Attending Rounds: Patient with Hypokalemia and Metabolic Acidosis

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Summary
Hypokalemic paralysis represents a medical emergency requiring both rapid diagnosis and treatment. In this Attending Rounds a patient with hypokalemia and metabolic acidosis is presented to emphasize the role of routine laboratory studies in the assessment of such patients so that a correct diagnosis can be made and appropriate treatment can be initiated promptly.


Introduction
A 39-year-old woman who had been in excellent health presented with a chief complaint of weakness in her lower extremities. She gave a history of intermittent vomiting for the past 2 months that was worse over the past 3 days. Two weeks before admission she was found to be positive for Helicobacter pylori antigen and was treated with amoxicillin, clarithromycin, and lanosoperazole. One day before admission she was seen in the emergency department complaining of 3 days of vomiting. The serum lipase was mildly elevated, and she was diagnosed with mild pancreatitis. The serum potassium concentration was 3.1 mEq/L. She was treated with intravenous fluids and prochlorperazine and sent home. On the day of admission, she noted onset of bilateral lower extremity weakness, inability to walk without a cane, and profound fatigue. She also stated that she had been having intermittent leg cramps and that she recalled having been told previously that she had a low serum potassium level on several occasions.

Her past medical history was unremarkable aside from migraine headaches during her menses. She took no medicines on a regular basis and denied use of nutritional supplements or herbs. She also reported no unusual dietary intake. She was married with one child and reported no tobacco, alcohol, or drug use. She had no occupational exposures. Her mother died in her 70s with what was thought to be either scleroderma or SLE, her father died at 81 years of intestinal obstruction, and she had two living brothers, one who had discoid lupus. A review of systems was unremarkable except for the symptoms described above.

On physical examination, she appeared weak and was shaking with any exertion. Her vital signs were as follows: temperature 98.5°F, heart rate 100/min, respiratory rate 20/min, BP 113/85 mmHg, and O₂ saturation 99% on room air. The conjunctiva were pink, and the oral mucosa was dry. Lungs were clear, and heart sounds were normal. The abdomen was mildly obese with normal bowel sounds and mild right upper quadrant and epigastric tenderness without hepatosplenomegaly. The neurologic exam was normal except for motor strength that was graded as 4/5 in the distal upper extremities, 3/5 in the proximal upper extremities, 4/5 in the distal lower extremities, and 1/5 in the proximal lower extremities. There was hyper-reflexia and gross tremor with extended effort.

Initial lab tests are shown in Table 1, with additional tests on admission showing creatine phosphokinase 241 U/L, MB 4 ng/ml, troponin I <0.03 ng/ml, liver function tests all within normal limits, total protein 9.4 g/dl, albumin 4.2 g/dl, globulin 5.2 g/dl, amylase 76 U/L, lipase 343 U/L, and erythrocyte sedimentation rate 45 ml/h. Electrocardiogram showed sinus rhythm, rate 96/min, and QTc 482 ms, with inferolateral ST depression. No U-waves were seen. Chest x-ray was unremarkable.

In the emergency department a central line was placed, and she received 80 mEq of KCl in 2 L of normal saline before being admitted to the hospital with telemetry monitoring. Additional tests included the following: arterial blood gas pH 7.26, Pco₂ 19 mmHg, Po₂ 147 mmHg, and bicarbonate 8 mEq/L, urinalysis pH 7.0, specific gravity 1.005, protein 1+, blood 1+, white blood cells 2 to 3/high-power field (hpf), and red blood cells 1 to 2/hpf. The urine K⁺ was 14.6 mmol/L. Later that night the patient complained of worsening weakness, and she was unable to hold a cup or lift her head off the pillow. A repeat serum K⁺ was 1.7 mEq/L. Forced vital capacity was 39% of predicted. She was subsequently given 480 mEq of oral and intravenous KCl overnight along with intravenous and oral phosphorous supplementation.

