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Acid-Base and Electrolyte Teaching Case

Evaluation of Hypomagnesemia: Lessons From Disorders of Tubular Transport

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Hypomagnesemia is a highly prevalent clinical condition affecting a large number of hospitalized patients. A decrease in systemic magnesium concentration may lead to impaired function of both neurologic and cardiovascular systems. The kidney has a pivotal role in magnesium handling by adjusting the urinary excretion of this ion in order to maintain systemic concentrations within a narrow range. As such, the cause of hypomagnesemia can be related to increments in the renal excretion of this cation. Many hypomagnesemic disorders also have characteristic changes in the renal reabsorptive capacity for other electrolytes, leading to symptoms that sometimes obscure the clinical presentation. For instance, changes in serum calcium concentration or its urinary excretion can aid in determining the underlying cause. Moreover, hypokalemia due to renal potassium losses often is associated with hypomagnesemia. Genetic defects in pathways controlling renal electrolyte transport impose the hypomagnesemic condition by facilitating renal losses. The discovery of the causative genes has greatly increased our understanding of how magnesium is transported by the kidney. Such knowledge is integral for the continued improvement of patient care with respect to bettering therapies and diagnosis.

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INDEX WORDS: Kidney; transient receptor potential melastin 6 channel (TRPM6); inherited renal disorders; Gitelman syndrome.

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting either the diagnosis or treatment of acid-base and electrolyte disorders.

INTRODUCTION

Hypomagnesemia is a clinical condition that arises frequently, with a prevalence of ~10% in hospitalized patients and up to 65% in intensive care unit patients.[1] Hypomagnesemia may be due to isolated losses, but commonly is associated with other electrolyte disorders (eg, hypokalemia or hypocalcemia) that may obscure the clinical presentation. By studying the causative genes in electrolyte disorders with disturbed magnesium handling and the pathophysiologic consequences of their absence, it is possible to increase our understanding of how magnesium homeostasis is maintained. Given the frequency of hypomagnesemia, it is essential for clinicians to understand its pathogenesis. The symptoms of complex electrolyte disorders involving hypomagnesemia are represented by the present teaching case. It is our intent to emphasize how magnesium balance is maintained, how it can be perturbed by genetic abnormalities in electrolyte transport pathways, and the steps that should be taken by clinicians to reach a diagnosis.

CASE REPORT

Clinical History and Initial Laboratory Data

A 16-year-old girl was admitted to the clinic because of persistent vomiting and abdominal pain. History did not show any prior illness. On repeated questioning, she mentioned carpopedal spasms during infections. At examination, there was diffuse abdominal pain with rebound, and bowel sounds were minimal. Elevated leukocyte count ($18.1 \times 10^3/\mu L$) supported a presumed diagnosis of appendicitis, and an appendectomy was performed. The appendix appeared to be grossly and histologically normal. Postoperatively, vomiting continued and bowel sounds remained absent. Determination of serum electrolyte levels indicated severe hypokalemia (Table 1). Intravenous supplementation with potassium chloride was started, which resulted in complete recovery within 24 hours, suggesting that the abdominal symptoms were due to hypokalemia-induced ileus.

Additional Investigations

An electrolyte panel drawn postoperatively showed abnormalities in serum and urinary electrolyte levels (Table 1).

Diagnosis

The combination of lower serum potassium and magnesium levels with increased renal loss, accompanied by low urinary calcium excretion, pointed to the diagnosis of Gitelman syndrome.

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Table 1. Electrolyte Panel From Index Patient

Parameter	Index Patient	Reference Range
Before intervention		
Serum [Mg^{2+}] (mEq/L)	1.18	1.4-2.2
Serum [K^+] (mEq/L)	2.3	3.5-5.1
Serum [Ca^{2+}] (mg/dL)	10	8.8-10.3
Serum [HCO_3^-] (mEq/L)	28.5	20-26
pH	7.47	7.35-7.44
P_{CO_2} (mm Hg)	40	35-45
Urinary Mg^{2+} excretion (mEq/kg/24 h)	0.60	0.16-0.30
Urinary K^+ excretion (mEq/24 h/1.73 m^2)	178	21-108
Urinary Ca^{2+}/Cr ratio	0.12	0.2-0.7
After intervention		
Serum [Mg^{2+}] (mEq/L)	1.42	1.4-2.2
Serum [K^+] (mEq/L)	3.5-4.0	3.5-5.1

Note: Conversion factors for units: magnesium in mEq/L to mmol/L, ×0.5; calcium in mg/dL to mmol/L, ×0.2495.

