collecting ducts, because it adjusts for the plasma potassium concentration and for water reabsorption in the medullary collecting ducts.[11,18] Although calculating the TTKG is a reliable way to distinguish between HPP and non-HPP, a TTKG is invalid if the U_{osm} is lower than the P_{osm} in a patient.[10] In our study, 1 patient with HPP and 2 with non-HPP had a U_{osm} that was less than the P_{osm}. In these patients, one must rely on another index of potassium excretion to establish the diagnosis.

The other variable reflecting potassium excretion, the potassium-creatinine ratio, has been used to evaluate the cause of hypokalemia; it is based on a near-constant rate of creatinine excretion.[19,20] Although the rate of creatinine excretion can affect the potassium-creatinine ratio, none of the patients with HPP had a low body mass index, which might have produced a lower rate of creatinine excretion and thereby a misleading elevated value for the potassium-creatinine ratio in the urine. If a patient has a reduced muscle mass, this should be considered in interpretation of the results. The potassium-creatinine ratio also was useful to differentiate between HPP and non-HPP; the diagnostic cutoff value for the potassium-creatinine ratio was approximately 2.5 mmol/mmol. In our patients, the body mass index and timed creatinine excretion rates were similar in patients with HPP and non-HPP.

The rate of potassium excretion is thought to be low if gastrointestinal loss of potassium is the presumed cause of hypokalemia.[21] Nevertheless, 1 patient in our study

