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An Easily Missed Cause of Hypokalemia and Paralysis: Chronic Glue-Sniffing

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Chronic glue-sniffing for illegal recreation is a little-recognized but reversible cause of hypokalemia and paralysis. We report a case of a 28-year-old obese Chinese female who suffered from repetitive inability to ambulate upon waking in the morning. She presented to the emergency department with proximal muscle weakness and symmetrical areflexia of all four limbs. The major biochemical abnormalities were profound hypokalemia (1.8 mmol/L) with elevated urinary K^+ excretion (urine K^+ concentration ÷ urine creatinine concentration = 5.7 mmol/mmol) and hyperchloremic metabolic acidosis (pH 7.25; HCO_3^-, 14.0 mmol/L; Cl^-, 112 mmol/L). A negative urinary anion gap and high urinary ammonium excretion suggested that renal tubular acidosis was not present. When questioned about her drug history, the patient admitted to habitual daily glue-sniffing for six months. After cessation of glue-sniffing and supplementation with a large quantity of potassium chloride (860 mmol), her muscle strength returned and her serum K^+ concentration increased to 4.2 mmol/L without further recurrence. Chronic glue-sniffing should be considered when patients present with unexplained hypokalemic paralysis.

Key words: Glue-sniffing, hypokalemia, paralysis, renal tubular acidosis

INTRODUCTION

Hypokalemia with paralysis is a heterogeneous disorder characterized by acute, reversible muscle weakness and hypokalemia. Neuromuscular sequelae, cardiac arrhythmia or respiratory failure may endanger the health of patients with hypokalemia with paralysis. Immediate K^+ supplementation and rapid differential diagnosis are necessary to avoid these complications. The following indices are useful for differential diagnosis: transtubular potas–sium concentration gradient (TTKG), ratio of urinary K^+ concentration to urinary creatinine concentration (U_{K^+}/U_{Cr}), concentration of urinary electrolytes, urinary acid-base status[1].

Toluene is an aromatic hydrocarbon and is used in glues, cements and solvents. It is widely used as an industrial organic solvent. Habitual inhalation or sniffing of toluene-containing paint thinners or glues causes electrolyte and acid–base disturbances (hypokalemia, hypophosphatemia and metabolic acidosis), gastrointestinal disturbances (abdominal pain and hematemesis) and neuropsychiatric disorders (altered mental state, cerebellar abnormalities and peripheral neuropathy)[2]. Hypokalemia and paralysis are rarely observed. In this report, we describe a young, obese female who suffered from hypokalemia and paralysis after habitual sniffing of toluene-containing glue.

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CASE REPORT

A 28-year-old obese Chinese female suffered from a sudden onset of general muscular weakness of all extremities and an inability to ambulate upon waking in the morning. She was referred to our emergency department in October 2002. There was no evidence of nausea, vomiting, diarrhea, palpitations, excessive sweating, symptoms of hyperthyroidism or use of steroids or diuretics.

Her family history was noncontributory. She weighed 84 kg and her height was 1.57 meters (body mass index 38.5). She was alert, had normal blood pressure (120/70 mmHg), a rapid heart rate (124 beats/min), a respiratory rate of 18 breaths/min and a body temperature of 36.9 °C. Skin turgor was low, the jugular vein was flattened and the mucosa of the mouth was dry. The thyroid gland was not enlarged. The heart rate was rapid and regular without audible murmurs. Neurological examination revealed symmetrical flaccid paralysis with grade 3/5 muscular strength and areflexia of all four limbs.