Case Discussion
In summary, this patient was admitted with the inability to walk. Physical examination indicated that this was primarily due to proximal muscle weakness, worse in the lower than upper extremities. Laboratory
Hypokalemia due to poor intake is most commonly seen in patients with malnutrition, anorexia nervosa, alcohol dependence, or a severely and chronically potassium-deficient diet. Although obligate urinary sodium losses can approach zero, there is an obligate renal and extrarenal potassium loss estimated to be about 10 to 15 mEq/d. This loss over time could lead to profound hypokalemia if intake is also poor. Our patient did not consume alcohol and was on a regular diet. Her oral intake had decreased recently due to nausea and vomiting, but this alone was unlikely to be the primary cause of such profound hypokalemia. We therefore should initially focus on increased urinary potassium output as the major underlying cause of her chronic hypokalemia, while searching for additional factors that could explain the additional recent rapid decline in serum potassium concentration.

Potassium losses can be renal and/or extrarenal in origin. The source of potassium loss can be ascertained by evaluating renal handling of potassium during hypokalemia. Normally potassium is freely filtered and extensively reabsorbed in the proximal tubule and loop of Henle, so that only about 10% of the filtered load of potassium reaches the distal convoluted tubule. In this segment and in the collecting duct potassium is passively secreted under the influence of multiple factors, most importantly potassium intake, sodium delivery, transepithelial potential difference, urine flow rate, and aldosterone level (3). The final urinary potassium excretion is a reflection of potassium secretion in the distal nephron. As indicated above there is an obligatory daily potassium loss of potassium by the gastrointestinal tract and kidney. However, a urinary potassium concentration >15 mEq/d in a patient with significant hypokalemia points to abnormal renal loss of potassium.

In patients with vomiting or diarrhea activation of the renin-angiotensin-aldosterone system due to volume depletion would be expected to lead to renal potassium loss. This hormonal influence is counterbalanced by a direct inhibitory effect of hypokalemia on aldosterone secretion. In addition, angiotensin II enhances proximal and distal convoluted sodium reabsorption by stimulating the Na⁺-H⁺ exchanger and NaCl cotransporter, respectively. This decreases sodium delivery to the more distal potassium secretory sites, reducing a major driving force for potassium secretion. With vomiting, compared with diarrhea, potassium loss in the urine is generally greater due to obligate loss of potassium secondary to bicarbonaturia resulting from the metabolic alkalosis of vomiting. Although hypovolemia and hyperkalemia stimulate aldosterone secretion, their effect on the ROMK potassium channel, and therefore potassium secretion, is in opposite directions. Hypovolemia down regulates and hyperkalemia up regulates ROMK channel function. This paradoxical effect is mediated through a network of kinases, named WNK [with no lysine (K)] kinases that regulate multiple channels and transporters including the sodium-potassium-chloride cotransport system, the NaCl cotransporter, the epithelial sodium channel, and the ROMK potassium channel. The effect of aldosterone on potassium secretion, regulated through this network, is dependent on the initial signal causing the rise in this hormone and is different for hyper-

### Table 1. Selected laboratory values

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TCO₂ = total CO₂.

studies showed severe hypokalemia (K⁺ 1.8 mEq/L). Although the family history of connective tissue disease raised the possibility of a myopathy, the normal creatine kinase is against this diagnosis in our patient. In this patient, the severity of hypokalemia is such that it alone could explain the clinical presentation. The patient’s history indicates that hypokalemia, although milder, had been present for several years and is therefore chronic in nature. Interestingly her serum potassium concentration 3 days before admission was 3.1 mEq/L and then declined rapidly along with worsening of generalized weakness. Our initial differential diagnosis therefore must focus first on this highly abnormal laboratory finding.

Potassium is 98% intracellular. Hypokalemia can be caused by an intracellular shift of potassium, a decrease in potassium intake, and an increase in potassium output. The serum potassium concentration does not decline significantly until there is substantial total body potassium deficit and/or a shift of potassium from the extracellular fluid to the intracellular fluid space occurs. Although there is no accurate method to calculate the absolute amount of potassium deficit in a patient, she probably had a deficit in excess of 500 mEq based on the severity of her hypokalemia (1). This is also supported by the amount of potassium (560 mEq) given orally and intravenously in the first 24 hours to raise her serum potassium concentration from 1.8 to 3.7 mEq/L. Hypokalemia due to intracellular shift is most often seen in association with an acute increase in blood pH, an increase in serum catecholamines or insulin, rapid cell proliferation, or genetic or acquired defects resulting in hypokalemic periodic paralysis (2).

