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Clinical Case Study

A Rare Case of Hypokalemia and Hypomagnesemia

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CASE DESCRIPTION

An 18-year-old adolescent male presented to our emergency department complaining of chest pain that started about 2 days earlier and remained unchanged. Chest x-rays revealed a right apical pneumothorax. The patient did not use any medication. Two months earlier he had presented to the emergency department with a similar episode that resolved spontaneously. Blood testing performed at the time of presentation showed severe hypokalemia with a potassium concentration of 2.5 mmol/L. He was admitted to our respiratory unit.

He was 180 cm (70.9 in) tall and weighed 64 kg (141 lb, body max index 19.8 kg/m^2). He was in good general health, and the physical examination was unremarkable. A renal ultrasound was normal. He noted an unintentional weight loss of 7 kg (15.4 lb) over the last 36 months. Furthermore, he reported fatigue and muscle weakness. His personal history and family history were unremarkable. He was delivered naturally at term and developed normally during childhood and puberty.

Further blood tests revealed moderate hypomagnesemia of 1.2 mg/dL [0.5 mmol/L; reference interval 1.7–2.2 mg/dL (0.7–0.9 mmol/L)]. Arterial blood gas analysis showed metabolic alkalosis (pH 7.46, bicarbonate 28.9 mmol/L). Sodium, chloride, and calcium were within reference intervals. Renal function, fasting blood glucose, and a complete blood count were normal. Table 1 provides a selection of relevant laboratory results at presentation and during follow-up.

As recommended by the British Thoracic Society, the patient was scheduled for video-assisted thoracoscopic surgery *(1)*. Before surgery, an endocrine specialist was consulted to further investigate the cause of the patient's hypokalemia and hypomagnesemia. The spontaneous pneumothorax was unrelated to the abnormal electrolyte results and is not further discussed here.

QUESTIONS

1. What are the most common causes of hypokalemia?
2. Which laboratory tests can differentiate between renal and nonrenal causes of potassium loss?
3. Describe some rare genetic causes of hypokalemia.

The patient's pronounced hypokalemia and hypomagnesemia were initially treated with potassium canrenoate, potassium chloride, and magnesium (Fig. 1). With this therapy, serum potassium improved and stabilized at 2.8–2.9 mmol/L. Subsequently, amiloride was added to the patient's therapy, which led to a further improvement of serum potassium. However, he reported increasing fatigue, which led to the discontinuation of potassium canrenoate, without which correction of potassium was insufficient. Therefore, it was decided to replace amiloride by potassium canrenoate and spironolactone. Three months after the initial presentation, his potassium had risen to 3.4 mmol/L.

Within 10 weeks after the initiation of spironolactone therapy, he developed gynecomastia, a well-known side effect of this drug. Consequently, spironolactone was again replaced by amiloride, although at a higher dose. As serum potassium remained low, at approximately 2.8 mmol/L, he was switched from amiloride to eplerenone, a mineralocorticoid receptor antagonist that does not cause gynecomastia. Potassium and magnesium supplementation were continued as before. With this therapy, serum potassium and magnesium concentrations stabilized near the lower limit of the reference interval.

DISCUSSION

Hypokalemia is common in clinical practice *(2–5)*. Most patients are asymptomatic, especially if hypokalemia is mild. Symptomatic patients can present with weakness, fatigue, and palpitations. In severe cases, muscle cramps, pain, and respiratory arrest can occur. To prevent complications and ensure appropriate treatment, it is important to understand the cause of hypokalemia. Common causes include diarrhea, vomiting, use of diuretics, and adrenal and renal disorders *(2)*.

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Table 1. Laboratory results at presentation and on further investigation.[a]

Parameter	Result	Reference interval
Presentation		
Blood Chemistry		
Potassium, mmol/L	2.5	3.6–5.0
Calcium, mmol/L	2.46	2.15–2.60
Sodium, mmol/L	140	135–145
Chloride, mmol/L	96	95–108
Magnesium, mg/dL	1.21	1.7–2.2
Creatinine, mg/dL	0.78	0.50–1.20
Urea, g/dL	34	18–55
Total protein, mg/dL	7.1	6.6–8.3
Glucose, mg/dL	85	60–99
Uric acid, mg/dL	5.7	3.6–7.0
Aspartate transaminase, U/L	20	<40
Alanine transaminase, U/L	16	<40
Lactate dehydrogenase, U/L	134	120–230
Bilirubin, mg/dL	1.2	<1.4
Complete blood count		
Leukocytes, $\times 10^3$ cells/μL	4000	3600–10 000
Erythrocytes, $\times 10^6$ cells/μL	5.36	4.50–5.90
Hemoglobin, g/dL	15.9	13.0–17.5
Platelets, $\times 10^3$ cells/μL	182	150–410
Further investigation		
Urine chemistry		
Potassium, mmol/24 h	126	25–125
Sodium, mmol/24 h	277	40–220
Calcium, mmol/24 h	1.5	2.5–7.5
Phosphate, mmol/24 h	21	13–42
Chloride, mmol/24 h	342	110–250
Hormones		
Testosterone, ng/mL	5.02	2.39–8.36
Cortisol, ng/mL	128	59–217
Adrenocorticotropic hormone, pg/mL	46.8	4.7–48.8
Thyroid-stimulating hormone, μIU/mL	2.49	0.5–4.3
Arterial blood gas analysis		
pH	7.45	7.35–7.45
pCO_2, mmHg	41.7	35–48
HCO_3^-, mmol/L	28.9	21–28
Base excess, mmol/L	4.9	−2 to 3

