CASE REPORT

Magnesium metabolism in chronic primary hypomagnesemia

Francisco R. Carrazza¹, Marilisa S.F. Souza², Ceres Romaldini³, Rubens Feferbaun⁵, Edna A. Diniz⁶

Abstract

Objectives: to report three cases of primary hypomagnesemia (PH) with secondary hypocalcemia in symptomatic infants, born to consanguineous parents, and to present Mg metabolic studies.

Methods: classic metabolic balances of Mg were performed during three consecutive days, using carmin as fecal marker, with and without Mg supplementation.

Results: the patients (one male) presented, between 15 and 28 days old, with convulsions and persistent hypocalcemias, which could not be controlled with anticonvulsivants and/or intravenous calcium gluconate. After diagnostic was established the above symptoms and hypomagnesemia were controlled with Mg supplementation. Without supplements, mean daily balances were negative or below daily needs, showing final magnesemias lesser than 0.7 mEq/L and hypocalcemias about 3 mEq/L. The renal conservation test performed for six days after Mg repletion showed at the beginning of the study normal magnesemias (1.4 to 1.5 mEq/L) decreasing to 0.7 or 0.8 mEq/L in the first 24 hours, indicating absence of response from the body stores. Mg total renal excretion was smaller than 1 mEq, during six consecutive days, indicating adequate renal Mg reabsorption. Intestinal absorption of Mg varied from 6 to 15% of intake. With Mg supplementation, daily balances were positive, correcting progressively the serum Ca and Mg. In patient LPCJ, urinary excretion was 35% of the administered dosis, confirming Mg depletion.

Conclusions: besides confirming specific intestinal malabsorption of Mg, adequate renal conservation and an homeostatic extracellular defect of Mg were observed, probably caused by an incapacity of mobilization of Mg from tissue reserves.


Introduction

Chronic primary hypomagnesemia is a rare condition inherited as an autosomal recessive¹ or X-linked² disease. This disease is characterized by irritability, tetany, and generalized seizures. It usually occurs in the neonatal period, and leads to death if not treated. The most widely accepted etiology and pathogenesis today is the specific intestinal malabsorption of magnesium conditioned by a defective carrier-mediated active transportation.³ Paunier et al.⁴ were the first to describe a chronic primary hypomagnesemia patient in Canada in 1965. Since then and up to 1995, 37 other patients were reported.³ In 1981, Carrazza et al.⁵ reported the first chronic primary hypomagnesemia patient in Brazil.

The clinical presentation for chronic primary hypomagnesemia includes neurological involvement characterized by restlessness, eye movements, jerks and

1. Professor, Department of Pediatrics, FMUSP.
2. Graduate Student, FMUSP.
3. Master, IBGESP.
4. Doctor, FMUSP.
5. Professor, FMUSP.
6. Instituto da Criança (I. Cr.), Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo – FMUSP.
shaking, muscular spasms, tetany, generalized seizures and perioral cyanosis. Biochemical findings reveal hypomagnesemia and secondary hypocalcemia. Whenever an early diagnosis is not established and treatment is not started immediately, chronic convulsions may be fatal or lead to neurological sequelae.

This paper reports three cases of hypomagnesemia out of a total of six consecutive patients seen in our outpatient service. These patients underwent metabolic studies to investigate the intestinal malabsorption of magnesium and the rapid onset of hypomagnesemia after supplementation withdrawal.

Methods

The patients were studied according to the classic 3-day metabolic balance technique, using carmine as fecal marker after formula balancing for 48 hours. For the balances without supplementation, we considered only the magnesium in their diets. For those that received supplementation, at least 1 mEq/kg/day of oral magnesium sulfate was offered. Urine was collected separately from feces. Although electrolytes, calcium, and phosphorus were dosed, only the magnesium balances are presented here.

Magnesium was dosed by atomic absorption spectrophotometry. The range 1.4 to 2.0 mEq/L was adopted as normal serum magnesium concentration.

Balance results are graphically presented in 3 day-mEq as follows: average ingestion is represented in the y axis, and the average added feces and urine excretions start with the average ingestion and are represented downwards by subtracting the ingestion values. When the added excretions (urine and feces) were below zero in the scale and had a negative value, the balance was considered negative, that is, losses were higher than gains. A positive balance was considered when urine and feces excretions, plotted below the average ingestion value, were above zero. Calculations were carried out according to the 3-day average in mEq/day.

