Hypokalemic Periodic Paralysis: An Unusual Cause

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Hypokalemic periodic paralysis is a rare disorder characterized by transient attacks of flaccid paralysis of varying intensity and frequency. Although mostly familial in etiology, several sporadic cases with different causes have been reported, including some resulting from renal tubular acidosis.[1] This article reports the case of a young man with secondary hypokalemic periodic paralysis caused by distal renal tubular acidosis, which was precipitated by glue sniffing.

CASE PRESENTATION

History

A 27-year-old man with a 13-year history of HIV infection came to the hospital because of a 24-hour history of episodic, gradually increasing weakness of the lower extremities. He reported having had similar episodes twice previously, most recently 6 weeks ago; on those occasions, parenteral administration of fluids improved his condition. Resting after exercise or eating did not precipitate the weakness, and there was no family history of similar illness. He reported no bladder or bowel involvement and had no history of fever, cough, or any recent illness. He had received a diagnosis of distal renal tubular acidosis with hypertension 7 months previously. Despite the strong smell of solvent emanating from him, the patient reported no history of glue sniffing, although family members suggested such a history.

Along with his antiretroviral medications (lamivudine 150 mg orally daily, efavirenz 600 mg once daily) his treatment regimen included metoprolol succinate 200 mg orally daily and diltiazem extended-release capsules 240 mg orally daily. He also had been prescribed potassium and bicarbonate supplementation. The patient, however, was poorly compliant and was taking no medications at the time of hospital admission and his other episodes of lower extremity weakness.

Physical Examination

On examination, there was a strong smell of solvent emanating from the patient. He was alert, awake, and oriented. Vital signs were stable, with normal heart rate and rhythm. Lungs were clear to auscultation, and abdominal examination revealed no abnormalities. Cranial nerves were all intact. The patient had hypotonic weakness in all four limbs (grade 3/4 strength) and generalized hyporeflexia. Plantar reflexes were negative, and there was no sensory deficit.

Laboratory Evaluation

Laboratory examination revealed a normal anion gap and hyperchloremic metabolic acidosis with severe hypokalemia. Blood urea nitrogen, serum creatinine, and uric acid levels were within normal limits. Results of a urine drug screen were negative. Urinalysis revealed a pH of 5.5, a specific gravity of 1.006, and no proteinuria or glycosuria. The patient was unaware of his last CD4+ cell count or his viral load.

Treatment

The patient was treated with intravenous administration of normal saline solution, potassium chloride, and sodium bicarbonate, which resulted in resolution of symptoms. He was advised to continue taking potassium and alkali supplementation along with his antiretroviral medications. He was also cautioned against the dangers of glue sniffing.

DISCUSSION

Hypokalemic Periodic Paralysis

Hypokalemic periodic paralysis can be classified as primary (familial) or secondary. The primary type of hypokalemic periodic paralysis is most common and is characterized by autosomal dominant inheritance and definite precipitating factors (eg, high dietary intake of carbohydrates, exposure to cold). Serum potassium levels are normal during the asymptomatic period and

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Table 1. Causes of Secondary Hypokalemic Periodic Paralysis

Barium poisoning
Gastrointestinal potassium wasting disorders
Licorice ingestion
Primary hyperaldosteronism
Renal potassium wasting disorders (eg, renal tubular acidosis)
Thyrotoxicosis

generally are only mildly reduced during the period of muscle weakness.

In contrast, secondary hypokalemic periodic paralysis is less common.[2] Clues indicating a secondary cause are the lack of family history and the time of onset of symptoms. Patients who have their first attack of weakness in adulthood should be screened carefully for a secondary cause.[3] Secondary hypokalemic periodic paralysis is nongenetic in origin and results from causes such as thyrotoxicosis, barium poisoning, primary hyperaldosteronism, licorice ingestion, and gastrointestinal potassium wasting disorders (**Table 1**). Renal tubular acidosis (RTA) can also cause hypokalemic periodic paralysis, as illustrated in the case presented. There are no specific precipitating factors. Serum potassium levels are less than 3 mEq/L in the asymptomatic period and decrease further during the attacks.[3]

Renal Tubular Acidosis

RTA is a metabolic hyperchloremic acidosis that occurs in patients with a nonazotemic renal acidification defect. RTA is characterized by decreased excretion of hydrogen ion in the urine. The 2 major types of RTA are proximal and distal (**Table 2**).