This patient also had a normal anion gap hyperchloremic metabolic acidosis (HCMA). The effect of acidemia on the serum potassium concentration depends on the nature of the acidosis as well its acuity, with the greatest effect seen with an acute mineral acidosis; there is little to no effect on serum potassium concentration with organic metabolic acidosis or respiratory acidosis (2). In our patient, if the metabolic acidosis was acute, causing potassium to be shifted out of cells, her total body potassium deficit would have been even greater than indicated by her serum potassium concentration. An intracellular shift of potassium can only explain acute hypokalemia but would not be a cause of chronic hypokalemia as was present in this patient.

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hypokalemia-induced compared with hypovolemia-induced increased aldosterone levels (for more detailed discussion see Reference 4).

Figure 1 shows a simple approach to the diagnosis of hypokalemia due to potassium loss in association with metabolic acid-base disturbances. We can quickly narrow our differential diagnosis by noting that our patient has HCMA. This combination of hypokalemia and HCMA can be due to loss of potassium and bicarbonate from either the gastrointestinal tract in the presence of diarrhea or the urinary tract. Our patient did not have a history of diarrhea. In addition, diarrhea-induced hypokalemia, as noted above, should be associated with appropriately low urine potassium excretion. In our patient the urinary potassium was reported to be 14 mEq/L, but one might wonder whether, given this patient’s dilute urine (specific gravity 1.005)—which could itself be a consequence of long-standing hypokalemia, if there was in fact a relatively large urine volume and therefore significant total potassium loss despite the low serum potassium concentration. If urinary osmolality is available, we could assess renal handling of potassium by calculating the transtubular potassium gradient (TTKG; urinary K⁺/plasma K⁺× urinary osmolality/plasma osmolality), which can be used to assess distal nephron potassium secretion while “correcting” for the effect of urinary concentration on the final urine potassium concentration. On a normal diet and with a normal serum potassium concentration, TTKG is between 7 and 9. On a high-potassium diet or with hyperkalemia the TTKG should be >11, and with a low-potassium diet or hypokalemia is should be <3. Proper use of the TTKG requires that the urine potassium concentration be >3. Despite lack of a more comprehensive evaluation, the data supporting renal potassium loss in association with HCMA is strongly supportive of the diagnosis of renal tubular acidosis (RTA) in our patient.

RTA is a group of disorders presenting as HCMA due to either renal loss of bicarbonate or inability to generate bicarbonate by the kidneys (Figure 2). We filter approximately 5000 mEq of bicarbonate daily and reabsorb 80% to 90% in the proximal tubule through secretion of hydrogen ion by the Na⁺-H⁺ cotransporter and to a lesser extent by a H⁺-ATPase. This process requires carbonic anhydrase, an enzyme located both in the brush border and intracellularly in renal epithelial cells. The remainder of filtered bicarbonate that is not reabsorbed in the proximal tubule is normally almost entirely reabsorbed in the more distal segments of the nephron. The kidneys also need to regenerate the bicarbonate used in neutralizing 50 to 70 mEq/d of acid in foodstuff. Bicarbonate regeneration results primarily from secretion of hydrogen by H⁺-ATPase pumps in α-intercalated cells of the collecting duct. Secreted hydrogen is buffered by titratable acids, primarily phosphate, and by ammonia produced in the proximal tubules. When faced with systemic acidosis, the kidneys are able to increase net acid excretion many fold, primarily by increasing ammoniagenesis and urinary ammonium excretion. A recently discovered G-protein–coupled receptor that accepts hydrogen as a ligand may be a sensor that relays information about changes in systemic pH to acid-secreting cells in the kidney (6). Although ammonia entry into collecting duct has been considered to be mostly passive, there is increasing evidence that this involves a specific membrane protein from the family of Rhesus proteins located in the distal nephron (7). A defect in this complex and highly integrated system resulting in decreased bicarbonate reclamation or regeneration would result in RTA (8).