Parental consent was obtained to perform the balances in accordance with the Research Ethics Committee at the institution in which the work was carried out.

Case Reports

1. LPJC, a term newborn male infant in good conditions, uneventful normal delivery and history, the son of consanguineous parents. After discharge from neonatal nursery, he developed frequent crying, restless sleep, eye movements and generalized shaking. At 15 days of age, he suddenly had generalized tonic-clonic seizures repeated approximately 10 times and followed by tetany and perioral cyanosis. Liquor and electroencephalogram findings were normal. Laboratory tests detected hypocalcemia and hypomagnesemia. The patient was initially treated with intravenous administration of calcium gluconate and presented transient improvement. As the clinic convulsive behavior continued, magnesium sulfate intravenous infusion was prescribed. The symptoms were alleviated, and the serum magnesium and calcium levels were corrected. Parathyroid hormone was normal. Patient was discharged after prescription of magnesium and vitamin D supplementation. At 2 months of age, patient was hospitalized for complementary investigation and underwent metabolic balances with and without magnesium supplementation. While hospitalized, patient underwent renal function analysis (acidification, concentration, clearances, etc.), and findings were normal, with no glycosuria or aminoaciduria. No other biochemical abnormality was found. Intestinal absorptive function findings (sugar overload, D-xylene, fat balance, histology of the jejunal mucosa) were normal. At 12 and 24 months, supplementation withdrawal was tried again and monitored by metabolic studies.

2. AFS, a term, cesarean-section delivery female infant, Apgar 9 and 10, uneventful history, weight = 2650 g. Parents were first-degree cousins. Family history revealed a 2-year-old brother under treatment with 20% magnesium sulfate solution. The patient was hospitalized at 17 days of age because of generalized convulsive episodes for 2 days. Presumptive diagnosis was chronic primary hypomagnesemia. While hospitalized, serum magnesium level was 0.54 mEq/L, and the patient developed secondary hypocalcemia (serum calcium was 3.1 mEq/L) and hyperphosphatemia (7.9 mg/dl), with normal parathyroid hormone and glucose. After intravenous administration of 20% magnesium sulfate and clinical improvement, metabolic balances for calcium and magnesium were performed, as well as clinical laboratory investigation (liquor, cranium sonography, cultures, EEG, etc.), and findings were normal.

3. MSR, a 28-day old female infant, presented with four generalized convulsive episodes with eye deviation and hypertonic limbs. Patient was a healthy, normal delivery term newborn, and weight at birth was 3100 g. The parents were first-degree cousins, and one brother had already died at 7 months of age with convulsions started at 15 days of age. When hospitalized, the patient presented tachypnea and sepsis, and required endotracheal intubation. The patient had several generalized convulsive crises, and was treated with diazepam and barbiturates. Liquor was normal. The subsequent investigation detected hypocalcemia (3.6 mEq/L and ionized calcium at 0.75 mEq/L), serum magnesium at 0.59 mEq/L, serum phosphate at 5.2 mg/dl, and normal glucose. The patient was treated with intravenous magnesium sulfate solution at first, and the convulsive crises were controlled. Neurological examination, cranium sonography, renal function test and EEG were normal, and no other biochemical abnormalities were detected.
Results

The clinical-biochemical findings for the three infants studied were very similar, and we thus decided to present graphs with data for the most representative patient only. Figure 1 shows the evolution of calcium and magnesium levels during the first 2 years of life, and Figure 2 shows magnesium balances carried out at 2 months of age, with and without oral magnesium supplementation.

Table 1 shows comparative data for magnesium balances (in mEq/day) for the three patients. At 2 months of age and without magnesium supplementation, LPCJ presented slight positive retention, around 0.4 mEq/day with 3.1 mEq/day ingestion (absorption was 16%). In this case, initial and final balance magnesemias did not vary and were kept low, at around 0.6 mEq/L. When total oral ingestion was 14.3 mEq/day, retention was significantly positive (3.1 mEq/day). Absorption was 22%, and magnesemia increased from 0.4 to 0.8 mEq/L.