Proximal RTA is characterized by a large excretion of bicarbonate in the urine, resulting in alkaline urine and development of hyperchloremic metabolic acidosis. Proximal RTA may be detected by the presence of concomitant defects in proximal reabsorption, such as aminoaciduria, glycosuria, and phosphaturia. The hallmark of proximal RTA is normal acidification of the urine in the presence of normal renal function when plasma bicarbonate concentrations are low. Administration of exogenous sodium bicarbonate further increases excretion of alkaline urine, driving potassium into the cells, and so should be preceded by administration of potassium when the serum potassium level is below normal.

Distal, or classic, RTA is characterized by a defect of the distal nephron in its ability to excrete hydrogen ion. The normal kidney can lower urine pH to 4.7, maintaining a urine concentration to plasma concentration ratio for hydrogen of approximately 800:1. However, in patients with distal RTA, the urine pH cannot fall below 6, regardless of the severity of the systemic acidosis. Distal RTA occurs in a sporadic congenital primary form, in certain hypergammaglobulinemic states, in nephrocalcinosis (which may result from various genetic and metabolic disorders), in distal tubule nephrotoxicity caused by certain drugs (eg, amphotericin B, excessive vitamin D, toluene), in medullary sponge kidney, and in interstitial renal disease (eg, pyelonephritis, collagen disorders). Distal RTA may also develop after renal transplantation.

Principal findings that lead to a strong suspicion of RTA are metabolic acidosis (ie, low serum bicarbonate level, low serum pH), normal blood urea nitrogen level, alkaline or neutral urine (ie, pH consistently above 5.9

Table 2. Comparison of 3 Types of Renal Tubular Acidosis*

Finding	Type 1 (Distal)	Type 2 (Proximal)	Type 4 (Generalized (Distal)
Non–anion gap acidosis	Yes	Yes	Yes
Minimum urine pH	> 5.5	< 5.5	< 5.5
Percentage of filtered bicarbonate excreted	< 10%	> 15%	< 10%
Serum potassium level	Low	Low	High
Fanconi's syndrome	No	Yes	No
Stones/nephrocalcinosis	Yes	No	No
Daily acid excretion	Low	Normal	Low
Ammonium excretion	High for pH	Normal	Low for pH
Daily bicarbonate replacement needs	< 4 mmol/kg	> 4 mmol/kg	< 4 mmol/kg

*Type 3 renal tubular acidosis is a rare form and represents a combination of types 1 and 2. This designation is no longer used.

Adapted with permission from Asplin JR, Coe FL. Hereditary tubular disorders. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, editors. Harrison's principles of internal medicine. 14th ed. New York: McGraw-Hill, Health Professions Division; 1998:1566.

on an average diet with inability to go below 5.5 after loading with ammonium chloride), and typical electrolyte abnormalities (eg, hyperchloremia, hypokalemia, hypocalcemia).

Hypokalemia

Hypokalemia is a cardinal feature of distal RTA. The degree of hypokalemia in this disorder is not directly correlated to the degree of acidosis but more likely reflects dietary sodium and potassium intake and serum aldosterone concentrations. Life-threatening hypokalemia (ie, serum potassium level < 2.0 mmol/L) can occur in patients with untreated distal RTA.[4] The administration of sodium bicarbonate ameliorates the hypokalemia, but potassium supplementation is usually required on a long-term basis to manage this disorder.[5,6]

The most common cause of hypokalemia is excess renal potassium loss. This can occur either because of administration of medications, endogenous hormone production or, in rare cases, intrinsic renal defects. **Table 3** summarizes these causes. Toluene exposure, which can result from sniffing certain glues, can also cause hypokalemia, presumably by renal potassium wasting.[7] The precise amount or frequency of toluene exposure that leads to potassium wasting (and RTA) has not been identified in the literature.