Proximal RTA (PRTA) is due to a decreased capacity for bicarbonate reabsorption in the proximal tubule. Whereas some patients have only impaired proximal tubule bicarbonate reabsorption, others have a more diffuse proximal tubular defect with aminoaciduria, glucosuria, uricosuria, and phosphaturia (Fanconi syndrome). Isolated hereditary PRTA may be due to mutations in the basolateral membrane sodium bicarbonate cotransporter (9). Patients with PRTA are able to reclaim filtered bicarbonate fully only if the filtered load is low but not when it is normal. Therefore
the urine is alkaline when serum bicarbonate is above the reabsorptive capacity of the proximal tubule and acid (pH <5.3) when it is below this level. In contrast, distal RTA (DRTA) is characterized by a defect in urinary acidification resulting in persistently alkaline urine (Figure 2).

Genetic forms of DRTA can arise due to mutations in H^+ -ATPase or in the chloride bicarbonate anion exchanger (AE1), both of which are crucial for reclamation and regeneration of bicarbonate along the nephron (9). A rare form of combined proximal and distal tubular RTA is due to mutations in carbonic anhydrase II (CAII) (10). Type IV RTA, a defect in bicarbonate regeneration due to lack of urinary buffers, specifically ammonia, associated with acid urine and hyperkalemia (2), is not pertinent to this case and is not discussed further.

PRTA and DRTA can be readily distinguished by several clinical and laboratory findings. First, hypokalemia is usually milder in PRTA. Patients with PRTA may present with osteomalacia and rickets, whereas patients with DRTA are more likely to present with kidney stones and nephrocalcinosis. Several laboratory studies evaluating the urine pH and the degree of bicarbonate and ammonia excretion (estimated by calculation of the urinary anion gap) can be used to classify RTA (Figure 2) (8). The urine pH in DRTA is always >5.3 (and commonly 6) but <5.3 in the presence of acidemia patients with PRTA. However, when the acidosis is corrected with sodium bicarbonate or other alkalinizing therapy, patients with PRTA excrete bicarbonate in the urine with an alkaline urine pH. This distinction is the basis for the ammonium chloride test developed more than 50 years ago by Davis and Wrong (11). In this test an acute metabolic acidosis is generated through ingestion of ammonium chloride, and urine pH is measured. With PRTA, the urine pH will be <5.3, whereas with DRTA it remains >5.3. A test that combines the acidifying effects of furosemide and fludrocortisone can also be used to evaluate these patients (12). The sensitivity and specificity of this test needs to be established. Such testing is not required, however, if the serum bicarbonate concentration is already low and the urine pH is >5.3 because this establishes the diagnosis of DRTA and excludes PRTA. Another distinguishing feature is that metabolic acidosis will improve or correct with a small amount of daily supplemental bicarbonate (1 mEq/kg per day) in DRTA but not with PRTA, which requires much larger amounts of bicarbonate replacement due to urinary loss of bicarbonate because the serum concentration (and filtered load) increases. Urinary citrate excretion tends to be very low in DRTA but not other RTAs. The urinary anion gap, an indirect measure of urinary ammonium excretion, is negative (usually < −20 mEq/L) in normal subjects and is positive (usually > +20 mEq/L) in DRTA and type intravenous RTA (2). A more physiologic test is to measure fractional excretion of bicarbonate (HCO_3^−) at a serum bicarbonate concentration of about 22 mEq/L achieved by an intravenous HCO_3^− infusion. This should be zero in normal subjects, >15% with PRTA, and <5% with DRTA (Figure 2). There are other more sophisticated tests such as urine/plasma Pco_2 and sodium sulfate tests, which are rarely done clinically and will not be discussed here (8).