The results of laboratory tests are shown in Table 1. Profound hypokalemia (K^+, 1.8 mmol/L) and hyperchloremic metabolic acidosis (Cl^-, 112 mmol/L; HCO_3^-,

Table 1. Biochemical studies on admission

	Normal range	On admission
Serum		
Na^+	(135-142 mmol/L)	137
K^+	(3.5-5.0 mmol/L)	1.8
Cl^-	(96-108 mmol/L)	112
HCO_3^-	(23-25 mmol/L)	14.0
pH	(7.38-7.42)	7.25
Total calcium	(8.1-10.4 mg/dL)	9.2
Inorganic phosphate	(2.6-4.5 mg/dL)	1.4
Urea nitrogen	(7-20 mg/dL)	1
Creatinine	(0.6-1.6 mg/dL)	0.8
Serum anion gap	(8-12 mEq/L)	11
Alkaline phosphatase	(64-306 U/L)	250
Albumin	(3.4-4.8 g/dL)	3.4
Urine		
pH		6.0
Na^+	(mmol/L)	58
K^+	(mmol/L)	6
Cl^-	(mmol/L)	71
NH_4^+	(mmol/L)	16
Urea nitrogen	(mg/dL)	34
Creatinine	(mg/dL)	12
Anion gap	(mEq/L)	-7
Osmolality	(mosm/kg.H_2O)	186
Osmolal gap	(mosm/kg.H_2O)	38
FE_{Na}	(%)	2.8
FE_K	(%)	22

14.0 mml/L; pH 7.25) were the most striking abnormalities. Concentrations of other biochemical indices were: Na^+, 137 mmol/L; inorganic phosphate, 1.4 mg/dL; total Ca^{2+}, 9.2 mg/dL; Mg^{2+}, 2.0 mg/dL; urea nitrogen, 1.0 mg/dL; creatinine 0.8, mg/dL; glucose, 102 mg/dL. Spot urine analyses revealed renal K^+ wasting (TTKG, 5.2; UK^+/U_{Cr}, 5.7 mmol/mmol). An electrocardiogram revealed sinus tachycardia and prominent U waves. A normal serum anion gap concomitant with metabolic acidosis and a negative urinary anion gap of -7, an index of high NH_4^+ excretion, indicated the renal tubular acidosis was unlikely. Our tentative diagnosis was hypokalemic paralysis with depleted volume status due to surreptitious use of a diuretic or laxative for weight reduction.

Intravenous infusion of KCl at a rate of 20 mmol/h was administered for 35 hours. Then oral KCl (Slow-K®) was provided at a rate of 600 mg twice per hour for the following 10 hours. After 45 hours, her muscular strength returned to normal and her serum K^+ concentration reached 2.6 mmol/L, at which time 860 mEq K^+ supplement had been administered. Although serum K^+ concentration increased to 3.5 mmol/L, the $NaHCO_3$ loading test was employed to rule out the possibility of renal tubular acidosis. A normal fractional excretion of HCO_3^- (7.1%) and urine-blood CO_2 gradient (34 mmHg) in alkaline urine (pH 7.5) were noted. During a detailed inquiry into her medication and drug history, she admitted to habitual use of glue to achieve an euphoric state because of her depressive mood during the previous six months. A psychologist was consulted who helped her abstain from glue-sniffing. Her serum K^+ and acid–base status remained in the normal range without further recurrence or sequelae by the two-year follow-up.

DISCUSSION

The patient presented with quadriplegia, hypokalemia and hyperchloremic metabolic acidosis. The procedure for differential diagnosis of hypokalemia is tedious, but fewer alternatives need be considered for differential diagnosis of hypokalemia with paralysis[3]. In general, patients with hypokalemic periodic paralysis (HPP) caused by an acute influx of K^+ into the cells have low urinary K^+ excretion and a relatively normal acid–base status. In contrast, patients with hypokalemia with paralysis caused by K^+ deficit (non-HPP) usually have high urinary K^+ excretion associated with either hypochloremic metabolic alkalosis or hyperchloremic metabolic acidosis. Direct measurement or indirect estimation of urinary ammonium excretion from the urinary anion gap and the osmolar gap facilitates definitive diagnosis of non-HPP with metabolic alkalosis; evaluation of blood pressure, plasma renin activity and aldosterone concentration facilitates definitive diagnosis of non-HPP with metabolic acidosis[4]. Only small doses of KCl are needed to avoid rebound hyperkalemia in patients with HPP whereas higher doses of KCl should be administered to replace the substantial K^+ deficiency in patients with non-HPP[5].

