

Case Report: Severe, Symptomatic Hypomagnesemia in Acute Leptospirosis

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Abstract. We report a case of severe hypomagnesemia in non-oliguric acute renal failure caused by leptospirosis that required large doses of magnesium replacement during the acute phase of disease. Biochemical studies confirmed kidney-related magnesium wasting and the mechanisms of this defect are discussed. Magnesium imbalance with its attendant clinical complications occurs in leptospirosis and should be monitored and treated aggressively in cases of leptospirosis-induced non-oliguric acute kidney injury.

INTRODUCTION

Leptospirosis is a zoonosis of worldwide distribution.¹ In the São Paulo metropolitan area of Brazil, the annual incidence of leptospirosis ranged from 1.7 to 2.7 cases per 100,000 inhabitants from 2004 through 2006 with a case-fatality rate of 11–18%. The most frequent infecting leptospire is *Leptospira interrogans* serovar Copenhageni.² Leptospirosis is a common reason for intensive care unit admission into Heliopolis Hospital in Sao Paulo, Brazil during the rainy season from January through April. This finding provides the opportunity for making careful clinical observations that will inform clinical management in similar settings elsewhere in the world.

The kidney is an important target organ in leptospiral infection. Clinically, renal involvement in leptospirosis occurs in 16–40% of cases and is unique because of the atypical presentations of polyuria, hypokalemia, and sodium and potassium wasting that may be observed in up to 45% of all patients with acute renal failure).³ Mechanisms to explain the electrolyte abnormalities in acute kidney injury in leptospirosis are postulated to include impaired expression of type 3 Na⁺/H⁺ exchanger (NHE3) and Na⁺-K⁺-Cl⁻ co-transporter (NKCC2),^{4–7} which are the major sodium transporters in the proximal renal tubule and thick ascending limb of the loop of Henle, respectively.

Leptospirosis-associated electrolyte disturbances have important clinical consequences. Most commonly, sodium and potassium depletion occur and magnesium imbalance has mostly been neglected. A case series of 17 patients from Brazil showed that during the acute phase of leptospirosis, patients with hepato-renal involvement had higher serum levels of magnesium compared with healthy controls; in the convalescent phase, magnesium levels decreased transiently.⁸ A recent series from Thailand reported elevated fractional excretion of magnesium in 15 of 20 patients and hypomagnesemia in 10 of 20 patients, nine of which were associated acute kidney injury. However, symptoms attributable to magnesium depletion were not reported.⁹

The major site of magnesium transport is the thick ascending limb of the loop of Henle where 65% is reabsorbed and 20–25% of filtered magnesium returns to the blood in the

proximal tubule and 5–10% in the distal tubule.¹⁰ Regardless of the precise molecular mechanisms of tubular dysfunction in leptospirosis, impaired ion transport is known to result in sodium and potassium wasting and to be clinically significant in management. A gradient of potassium and sodium is the major driving force accountable for the paracellular reabsorption of magnesium in the thick ascending limb of the loop of Henle. Thus, some degree of magnesium loss may be expected in potassium/sodium wasting states. This case report closely examines magnesium dynamics in a severe case of leptospirosis with a focus on its clinical consequences.

CASE REPORT

A 15-year-old woman had acute onset of fever, myalgia, jaundice, and dyspnea that started five days before admission to a hospital. She reported that rats were common in her neighborhood and that she was exposed to floodwaters one week prior to symptoms. Past medical history was unremarkable.

On physical examination, she was alert, jaundiced, and lungs were clear to auscultation. Blood counts showed 9,500 leukocytes/mm³ (88% neutrophils, 10% lymphocytes, and 2% monocytes). The hematocrit was 26% and the platelet count was 46,000 cells/mm³. She had the following laboratory test values: blood urea nitrogen = 108 mg/dL (reference range = 10–50 mg/dL), serum creatinine = 2.6 mg/dL (0.7–5 mg/dL), sodium = 133 mmol/L (135–145 mmol/L), potassium = 3.0 mmol/L (n: 3.5–5.0 mmol/l), serum magnesium = 1.5 mg/dL (0.56 mmol/L) (1.9–2.5 mg/dL), total bilirubin = 11 mg/dL (0.2–1.2 mg/dL), and creatine kinase = 620 U/L (0–190 U/L). Alanine aminotransferase and aspartate aminotransferase levels were normal. Urinalysis showed a protein level of 30 mg/dL (reference range = 30–140 mg/dL). Urine output was 3.3 liters in the first 24 hours. The results of blood and urine cultures and serologic tests for hepatitis viruses and human immunodeficiency virus were negative.

Diagnosis of leptospirosis was demonstrated by a positive IgM enzyme-linked immunosorbent assay result on day 15 of illness. This result was confirmed by seroconversion between paired serum samples analyzed by the microscopic agglutination test (highest titer against serovar Copenhageni, titer = 1:800).