Should our patient have further tests to establish the nature of her RTA? Her urine pH was 7 on admission when her serum bicarbonate concentration was 8 to 12 mEq/L. This easily establishes a diagnosis of DRTA, and no further test is needed. However, the uric acid of 1.1 mg/dl and phosphate of 1.2 mg/dl are not expected with DRTA. Both uric acid and phosphate are reabsorbed primarily by the proximal tubule. The patient did not have glucosuria, and urinary amino acids were later shown to be normal. This suggests that she could have had a partial Fanconi syndrome and therefore a mixed PRTA and DRTA. We now need to explain her hypokalemia, leading to the question of how defects in renal bicarbonate and hydrogen handling cause urinary potassium wasting? One popular theory has been that obligatory sodium excretion resulting from bicarbonaturia in PRTA leads to hypovolemia and activation of the renin-angiotensin-aldosterone system and resultant hypokalemia. Hypovolemia is however usually very mild and clinically inapparent in patients with RTA, and as discussed above, should in itself not result in severe hypokalemia. Another possibility is loss of positively charged potassium ions accompanying the poorly reabsorbable bicarbonate anions. A defect in the H^+ -K^+ -ATPase pump in α-intercalated cells of the distal convoluted tubule could also lead to potassium loss and metabolic acidosis, but such an abnormality has not yet been well documented. The exact mechanism(s) leading to hypokalemia in RTA remain unknown (13).

Subsequent hospital course (Table 1): The patient was treated with 2 L of 0.9% saline and a total of 560 mEq KCl. She had greatly improved and was able to sit up in bed. The EKG normalized. She was started on oral potassium citrate 30 mEq twice daily. The initial treatment of this patient focused appropriately on her hypokalemia, the most serious life-threatening abnormality, rather than metabolic acidosis. The fluid infused was devoid of glucose as well as bicarbonate, which could have worsened her hypokalemia through rapid shifts of potassium into the ICF and increased urinary potassium excretion. The potassium deficit was correctly replenished initially with intravenous then oral potassium supplementation (14).

Further history obtained from the patient revealed that 2 years ago she had an episode of iritis that resolved spontaneously. She also reported dry eyes and mouth and dental caries. Serologic studies included (normal values in parentheses) the following: antinuclear antibodies 1:128 with finely speckled pattern, RF 135 IU (0 to 39 IU), C4 26 mg/dl (16 to 47 mg/dl), CH50 86 U/ml (26 to 58 U/ml), anti-La/SS-B antibody 57 EU (<3 EU); tests for anti-Ro/SS-A, anti-double-strand DNA, anti-Sm, anti-ribonucleoprotein, and anti-centromere, and anti-Scl antibodies were negative. Based on the clinical findings and laboratory tests, a diagnosis of Sjögren syndrome was made.

Sjögren syndrome is an important cause of acquired DRTA but has less commonly been associated with proximal tubule defects. Although overt RTA is reported in only 3% to 5% of patients with Sjögren syndrome, incomplete RTA defined by normal serum electrolytes but inability to acidify urine normally is common in response to metabolic acidosis. In one study of 78 such patients, 33% had abnormal ammonium chloride tests (15). In the largest
study to date, of 130 patients with Sjögren syndrome and renal involvement, 95 (73%) developed RTA, 91 with DRTA (66 complete and 25 incomplete), and four with PRIA and Fanconi syndrome. Nine of these patients presented with hypokalemic paralysis (16). Other reports have also described patients with Sjögren syndrome and mixed DRTA and Fanconi syndrome with hypokalemia that ranged from very severe to more mild (17).

Kidney biopsies in patients with Sjögren syndrome typically show features of chronic interstitial nephritis with focal or diffuse plasmalymphocytoid infiltration (16). The pathogenesis of the RTA in Sjögren syndrome is unclear, although immune-mediated damage to acid secreting cells in the kidney has been proposed. In study of a patient with Sjögren syndrome and DRTA, Defranco et al. used antibodies to the 31- and 56-kD kidney-specific subunits of H+ -ATPase to demonstrate complete absence of these vacuolar pumps. In addition, an antibody against the anion exchanger (AE1) present in the basolateral membrane of α-intercalated cells did not react with the patient’s kidney (18). Similar findings have been reported in other patients with Sjögren syndrome as well as SLE with RTA. In another study of 46 patients with Sjögren syndrome (13 with RTA) and 19 controls, the patients with RTA had significantly elevated antibody levels to CAII (19). In an intriguing study by the same authors, mice injected with human CAIL developed antibodies against CAIL and a syndrome pathologically similar to Sjögren syndrome with lymphocyte and plasma cell infiltration of the salivary glands and kidneys. When challenged with an acid load, the animals were unable to acidify their urine (20). It is however unclear if these findings are pathogenic or are secondary to immune-mediated cellular damage, because similar findings have been reported in patients with both immune and nonimmune tubulointerstitial diseases complicated by RTA (21).