©2004 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 10/18/2014

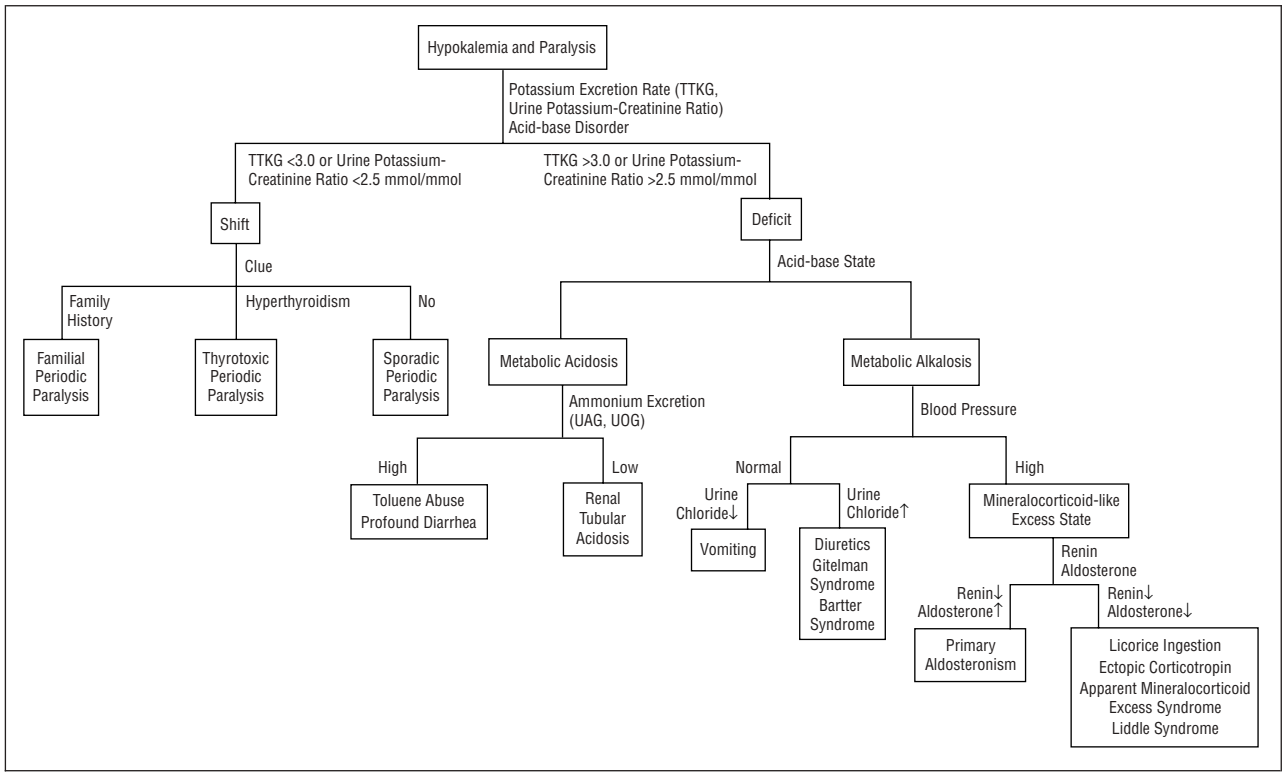

Figure 4. Algorithm for an approach to patients with hypokalemia and paralysis in the emergency department. UAG indicates urine anion gap (sodium + potassium – chloride); UOG, urine osmolar gap ([measured – calculated] osmolality/2); and TTKG, transtubular potassium concentration gradient.

had non-HPP due to profound diarrhea; her potassium-creatinine ratio and TTKG were high, suggesting that renal potassium wasting was also present. Because many patients experiencing diarrhea with hypokalemia have low fecal potassium excretion, fecal losses cannot explain the entire potassium deficit.[22] Secondary hyperaldosteronism caused by circulating volume depletion resulting from fecal sodium loss may lead to an increased urine potassium concentration excretion and play a contributory role in the development of hypokalemia.[22] Other factors, including metabolic alkalosis with bicarbonaturia, hypomagnesemia, and intrinsic renal disorders, may be involved in renal potassium wasting during certain diarrheal states.[22,23]

With respect to therapy, vigorous potassium replacement has been advocated for the treatment of paralysis and prevention of a fatal cardiac arrhythmia in patients with HPP.[24,25] However, the effectiveness of this therapeutic approach is questionable because there is no correlation between the dose of potassium chloride administered and recovery time.[1] Furthermore, spontaneous recovery from paralytic attacks with subsequent normalization of the plasma potassium concentration occurs in some patients with HPP who do not receive potassium replacement.[6]

Failure to distinguish HPP from non-HPP may lead to overly aggressive treatment of an apparent potassium deficit, with rebound hyperkalemia on recovery. In retrospective studies by Manoukain[26] and Lin[9] and colleagues, rebound hyperkalemia occurred in 30% to 42% of patients with HPP, especially if more than 90 mmol of potassium chloride was given within 24 hours. In our study, rebound hyperkalemia (>5 mmol/L) occurred in 19 (63%) of 30 patients with HPP, although only a mean of 63 mmol was administered before recovery. This result suggests that potassium chloride supplements in patients with HPP should be minimal to prevent rebound hyperkalemia. In contrast, in patients with non-HPP, excessive renal potassium excretion required therapy with much more potassium (mean, 170 mmol) to reverse the paralysis; rebound hyperkalemia did not occur. In cases of severe potassium depletion (400-500 mmol), this amount of potassium supplementation should be provided.[27]

To confirm the etiology of HPP, genetic studies were carried out because clinical neuromuscular presentations in TPP and SPP are indistinguishable from FPP, in which an ion channel abnormality in skeletal muscle is involved. Thyrotoxic periodic paralysis and SPP were suggested to be ion channelopathies.[28] In this study, we examined 3 hot spots (R528H, R1239H, and R1239G) for HPP. The patient with FPP had an R528H point mutation, and only one patient with SPP had a de novo mutation (R528H). However, none of the patients with TPP had mutations in the 3 hot spots, consistent with a recent report by Dias da Silva and colleagues.[29] This suggests that mutations linked to FPP in *CACNA1S* may be shared with SPP but not with TPP. Gene analysis of other calcium, sodium, or potassium channels should be examined in patients with TPP with *CACNA1S* to determine whether common ion channel defects are involved in TPP.