Hypokalemia severe enough to cause extensive paralysis has occasionally been reported as a complication of RTA. Distal and proximal RTA are commonly associated with kaliuresis and hypokalemia. In proximal RTA, kaliuresis is caused by an increase in the delivery of bicarbonate to the distal secretory sites, resulting in increased potassium secretion. In distal RTA, however, there is excessive potassium secretion, which facilitates sodium reabsorption.[8]

More complicated diagnostic tests of renal function have been developed, such as hydrogen ion clearance indices and paper chromatographic studies of urine to determine amino acid content. These studies, when they can be performed, help to conclusively establish the diagnosis and to aid in the understanding of RTA.[9]

Toluene Exposure and Renal Tubular Acidosis

RTA—distal, proximal, and associated with Fanconi's syndrome—has been linked to exposure to toluene or toluene-containing substances. Deliberate inhalation of such volatile hydrocarbons among teenagers is an increasing social problem. Popularly referred to as glue sniffing, this practice may be associated with neurologic, hematologic, hepatic, and renal toxic effects and can cause sudden death from cardiac arrhythmias.[2]

Table 3. Causes of Renal Potassium Loss

Drugs
Antibiotics: penicillin and penicillin analogues, amphotericin B, aminoglycosides
Diuretics: thiazides, loop diuretics, osmotic diuretics
Hormones: aldosterone and glucocorticoid excess states
Bicarbonaturia
Correction phase of metabolic alkalosis
Distal renal tubular acidosis
Treatment of proximal renal tubular acidosis
Magnesium deficiency
Primary hyperaldosteronism*
Intrinsic renal transport defects
Bartter's syndrome
Gitelman's syndrome
Liddle's syndrome
Other, less common causes
Ammonium chloride ingestion
Carbonic anhydrase inhibitor administration
Cisplatin administration
Diuretic phase of acute tubular necrosis
Leukemia
Licorice ingestion
Recovery phase of diabetic coma
Toluene toxicity

*Conn's syndrome.

The case patient experienced repeated episodes of hypokalemic periodic paralysis while not taking antiretroviral medications or potassium and bicarbonate supplementation. The constellation of clinical and biochemical findings were consistent with a diagnosis of distal RTA, most likely caused by toluene inhalation. The smell of solvent emanating from the patient and the history provided by his family supported our suspicions that he had been sniffing glue.

The deliberate inhalation of volatile substances for recreational purposes (ie, volatile substance abuse), also known as solvent abuse or glue sniffing, is not a new phenomenon. The compounds used as early anesthetics (eg, diethyl ether, chloroform, nitrous oxide) were among the first used for recreational purposes. The modern consumer society provides a wide range of products containing volatile compounds, many of which may be abused (**Table 4**). Inhalant abuse in

Table 4. Products Involved in Solvent Abuse and Their Principal Constituents

Product	Main Solvents
Aerosols	Dichlorodifluoromethane (propellant 12), trichlorofluoromethane, isobutane
Fingernail polish	Acetone, aliphatic acetates, benzene, alcohol
Gasoline	Mixture of petroleum hydrocarbons, paraffins, naphthenes, aromatics (chiefly, benzene, toluene, xylenes)
Household cements	Toluene, acetone, isopropanol, methyl ethyl ketone, methyl isobutyl ketone
Lacquer fluid and cleaning fluid	Naphtha, perchlorethylene, carbon tetrachloride, trichloroethane
Model cements	Acetone, toluene, naphtha
Plastic cements	Toluene, acetone, aliphatic acetates (eg, ethyl acetate, methyl cellosolve acetate)

Table 5. Renal Syndromes Associated with Toluene Inhalation

Syndrome	Substance Inhaled
Abnormal urinalysis	Lacquer thinner, various toluene compounds
Acute renal failure	Toluene, adhesive
Chronic renal failure	Glue
Distal RTA	Glue, paint, transmission fluid, lacquer thinner, various toluene compounds, toluene
Fanconi's syndrome	Glue
Hepatorenal syndrome	Cleanser
High–anion gap acidosis	Transmission fluid
Nephrolithiasis	Toluene

RTA = renal tubular acidosis.