With another oral supplementation, balance became positive, and magnesemia increased to 1.2 mEq/L. Supplementation has been kept since then.

We also observed that intestinal absorption of magnesium was above 22% when the patient received supplementation, and ranged from 6 to 15% without supplementation.

Table 1 - Magnesium balances (mEq/day) for the three patients around 2 months of age, with and without magnesium supplementation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Magnesium supplementation</th>
<th>Urine</th>
<th>Feces</th>
<th>Magnesium ingestion</th>
<th>Balance</th>
<th>Magnesemia (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>LPCJ</td>
<td>2 mo.</td>
<td>without</td>
<td>0.1</td>
<td>2.6</td>
<td>3.1</td>
<td>+0.4</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with</td>
<td>0.1</td>
<td>11.1</td>
<td>14.3</td>
<td>+3.1</td>
<td>0.4</td>
</tr>
<tr>
<td>AFS</td>
<td>2 mo.</td>
<td>without</td>
<td>0.01</td>
<td>1.4</td>
<td>1.2</td>
<td>-0.2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with</td>
<td>0.1</td>
<td>7.6</td>
<td>12.6</td>
<td>+4.9</td>
<td>0.6</td>
</tr>
<tr>
<td>MSR</td>
<td>1.5 mo.</td>
<td>without</td>
<td>0.1</td>
<td>2.8</td>
<td>2.9</td>
<td>-0.03</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with</td>
<td>1.2</td>
<td>5.9</td>
<td>11.4</td>
<td>+5.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

With another oral supplementation, balance became positive, and magnesemia increased to 1.2 mEq/L. Supplementation has been kept since then.

We also observed that intestinal absorption of magnesium was above 22% when the patient received supplementation, and ranged from 6 to 15% without supplementation.
Table 2 - Magnesium balance (mEq/L) for patient LPCJ at 12 and 24 months of age, without supplementation

<table>
<thead>
<tr>
<th>Age</th>
<th>Urine</th>
<th>Feces</th>
<th>Ingestion</th>
<th>Balance</th>
<th>Magnesemia (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>12m</td>
<td>0.3</td>
<td>6.5</td>
<td>6.9</td>
<td>+0.1</td>
<td>1.6</td>
</tr>
<tr>
<td>24m</td>
<td>0.1</td>
<td>8.4</td>
<td>7.9</td>
<td>-0.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>

At 12 months, after magnesium repletion by parenteral administration, supplementation was withdrawn, and the amount of magnesium excreted in urine was measured daily. The total amount of magnesium excreted in urine in 6 days was 0.9 mEq, while 0.8 (89%) was excreted in the first 24 hours. Serum magnesium decreased from 1.56 to 0.8 mEq/L after 6 days.

At 24 months, the 6-day renal excretion study was repeated without supplementation. We observed that serum magnesium fell from 1.4 to 0.7 mEq/L after 24 hours. Total urinary excretion in 6 days was 0.7 mEq (0.3 mEq on the 1st day). More than 60% was excreted in the first 24 hours. For the rest of the period, renal loss was only 0.1 mEq magnesium.

Discussion

Presently, the most accepted etiology and pathogenesis of chronic primary hypomagnesemia is a selective defect of magnesium absorption in the intestine. Two independent mechanisms are described for the intestinal absorption of magnesium: an active system mediated by a carrier, saturated at low lumen concentrations; and a passive system that acts in high magnesium concentrations through a gradient.

The genetic transmission mechanism has not been adequately explained yet, but two mechanisms are accepted: one, autosomal recessive, since most patients were born to consanguineous parents; the other, X-linked, with male predominance. It has been suggested that intestinal absorption of magnesium is regulated by the synergistic action of two genes, autosomal recessive and X-linked, and that a defect in one of them may influence the whole mechanism. All the three patients studied here had consanguineous parents, and two had a previous history of a sibling who died with similar problems.