Intravenous penicillin G (1.5 million units every six hours) was started on admission and maintained for seven days. Supportive therapy in the intensive care unit focused on hydration and potassium/magnesium (in the form of MgSO₄) re-

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placement. Polyuria continued until the fourth day, reaching a peak of 6.3 liters/24 hours on day 3. Severe myalgia and lethargy continued until hospital day 6, concomitant with restoration of normal serum magnesium levels. Standard blood values improved with supportive management except for magnesium, which reached its lowest level of 0.5 mg/dL (0.038 mmol/L) on day 3 (hypomagnesemia grade 4 defined as < 0.7 mg/day) despite magnesium replacement of 6 g/day. Fractional magnesium excretion was markedly elevated at 35% (2–4%) and an extremely high value of 54% on the second and third days, respectively. Hydration with saline fluids and potassium and magnesium replacement were continued and serum magnesium levels returned to normal on day 6. She fully recovered.

The patient had no history of furosemide use, and this drug was not given during inpatient treatment. Metabolic alkalosis was not observed at admission or during clinical monitoring.

DISCUSSION

We describe a case of severe hypomagnesemia associated with myalgia and lethargy in the acute phase of leptospirosis. Although a direct causal relationship between these clinical manifestations and serum magnesium level cannot be demonstrated in a single case, this association is consistent with known manifestations of magnesium deficiency. The relationship between magnesium depletion and acute leptospirosis is suggested by the clinical course of illness and serologic diagnosis of infection. Antimicrobial treatment, K^+/Mg^+ replacement, and clinical recovery was associated with normalization of serum electrolytes. The mechanisms for the hypomagnesemia in severe leptospirosis remain unclear but likely relate to the direct effect of leptospiral biochemical components on proximal and loop of Henle function.

In severely ill patients, magnesium deficiency worsens clinical outcome,¹¹ potentially related to complicating hypokalemia, hypocalcemia, tetany, dysrhythmia, acute coronary syndromes, and acute cerebral ischemia.¹⁰ We suggest that the present case demonstrates that careful attention to early magnesium replacement is important in avoiding such clinical complications in acute leptospirosis.

Although hypomagnesemia is common in critically ill patients, this finding is not due to urinary wasting of magnesium. Hypomagnesemia in this setting is usually related to prolonged administration of magnesium-free parenteral fluids, nasogastric suction, or diarrhea.¹² Urinary evaluation confirmed magnesium wasting in the presence of severe hypomagnesemia, which was similar to previous reports of sodium and potassium depletion in the presence of severe dehydration.^{13,14} Furosemide, an alternative cause of increased magnesium excretion, was not used in our patient. The absence of metabolic alkalosis makes unlikely the diagnosis of Bartter's syndrome, a condition associated with chronic hypermagnesemia and hypercalciuria.

A previous report describes serum magnesium serum levels in patients with acute leptospirosis, which were higher than in healthy controls during (2.83 versus 2.09 mg/dL, reference range = 1.8–2.4 mg/dL). However, whether these patients had oliguric or non-oliguric renal failure was not reported. Interestingly, magnesium levels decreased to low levels in the convalescence phase (1.79 versus 2.09 mg/dL).⁸ A recent re-

port from Thailand observed hypermagnesuria and hypomagnesemia in 75% and 50%, respectively, in a population of 20 patients with acute leptospirosis. Magnesium excretion and serum magnesium levels were associated with serum creatinine. In addition, 9 of 10 patients with magnesium depletion had acute kidney injury, which provided evidence that tubular dysfunction in leptospirosis may cause dramatic changes in magnesium imbalance, a finding with which the present case is consistent. However, our study did not describe the range of magnesium wasting and hypomagnesemia, which would enable comparison in which extent those cases mirror severe depletion as described in this report.

Clinical consequences of hypomagnesium (myalgia, lethargy) or the potential need for large amounts of magnesium replacement therapy were not described in these cases.⁹ The present case report extends these previous reports by showing the potential clinical consequences and need for early clinical recognition of and intervention for disordered magnesium homeostasis in acute leptospirosis. Although clinical observations of one case are necessarily limited in their generalizability, this case, together with previous reports, indicates the need to carry out a prospective clinical evaluation of magnesium homeostasis in acute leptospirosis where severe disease commonly results in hospitalization, especially because magnesium can result in an altered mental state that is a well-established predictor of death from this disease.^{15,16}

This case report highlights hypomagnesemia as a potentially important complication in acute leptospirosis. We suggest that magnesium levels should be monitored in hospitalized cases of suspected leptospirosis, especially in those with non-oliguric renal failure. The approach to these patients should include early targeted correction of magnesium levels, as well as other electrolyte imbalances to forestall severe clinical consequences of hypomagnesemia.

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