Adapted with permission from Patel R, Benjamin J Jr. Renal disease associated with toluene inhalation. J Toxicol Clin Toxicol 1986;24: 213–23.

general has been linked to sudden death and chronic damage to the heart, lungs, kidneys, liver, peripheral nerves, and brain.[10,11]

The renal toxicity of volatile glues appears to be caused by toluene. Various renal disorders have been associated with toluene abuse (**Table 5**), including distal RTA, high–anion gap metabolic acidosis, Fanconi's syndrome, urinary calculi, glomerulonephritis, and Goodpasture's syndrome. Hematuria, sterile pyuria, and proteinuria in the presence of otherwise normal renal function have been described in chronic toluene abusers.[12] Toluene inhalation should be considered in the differential diagnosis in any young patient who presents with an unexplained renal disorder.

Table 6. Pathophysiology of Metabolic Acidosis in Cases of Toluene Abuse

- High rate of production of organic acids (eg, hippuric, benzoic acids) in the presence of normal renal function
  - Usually resulting in hyperchloremic acidosis
  - Presence of a wide anion gap, if production exceeds excretion of these anions
- High rate of production of organic acids with the presence of some impairment in the rate of excretion of ammonium ion
  - High rate of production of hippuric and benzoic acids in the presence of normal renal function
  - Low rate of excretion of ammonium ion
    - Reduced production of ammonium ion in the renal cortex
    - Usually resulting in a low glomerular filtration rate
    - Low transfer of ammonium ion to the urine (low secretion of hydrogen ion in the distal nephron)
    - Related to a direct effect of toluene?
    - Medullary damage that is an indirect effect of toluene or unrelated to this agent
- Other causes of metabolic acidosis unrelated to toluene

Adapted with permission from Carlisle EJ, Donnelly SM, Vasuvattakul S, et al. Glue-sniffing and distal renal tubular acidosis: sticking to the facts. J Am Soc Nephrol 1991;1:1019–27.

The mechanism by which toluene interferes with the hydrogen ion gradient in distal renal tubules may be related to structural damage to the tubular epithelium or inhibition of intracellular processes. A spectrum of pathophysiologic mechanisms is responsible for metabolic acidosis associated with toluene abuse (**Table 6**). It remains unclear, however, whether the renal toxicity of glue sniffing is caused by toluene directly or by one of its metabolites. Toluene-induced RTA appears to be reversible with prolonged abstinence from volatile solvents.

Treatment of Secondary Hypokalemic Periodic Paralysis

Treatment of secondary hypokalemic periodic paralysis involves treatment of the primary cause and maintenance of serum potassium levels within the normal

range. Three salts are available for repletion of body potassium stores: potassium chloride, potassium phosphate, and potassium bicarbonate. Potassium phosphate is used to replace phosphate losses. Potassium combined with bicarbonate or an organic anion is only recommended when potassium depletion occurs with metabolic acidosis. In all other situations, potassium chloride should be used because of its unique effectiveness in treating the more common causes of potassium depletion.[13]

CONCLUSION

A constellation of renal abnormalities may occur as a consequence of toluene inhalation, ranging from abnormal results on urinalysis in an asymptomatic patient to symptomatic acute and chronic renal failure. Neither the number of toluene inhalation incidences nor the number of patients who develop these complications is known. Thus, any patient who presents with unexplained quadriparesis, rhabdomyolysis, RTA, or other renal disease should be questioned about the possibility of toluene inhalation. **HP**

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