Thirty-one percent (4/13) of patients with non-HPP had GS, an inherited renal electrolyte disorder mainly due to mutations in the thiazide-sensitive sodium chlo-

©2004 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 10/18/2014

ride cotransporter.[30] The degree of hypokalemia is usually mild to moderate. Recently, however, more patients with GS have been found with a degree of hypokalemia that is similar to that in patients with Bartter syndrome with sodium-potassium-chloride cotransporter (*NKCC2*) and chloride channel (*ClC-Kb*) gene mutations.[31] As reported by Cruz el al,[32] approximately 6% of patients with GS present with HP. Many patients in Asia with GS present with paralysis related to profound hypokalemia.[10,33,34]

The limitation of this study was that we had a small number of patients with non-HPP. Nevertheless, we identified a cost-effective, rapid, safe, and reliable bedside tool to differentiate HPP from non-HPP. A prospective study is needed to validate the diagnostic value of using spot urine samples in emergency situations.

CONCLUSIONS

In conjunction with plasma acid-base values, an appropriate index of potassium excretion helps distinguish the diagnostic categories of HPP from non-HPP. The TTKG and urine potassium-creatinine ratio are useful estimates of the potassium excretion process. However, the TTKG is invalid if the U_{osm} is less than the P_{osm}; the potassium-creatinine ratio is independent of the U_{osm}. Urine potassium-creatinine ratios less than 2.5 mmol/mmol and TTKGs less than 3.0 in hyperosmolar urine were reliable cutoff values to differentiate between patients with HPP and non-HPP. A diagnostic flowchart is provided to illustrate our approach to HP in the emergency department (**Figure 4**). In patients with HPP, the dose of potassium chloride supplementation should be minimal (<10 mmol/h) to avoid rebound hyperkalemia.

Accepted for publication October 31, 2003.

This study was supported by grant 91-2314-B-016-093 from the National Science Council, Taipei.

We thank Kamel S. Kamel, MD, for his critique of the manuscript.

Correspondence: Shih-Hua Lin, MD, Division of Nephrology, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, No. 325, Section 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan (l521116@ndmctsgh.edu.tw).