Follow-up. The goal of the treatment in adults with RTA is to correct the acidosis to prevent chronic calcium efflux from bone, which can lead to hypercalciuria, nephrocalci- nosis, nephrolithiasis, and bone demineralization (22). In children it is critical to normalize serum bicarbonate to ensure appropriate growth. Chronic acidosis in both adults and children has adverse effects on muscle metabolism and other organ systems. Our patient was treated with prednisone 20 mg/d as well as potassium citrate 30 mEq twice daily. She improved dramatically on this treatment (Table 1). One year later she was readmitted during her 18th week of pregnancy with moderate HCMA and hypokalemia. This resolved quickly with potassium and bicarbonate repletion. During the subsequent 9 years she had multiple flares of her Sjögren syndrome, and her creatinine slowly rose to 1.9 mg/dl. Although her serum bicarbonate remained relatively stable at approximately 22 mEq/L on this therapy, she became acidoic with even mild diar- rhea.

Final diagnosis. Mixed proximal and distal RTA secondary to Sjögren syndrome.

Dr. Jeffrey Berns. Is there a role for corticosteroid or other immunosuppressive treatment or even therapeutic plasmapheresis in Sjögren syndrome-related RTA given the evidence of an autoimmune pathophysiology?

Dr. Rastegar. Corticosteroids and less frequently other immunosuppressives are used successfully to treat Sjögren syndrome flares, including renal failure associated with this syndrome (16,23). The effect of immunosuppressives on tubular dysfunction, including RTA, is variable and most patients require long-term treatment with alkali and potassium supplementation (17,22). Rituximab has been used in a small number of patients with severe Sicca syndrome and only rarely in patients with renal involvement (23,24). Given this very limited experience, it is difficult to assess the effectiveness of this therapy at this time. Plasmapheresis has been used in rare patients with Sjögren syndrome, primarily in the setting of severe neurologic symptoms, with occasional dramatic and sustained re- sponse (25).

Dr. Paul Palevsky. It appears that the patient had modest hypokalemia from her combined proximal and distal RTA before this acute episode. What mechanism accounted for the profound worsening of her hypokalemia?

Dr. Rastegar. Although the patient had mild-to-moderate chronic hypokalemia, she probably had significant total body potassium deficiency. The recent worsening of her hypokalemia was most likely due to further loss of potas- sium in the urine secondary to vomiting as well as possible worsening of the underlying RTA.

Dr. Gary Curhan. Is there a recommended rate of increase for serum potassium in hypokalemia as there is for correction of hyponatremia?

Dr. Rastegar. The major concern is the development of severe hyperkalemia. As noted above, the vast majority of potassium is intracellular and therefore potassium infusion should be slow enough to allow shift of potassium into this compartment. To prevent sudden rise in serum potassium, intravenous supplementation should generally be at a rate no faster than 40 mEq/hour although with severe hypo- kalemia up to 80 mEq/hour can be infused with cardiac monitoring. Absorption of oral potassium is associated with a hormonally regulated intracellular shift of potas- sium and is rarely associated with hyperkalemia. In prac- tice it is always best to replace potassium orally if possible, especially if the total body potassium deficiency is severe and large amounts of potassium replacement are needed. In rare cases when severe hypokalemia is also associated with severe hyponatremia, it is important to recognize that potassium replacement will result in a predictable rise in serum sodium.

Dr. Curhan. What is the recommended frequency of dosing of supplemental alkali in an outpatient with RTA?

Dr. Rastegar. There are no strict guidelines. Alkali re- placement is often given in two or three divided doses daily but could be given as a single dose if tolerated by the patient.

Acknowledgments

I thank Dr. Paul Pronovost, the nephrologist who initially pre- sented this patient to me and has cared for her for many years, and all other physicians and nurses at the Waterbury Hospital who were involved in her care during her initial admission.

Disclosures

None.
References