Abbreviations: [Ca^{2+}], calcium concentration; Cr, creatinine; [HCO_3^-], bicarbonate concentration; [K^+], potassium concentration; [Mg^{2+}], magnesium concentration.

A homozygous nonsynonymous mutation (a threonine to arginine change at amino acid 649 [T649R]) subsequently was discovered in the thiazide-sensitive sodium/chloride cotransporter (NCC), which is encoded by the *SLC12A3* gene. The family history of our patient has been described previously in a Dutch-language medical journal.[2]

Clinical Follow-up

The patient was treated with oral potassium chloride (2 g 4 times daily; 4 mEq of potassium per kilogram of body weight every 24 hours) and magnesium oxide (500 mg thrice daily; 18 mg of magnesium ion per kilogram of body weight every 24 hours), which normalized serum electrolyte levels (Table 1).

DISCUSSION

Disorders of hypomagnesemia are characteristic of a subset of conditions that may result from disturbances in renal electrolyte transport. The extracellular concentration of magnesium is maintained at 1.4-2.2 mEq/L.[3] Hypomagnesemia is diagnosed when serum magnesium concentration is decreased to <1.4 mEq/L. Failure to maintain serum magnesium levels within the normal range is not inconsequential. Hypomagnesemia results in a whole range of symptoms, including neuromuscular irritability such as tetany, positive Chvostek and Trousseau signs, seizures, and cardiac arrhythmias.[4,5] A list of frequently reported symptoms of hypomagnesemia can be found in Box 1. In our index patient, carpopedal spasms were observed during infections, which could be attributed to hypomagnesemia. It has been reported that symptomatic hypomagnesemia is particularly apparent during common infections of childhood in patients with hereditary hypomagnesemic conditions.[6]

Symptoms of hypomagnesemia due to renal wasting can be dissociated from other causes by measuring renal excretion of the ion. This most commonly is done by determining the fractional excretion of magnesium (FE_{Mg}) or total 24-hour urinary excretion of magnesium. FE_{Mg} can be calculated from magnesium (Mg^{2+}) and creatinine (Cr) concentrations using the formula: $FE_{Mg} = [Mg^{2+}]_{urine} \times ([Cr]_{blood}/(0.7 \times [Mg^{2+}]_{blood})) \times [Cr]_{urine} \times 100$. To adjust for the amount of magnesium filtered by the kidney, serum magnesium concentration is multiplied by 0.7.[1] In the presence of hypomagnesemia, decreased FE_{Mg} (<2%) suggests that the kidney is responding appropriately to a decreased serum magnesium ion concentration.[1,7] Thus, normal urinary excretion of magnesium (in children, 0.16-0.30 mEq per kilogram of body weight in a 24-hour period) in the presence of hypomagnesemia may indicate a renal defect.

Hypomagnesemia frequently is observed in conjunction with other electrolyte imbalances, including hypokalemia and hypocalcemia, as well as metabolic acid-base disturbances. The exact reason for the secondary hypocalcemia observed during severe magnesium depletion is unclear, but may be due to blunted release of parathyroid hormone or desensitization to parathyroid hormone in bone.[8,9] Hypokalemia is an often-encountered condition associated with hypomagnesemia and may be present in a large number of patients with hypomagnesemia.[10,11] Hypokalemia can be refractory to potassium administration in certain cases. During these conditions, the addition of magnesium can aid in correcting potassium losses.[11] Interestingly, disorders leading to isolated hypokalemia do not promote magnesium wasting, whereas hypomagnesmia can, but does not necessarily, produce secondary decreases in serum potassium levels. One proposed explanation for this phenomenon involves ROMK (the renal outer medullary K^+ channel), which is a key player in potassium secretion from the collecting system.[11,12] Potassium permeation through ROMK channels can be blocked by physiologic levels of magnesium.[12] In conditions of hypomagnesemia, this blockage probably is lifted.[11,12]

Hypomagnesemia most often is the result of acquired disorders. Causes due to renal magnesium wasting are listed in Box 2. However, hypomagnesemia also can

Box 1. Clinical Manifestations Attributed to Hypomagnesemia

- Weakness and fatigue
- Muscle facilitations-cramps
- Tetany-carpopedal spasm
- Numbness-paresthesias
- Seizures
- Positive Chvostek sign (facial twitching after tapping of the facial nerve)
- Positive Trousseau sign (muscle spasm in hand and forearm after occlusion of the brachial artery)
- Arrhythmias