Chronic primary hypomagnesemia onset is usually observed in the neonatal period, from the 1st to the 16th week of life. Initial symptoms include irritability, generalized seizures, and tetany. In this phase, liquor examination and total serum calcium dosage are performed. This was the procedure for the three patients reported here. Calcium or vitamin D administration improved tetany but did not avoid new seizures. Therefore, serum magnesium dosage was necessary to establish the diagnosis. For two other patients, not described in this paper, the diagnosis was evident as they were siblings. Biochemically, chronic primary hypomagnesemia is characterized by hypomagnesemia, hypocalcemia, normophosphatemia, and normal parathyroid hormone. At admission, our patients presented with serum calcium around 3 mEq/L, and magnesium from 0.4 to 0.6 mEq/L. Administration of magnesium salts corrected calcemia without calcium supplementation. The association of hypomagnesemia and hypocalcemia has been explained by the fact that magnesium deficiency conditions the synthesis or the diminished secretion of parathyroid hormone. In the three patients reported here, the results of metabolic balances showed specific intestinal malabsorption of magnesium. None of the balances without magnesium supplementation (considering only the amounts supplied by the diet) presented magnesium retention compatible with the daily needs required for growth, and the percentage of absorption (15 to 25%) was low. Our patients had 16% absorption in comparison with the 67% found in medical literature. Stromme et al. reported only 10% absorption against 55% control. When magnesium was supplemented orally, the balances were significantly positive, and showed that the passive absorption system allowed adequate levels of absorption and promoted the corporeal repletion of magnesium and normal magnesemias.

The results of magnesium urinary excretion during 6 days were a very important finding. These assessments
were carried out for LPCJ at 12 and 24 months of age, and for AFS at 1 year of age. To start this study, the stocks of magnesium were replenished by parenteral administration of magnesium for 3 days, 2 mEq/kg/day, and interrupted after that. At the beginning of the study and on consecutive days, serum magnesium was dosed and 24-hour urine was collected for 6 consecutive days. Daily magnesium excretion was quantified. LPCJ, at 12 months of age and after repletion, presented magnesemia at 1.56 mEq/L. After 24 hours, magnesemia fell to 0.8 mEq/L, and only 0.8 mEq were excreted in urine. After 6 days, total excretion was 0.9 mEq. Final magnesemia was 0.6 mEq/L. At 24 months, magnesemia was 1.4 mEq/L after repletion and, after 24 hours, it fell to 1.1 mEq/L. After 48 hours, it was 0.8 mEq/L, and ended at 0.5 mEq/L. Total urinary excretion was 0.7 mEq, while 0.3 mEq were excreted on the 1st day. In the following days, there was maximum magnesium renal conservation, and only insignificant amounts of magnesium were excreted in urine.

We conclude that there is magnesium intestinal malabsorption in chronic primary hypomagnesemia as a consequence of a disturbance in the active mechanism of transport through the membrane. The simple passive diffusion by concentration gradient proved to be present by the proportionality found between oral overload and magnesium intestinal absorption. However, defective absorption is not the only factor responsible for hypomagnesemia. It was evident that magnesia fall to low values was rapid (24 hours) in all the cases of renal conservation. In fact, chronic primary hypomagnesemia patients do not lose 1 mEq in 6 days, but show hypomagnesemia on the 1st day, with total renal loss of 80% of the total. This characterizes a problem in the extracellular magnesium homeostasis.

We do not know why these patients were incapable of mobilizing magnesium from the tissue cells and normalize extracellular magnesium concentration. This conclusion concurs with those of Paunier et al., 1968, and of Salet et al., 1966. These authors called this incapacity to mobilize magnesium from the residual reserves “magnesium osteopetrosis”. Paunier et al. showed that the magnesium and K concentrations in the muscle were reduced even when the patient was ingesting high doses of magnesium. A lower concentration was observed after magnesium supplementation withdrawal. In this study, when 6.4 mEq/day was administered intramuscularly, 35% of the total magnesium dose was excreted in urine, which confirms the state of magnesium depletion.

Until now, no neurological or any other sequelae have been observed in long-term clinical studies. There was variation in the levels of magnesium according to the growth phase and the correct administration of magnesium. In our group of patients, we have a 21-year old patient with normal intelligence, although his mother says he is very “nervous”.

References

Correspondence:
Dr. Francisco R. Carrazza
Avenida Dr. Enéias de Carvalho Aguiar, 647
São Paulo, SP, Brazil – CEP 05403-090
Phone: + 55 11 572.9718 – Fax: 572.2604