In patients such as ours, a low urinary K^+ concentration (6 mmol/L) in the presence of profound hypokalemia may result in a diagnosis of poor K^+ intake, gastrointestinal K^+ loss, or increased K^+ shift into the cells. Although a urine osmolality less than the plasma osmolality invalidates the use of TTKG, both U_{K^+}/U_{Cr} (5.7 mmol/mmol) and the fractional excretion of K (FE_{K^+}) (20 >10%) were high, indicating that hypokalemia was primarily due to excessive renal K^+ excretion. Her hyperchloremic normal serum anion gap metabolic acidosis was accompanied by high urinary excretion of NH_4^+ reflected as a negative urinary net anion gap, suggesting that extrarenal loss of bicarbonate, renal loss of potential bicarbonate and preceding acid production occurred with excessive renal excretion of the accompanying anion rather than renal tubular acidosis. Extrarenal bicarbonate loss was excluded because there were no indications of profound diarrhea or surreptitious use of laxatives. Chronic glue-sniffing was established as the cause of her condition because she admitted sniffing

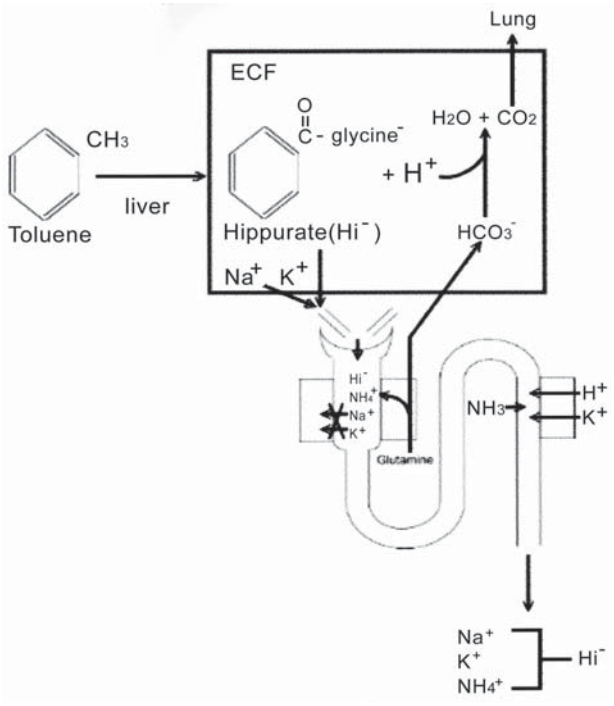

Fig. 1 Metabolism and excretion of toluene

glue for six months and other causes of hypokalemia were excluded.

Patients with glue-sniffing induced hypokalemia with paralysis are often diagnosed as having renal tubular acidosis or having been overzealous in their use of laxatives because of the presence of hyperchloremic metabolic acidosis. In addition, the possibility of toluene abuse is often neglected by clinicians or is not disclosed by patients. The clinical presentations of chronic glue-sniffing are variable but mainly involve the neuropsychiatric, gastrointestinal and muscular systems. Electrolyte and acid/base abnormalities such as hypokalemia, hypophosphatemia and hyperchloremic metabolic acidosis have never been reported in cases of toluene abuse[6-12]. Toluene (methylbenzene), a volatile compound, is inhaled during the sniffing of glue and accumulates in fat tissue. Methylbenzene is initially metabolized to benzoic acid in the liver through the cytochrome P-450 enzyme system and alcohol aldehydrogenases. An acid load (H^+) is incurred during this metabolic process. Benzoic acid conjugates with the amino acid, glycine, to form hippurate, which is excreted by filtration or tubular secretion in the urine at an extremely rapid rate along with the cations, NH_4^+, K^+, or Na^+ (Fig. 1). When hippurate is excreted together with NH_4^+, the acid load is neutralized by renal production of HCO_3^-. If hippurate is excreted together with K^+, metabolic acidosis and hypokalemia results. When hippurate is excreted with Na^+, loss of extracellular fluid volume will decrease the glomerular filtration rate. In the event of reduced glomerular filtration, the rates of excretion of both NH_4^+ and hippurate will decrease further, prolonging the duration of acidemia and possibly increasing the plasma anion gap. On the other hand, if ECF volume contraction is avoided by adequate Na^+ and fluid intake, toluene intoxication should present as metabolic acidosis with a normal anion gap[13]. People with low body weights, those that abuse drugs or alcohol (which activates the cytochrome P-450 system) and those with coexisting K^+ loss or a shift of K^+ into the cells have elevated susceptibility to hypokalemic paralysis.