[a] To convert magnesium from mg/dL to mmol/L, multiply by 0.411; creatinine from mg/dL to μmol/L, multiply by 88.4; urea from g/dL to mmol/L, multiply by 166.5; glucose from mg/dL to mmol/L, multiply by 0.0555; uric acid from mg/dL to mmol/L, multiply by 0.059; bilirubin from mg/dL to μmol/L, multiply by 17.1; calcium from mmol/24 h to mg/dL, multiply by 40; and phosphate from mmol/24 h to g/24 h, multiply by 0.033.

The first step is to understand if and how the patient loses potassium. Measurement of urinary potassium on a spot urine sample allows one to distinguish renal from nonrenal losses. If urine potassium is <15 mmol/24 h, gastrointestinal potassium loss (commonly diarrhea and vomiting) is most likely *(2)*. A detailed history is usually

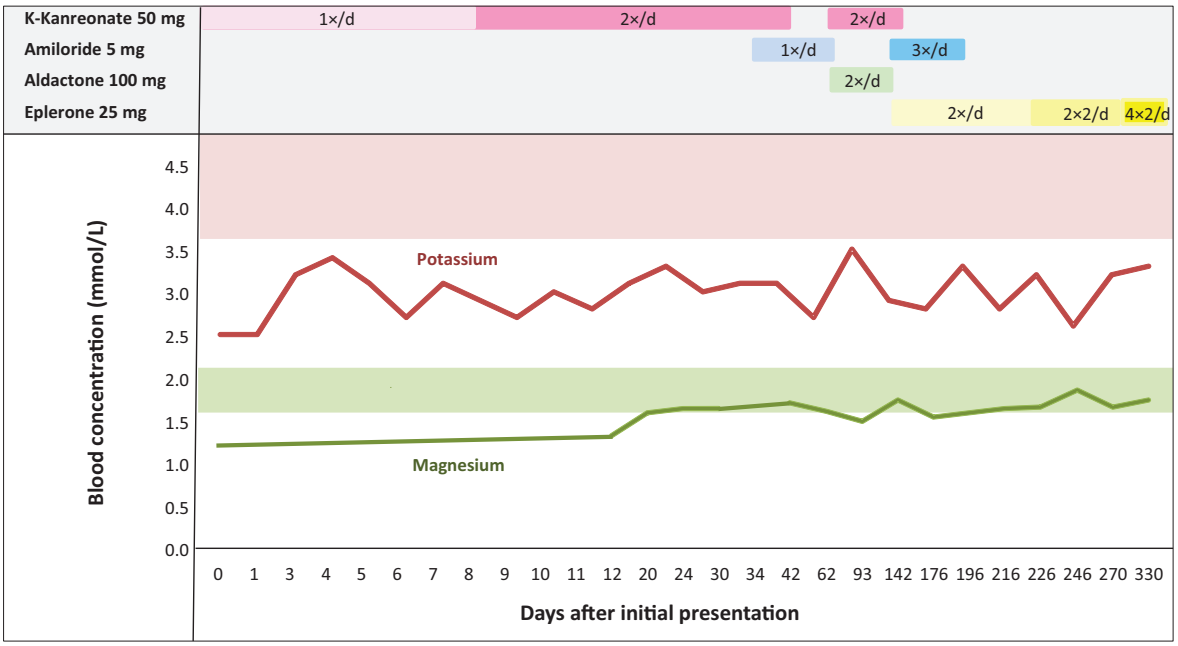

Fig. 1. Blood concentrations of potassium and magnesium over time.