REFERENCES

1. Stedwell RE, Allen KM, Binder LS. Hypokalemic paralyses: a review of the etiologies, pathophysiology, presentation and therapy. *Am J Emerg Med*. 1992;10:143-146.
2. Ober KP. Thyrotoxic periodic paralysis in the United States: report of 7 cases and review of the literature. *Medicine*. 1992;71:109-120.
3. McFadzean AJS, Yeung R. Periodic paralysis complicating thyrotoxicosis in Chinese. *BMJ*. 1967;25:451-455.
4. Ko GT, Chow CC, Yeung VT, Chan HH, Li JK, Cockram CS. Thyrotoxic periodic paralysis in a Chinese population. *QJM*. 1996;89:463-468.
5. Lin SH, Lin YF. Propranolol rapidly reverses paralysis, hypokalemia, and hypophosphatemia in thyrotoxic periodic paralysis. *Am J Kidney Dis*. 2001;37:620-623.
6. Huang YY, Hsu RS, Tsai JS. Paralytic myopathy: a leading clinical presentation for primary aldosteronism in Taiwan. *J Clin Endocrinol Metab*. 1996;81:4038-4041.
7. Dowd JE, Lipsky PE. Sjögren's syndrome presenting as hypokalemic periodic paralysis. *Arthritis Rheum*. 1993;36:1735-1738.
8. Ahlawat SK, Sachdev A. Hypokalemic paralysis. *Postgrad Med J*. 1999;75:193-197.
9. Lin SH, Lin YF, Halperin ML. Hypokalemia and paralysis. *QJM*. 2001;94:133-139.
10. West ML, Bendz O, Chen CB, et al. Development of a test to evaluate the transtubular potassium concentration gradient in the cortical collecting duct in vivo. *Miner Electrolyte Metab*. 1986;12:226-233.
11. Ethier JH, Kamel KS, Magner PO, Lemann J Jr, Halperin ML. The transtubular potassium concentration in patients with hypokalemia and hyperkalemia. *Am J Kidney Dis*. 1990;15:309-315.
12. Cheng NL, Kao MC, Hsu YD, Lin SH. Novel thiazide-sensitive Na-Cl cotransporter mutation in a Chinese patient with Gitelman's syndrome presenting as hypokalaemic paralysis. *Nephrol Dial Transplant*. 2003;18:1005-1008.
13. Narins RG, Jones ER, Stom MC, Rudnick MR, Bastl CP. Diagnostic strategies in disorders of fluid, electrolyte and acid-base homeostasis. *Am J Med*. 1982;72:496-520.
14. Weiner ID, Wingo CS. Hypokalemia: consequences, causes and correction. *J Am Soc Nephrol*. 1997;8:1179-1188.
15. Gennari FJ. Hypokalemia. *N Engl J Med*. 1998;339:451-458.
16. Berl T, Linas SL, Aisenbrey GA, Anderson RJ. On the mechanism of polyuria in potassium depletion: the role of polyuria. *J Clin Invest*. 1977;60:620-625.
17. Marples D, Frokiaer J, Dorup J, Knepper MA, Nielsen S. Hypokalemia-induced down-regulation of aquaporin-2 water channel expression in rat kidney medulla and cortex. *J Clin Invest*. 1996;97:1960-1968.
18. West ML, Marsden PA, Richardson RMA, Zettle RM, Halperin ML. New clinical approach to evaluate disorders of potassium excretion. *Miner Electrolyte Metab*. 1986;12:234-238.
19. Halperin ML, Kamel KS. Electrolyte quintet: potassium. *Lancet*. 1998;352:35-40.
20. Kamel KS, Ethier JH, Richardson RM, Bear RA, Halperin ML. Urine electrolytes and osmolality: when and how to use them. *Am J Nephrol*. 1990;10:89-102.
21. Elisaf M, Siamopoulos KC. Fractional excretion of potassium in normal subjects and in patients with hypokalemia. *Postgrad Med J*. 1995;71:211-212.
22. Agarwal R, Afzalpurkar R, Fordtran JS. Pathophysiology of potassium absorption and secretion by the human intestine. *Gastroenterology*. 1994;107:548-571.
23. Kim HJ, Yoon YM, Park KN. The change in electrolytes and acid-base after artificially induced acute diarrhea by laxatives. *J Korean Med Sci*. 1994;9:388-393.
24. Conway MJ, Seibel JA, Eaton RP. Thyrotoxicosis and periodic paralysis: improvement with beta blockage. *Ann Intern Med*. 1974;81:332-336.
25. Kodali VRR, Jeffcote B, Clague RB. Thyrotoxic periodic paralysis: a case report and review of the literature. *J Emerg Med*. 1999;17:43-45.
26. Manoukian MA, Foote JA, Crapo LM. Clinical and metabolic features of thyrotoxic periodic paralysis in 24 episodes. *Arch Intern Med*. 1999;159:601-606.
27. Sterns RH, Cox M, Feig PU, Singer I. Internal potassium balance and the control of the plasma potassium concentration. *Medicine*. 1981;60:339-354.
28. Gallagher EJ. Is thyrotoxic periodic paralysis a channelopathy? *J Emerg Med*. 1999;17:123-127.
29. Dias da Silva MR, Cerutti JM, Tengan CH, et al. Mutations linked to familial hypokalemic periodic paralysis in the calcium channel α1 subunit gene (*Cav1-1*) are not associated with thyrotoxic hypokalemic periodic paralysis. *Clin Endocrinol (Oxf)*. 2002;56:367-375.
30. Simon DB, Nelson-Williams C, Bia MJ, et al. Gitelman's variant of Bartter's syndrome, inherited hypokalemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. *Nat Genet*. 1996;12:24-30.
31. Peters M, Jeck N, Reinalter SS, et al. Clinical presentation of genetically defined patients with hypokalemic salt-losing tubulopathies. *Am J Med*. 2002;112:183-190.
32. Cruz DN, Shaer AJ, Bia MJ, Lifton RP, Simon DB. Gitelman's syndrome revisited: an evaluation of symptoms and health-related quality of life. *Kidney Int*. 2001;59:710-717.
33. Tang NL, Hui J, To KF, Ng HK, Hjelm NM, Fok TF. Severe hypokalemic myopathy in Gitelman's syndrome. *Muscle Nerve*. 1999;22:545-547.
34. Tajima T, Kobayashi Y, Abe S, et al. Two novel mutations of thiazide-sensitive Na-Cl cotransporter (*TSC*) gene in two sporadic Japanese patients with Gitelman syndrome. *Endocr J*. 2002;49:91-96.

©2004 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 10/18/2014