Table 2 Laboratory findings in different status of glue-sniffing

Laboratory data	Early	Late	Renal failure
ECF volume	↓	↓ ↓	variable
Serum hippurate	↑ ↑	negative	↑ ↑ ↑
Serum anion gap	normal or slightly ↑	Normal	↑
Urine anion gap	Positive	negative	Positive
Urine NH_4^+ excretion	↑	↑ ↑	↓

In addition to serum electrolyte concentrations and acid–base status, estimates of urinary anion gap and NH_4^+ excretion are helpful for predicting the clinical course of toluene intoxication (Table 2). After toluene is inhaled, it is rapidly metabolized to hippurate and excreted with NH_4^+, Na^+ and K^+ in the urine. Because the production of hippuric acid exceeds its excretion, the serum anion gap is normal or slightly elevated. At this stage, urinary hippurate is mainly excreted with Na^+ and K^+, which results in a positive anion gap in the urine. When some time has elapsed after glue-sniffing, the extracellular fluid volume decreases and urinary NH_4^+ excretion increases in response to the acid load. A normal serum anion gap and a negative urinary anion gap with a high rate of urinary NH_4^+ excretion is expected. In patients with preexisting renal failure or hippurate-induced severe volume depletion with acute renal failure, the urinary excretion of hippurate and H^+ will be much impeded, resulting in the retention of serum hippurate and the generation of a high serum anion gap. Under these conditions, low urinary NH_4^+ excretion and a positive urinary anion gap is often present.

It is noteworthy that the low serum urea nitrogen concentration in our patient may also have been indicative of chronic glue-sniffing. Although a low protein diet or high urinary NH_4^+ excretion could have caused the low serum urea concentrations, benzoate, which is generated during the metabolism of toluene, can conjugate glycine, a com-

mon precursor for gluconeogenesis and ureagenesis, into hippurate, thus increasing the disposal of urea nitrogen and inducing low serum urea concentrations.

Two points concerning therapy of glue-induced metabolic acidosis associated with hypokalemic paralysis should be emphasized. Aggressive K^+ supplementation at a rate of 20 mmol per hour should be applied immediately because of the large deficit of K^+. Alkali therapy with $NaHCO_3$ should be postponed until K^+ is replenished because alkali therapy will aggravate the hypokalemia and can result in life-threatening conditions such as acute respiratory failure and fatal cardiac arrhythmia. Because the patient usually has volume depletion with enhanced adrenergic activity, which causes reduced K^+ movement into cells in a way similar to that in diabetic ketoacidosis, a paradoxical fall in K^+ concentration is usually evident during KCl supplementation. This is the reason why such patients require 860 mmol KCl to restore muscle strength and at least 1000 mmol KCl to achieve normal serum K^+ concentrations. If the patient abuses alcohol or is obese, acidosis may be elevated as a result of induction of the cytochrome P-450 system by alcohol or by greater storage capacity for toluene in those with excess amounts of adipose tissue[13]. The outcome is usually good with rapid and complete recovery within several days. However, respiratory failure and even death have been reported[14,15]. Hemodialysis has been used in cases of severe toluene-induced hypokalemia with respiratory failure. A K^+-rich dialysis bath for rapid reversal of life-threatening toluene-induced hypokalemia via passive diffusion may reduce the burden of toluene but the magnitude of the reduction would not be substantial because of the large volume of distribution and fat solubility of toluene[16].

In conclusion, severe hypokalemia with paralysis is a potentially life-threatening medical emergency. Besides KCl supplementation, a vigorous search for the underlying causes of hypokalemia with paralysis, including a detailed history, is warranted to avoid missing treatable causes such as chronic glue-sniffing. As inhalation of toluene-containing solvents and glues is now widespread, it is important for physicians include chronic glue-sniffing as a potential cause of hypokalemic paralysis.

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