sufficient to identify nonrenal causes of potassium loss. A value >15 mmol/24 h indicates an inappropriate renal loss of potassium. In our patient, urine potassium was 126 mmol/24 h. Renal potassium loss can be caused by drugs (diuretics, gentamycin, mineralocorticoids, etc.), endocrine conditions (excess of mineralocorticoids or glucocorticoids), and renal problems (renal tubular acidosis, renal artery stenosis, rare genetic diseases). The measurement of blood pressure (BP),[4] blood gases, aldosterone, and renin will help in the differential diagnosis. An increased BP points toward an excess of mineralocorticoids or glucocorticoids. In our patient, BP was normal (120/70 mmHg), making mineralocorticoid excess unlikely. Blood gas analysis revealed a metabolic alkalosis excluding renal tubular acidosis. The use of diuretics and vomiting (postemetic bicarbonaturia forces urinary potassium excretion, and the decrease in extracellular fluid increases aldosterone secretion) were excluded, so the remaining options were hypomagnesemia or genetic channelopathies, such as Bartter syndrome (BS) or Gitelman syndrome (GS). Because of the patient's hypocalciuria and the insufficient correction of hypomagnesemia by magnesium supplementation, GS was the most likely diagnosis, pending the genetic testing required to establish the diagnosis *(3, 5)*.

GS is an autosomal recessive salt-losing disorder of the kidneys (prevalence 1:40 000) *(3)*. Key laboratory findings include hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria *(3–11)*. GS most commonly manifests with muscle weakness, salt craving, thirst, nocturia, paresthesia (especially in the face), tetany, and abdominal pain *(3)*. Blood pressure is typically lower than that in the general population. Typically, symptoms appear after the age of 6 years, and the diagnosis is usually made during adolescence or adulthood. The disease can also be asymptomatic, and some patients present only with chondrocalcinosis that appears at adult age *(3)*. In our patient, no symptoms were present.

In most GS patients, the disease is caused by mutations in the thiazide-sensitive sodium-chloride cotransporter (NCCT) located in the apical membrane of the cells in the distal convoluted tubule *(3, 10)*. Mutations in *SLC12A3* [solute carrier family 12 (sodium/chloride transporter), member 3][5] account for approximately 70% of all adult GS patients *(9)*, of whom 75% are compound heterozygous with different mutations in the

[4] Nonstandard abbreviations: BP, blood pressure; BS, Bartter syndrome; GS, Gitelman syndrome; NCCT, thiazide-sensitive sodium-chloride cotransporter; TAL, thick ascending limb of the loop of Henle.

[5] *SLC12A3*, solute carrier family 12 (sodium/chloride transporter), member 3; *CLCNKB*, chloride channel, voltage-sensitive Kb; *SLC12A2*, solute carrier family 12 (sodium/potassium/chloride transporter), member 2; *KCNJ1*, potassium channel, inwardly rectifying subfamily J, member 1; *CLCNKB*, chloride channel, voltage-sensitive Kb; *BSND*, barttin CLCNK-type chloride channel accessory β subunit; *CASR*, calcium-sensing receptor.

2 alleles *(9)*; 25% are homozygous, and 20% harbor only 1 mutant allele *(9)*.

Disease-causing mutations in *SLC12A3* decrease NCCT activity and reduce NaCl reabsorption in the distal collecting duct, which leads to volume depletion. The consequent activation of the renin-aldosterone axis causes potassium wasting and ultimately leads to hypokalemia. Aldosterone acts on principal cells in the distal nephron, stimulating sodium reabsorption and potassium secretion *(7)*. Furthermore, aldosterone increases proton secretion by intercalated cells in the distal nephron in exchange for potassium. Hypocalciuria is another biochemical hallmark of GS that can be explained by increased passive calcium absorption secondary to extracellular volume contraction. Hypomagnesemia in GS is the consequence of a reduced expression of the epithelial Mg^{2+} transport channel TRPM6 in the distal convoluted tubule, which results in decreased magnesium reabsorption *(10)*.

BS is the most important genetic disorder in the differential diagnosis of GS *(3)*. Classic BS is caused by mutations in *CLCNKB* (chloride channel, voltage-sensitive Kb). The phenotype of BS is highly variable, ranging from antenatal onset to a picture resembling GS. Urine calcium helps one distinguish GS from BS *(7)*. Ninety percent of filtered calcium is reabsorbed in the thick ascending limb of the loop of Henle (TAL). In BS, defective sodium and potassium reabsorption in the TAL results in reduced calcium reabsorption and excessive delivery of calcium to more distal parts of the nephron. This explains the occurrence of nephrocalcinosis. Hypomagnesemia is common in GS, but some types of BS can also present with such a phenotype. The 5 subtypes of BS are caused by different mutations affecting the TAL: type 1, *SLC12A2* [solute carrier family 12 (sodium/potassium/chloride transporter), member 2] (Na^+-K^+-$2Cl^-$ symporter); type 2, *KCNJ1* (potassium channel, inwardly rectifying subfamily J, member 1) (K^+ channel); type 3, *CLCNKB* (chloride channel, voltage-sensitive Kb) (Cl^- channel); type 4, *BSND* (barttin CLCNK-type chloride channel accessory β subunit) (Cl^- channel); and type 5, *CASR* (calcium-sensing receptor) (activating mutation of the calcium-sensing receptor accessory subunit).

Our patient harbors 2 heterozygous *SLC12A3* missense mutations in exon 7 (c.947G>T) and exon 18 (c.2221G>A) causing nucleotide substitutions (Gly316Val and Gly741Arg). The similarities between GS patients and thiazide users are because the mutated NCCT is also the site of action for thiazide diuretics. In contrast, loop diuretics act on the TAL, the site where the affected proteins are located in BS patients.

Treatment and follow-up of GS patients depends on phenotype. Asymptomatic patients are monitored by 1–2 ambulatory visits per year. All GS patients are encouraged to maintain a high-sodium and high-potassium diet *(3)*. Lifelong supplementation of magnesium is also recommended, as hypomagnesemia is believed to be the cause of chondrocalcinosis *(3)*. In some patients, supplementation with $MgCl_2$ is sufficient to correct hypokalemia. If electrolyte supplementation is insufficient, aldosterone antagonists or EnaC (sodium channel in the collecting duct) inhibitors should be considered. The combination of amiloride and KCl has been successfully used in the past *(3)*. Spironolactone or eplerenone can be added if required. In our patient, potassium replacement and amiloride were insufficient to correct hypokalemia. Therefore, spironolactone was added. Because our patient developed gynecomastia, the drug was replaced by eplerenone. With this treatment, the patient is asymptomatic and potassium levels are at the lower reference limit. The long-term prognosis of GS is excellent *(3)*.

In conclusion, GS should be considered in the differential diagnosis of otherwise unexplained hypokalemia. Characteristic biochemical features include hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. The phenotype is highly variable and mimics prolonged thiazide administration.

POINTS TO REMEMBER

- Hypokalemia is a potentially life-threatening condition most commonly caused by the use of diuretics and diarrhea and vomiting.
- In the differential diagnosis, urine potassium measurement is essential to differentiate renal from nonrenal potassium losses.
- In hypokalemic patients with excessive renal potassium excretion, rare genetic tubulopathies, such as Gitelman syndrome and Bartter syndrome, should be considered.
- Hypokalemia, metabolic alkalosis, hypomagnesemia, and reduced urinary calcium excretion are the characteristic features of GS.
- GS is typically caused by mutations in *SLC12A3* resulting in decreased NCCT activity in the distal convoluted tubule.

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Commentary

John C. Lieske*

Hypokalemia is commonly encountered in clinical medicine. In the vast majority of cases, it is a result of losses in the gastrointestinal tract or urine. Thus, the key diagnostic test is urine potassium measurement. If low, gastrointestinal losses are likely; if, as in this case, urine potassium is high, then the kidney is implicated (i.e., renal potassium wasting), and serum aldosterone, the key hormone that stimulates renal potassium excretion, is likely to be high. The question then becomes whether the patient clinically appears volume expanded (suggestive of primary hyperaldosteronism or perhaps licorice ingestion) or volume depleted (in which case aldosterone is still high but "appropriate" and secondary). In this case, the patient apparently did not appear volume expanded, and indeed there was evidence for metabolic alkalosis, which is consistent with volume contraction. Overall, this common scenario results when a patient is taking diuretics. But what if, as in this case, none are being taken? Think Bartter or Gitelman syndrome.

The key to next differentiate these 2 possibilities is measuring urine calcium excretion, which is high in BS (owing to a mutation in 1 of 5 different genes in the TAL, the region of the kidney impacted by loop diuretics and important for calcium reabsorption), but low in GS (owing to a mutation in NCCT). Indeed, thiazides are used in hypercalciuric stone formers because they slightly volume-deplete patients and secondarily increase sodium, chloride, and calcium reabsorption in the TAL. In sum, this case nicely illustrates that if a patient appears as if they are taking a thiazide but are not, they have Gitelman syndrome. Of course, a genetic test would be needed to make this definitive!

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Commentary

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The combination of hypokalemia, hypomagnesemia, and normal BP raises the specter of external loss of sodium, potassium, and magnesium; the absence of hypertension excludes untreated mineralocorticoid/glucocorticoid excess and similar syndromes. This type of external solute loss suggests disease of either the gastrointestinal tract or kid-

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