Primary Hypomagnesemia in Thai Infants : A Case Report with 7 Years Follow-Up and Review of Literature

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Abstract

A female Thai baby born to non-consanguineous parents, presented with primary hypomagnesemia at 10 weeks of age, and suffered recurrent convulsions that responded to magnesium supplementation. She was found to have hypomagnesemia (Mg 0.35-1.02 mEq/L) and a low urinary magnesium excretion of less than 10 mg per day, or urinary Mg/Cr that ranged from 0.005-0.01 mg/mg. Intermittent hypomagnesemia and one episode of hypocalcemia with occasional convulsions developed, due to irregular consumption of oral magnesium sulfate, which had a bitter taste, caused frequent loose stools and black staining of the teeth. Better compliance after switching from magnesium sulfate to magnesium oxide resulted in an increased level of serum magnesium and the gradual disappearance of the black staining of the teeth and frequent loose stools. The patient required an oral elemental magnesium dosage of 15-30 mg/kg/day to maintain the serum magnesium level at between 1.02-1.33 mEq/L and keep her free from convulsions. The follow-up period was 7 years during which the patient showed normal physical growth and a mild degree of mental retardation.

Key word : Hypomagnesemia, Hypocalcemia, Convulsions, $MgSO_4$, MgO

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Hypomagnesemia is defined as a decrease in plasma magnesium concentration to less than 1.5 mg/dL, 1.25 mEq/L or 0.62 mmol/L[1]. It is often found in adults (65%)[2] and pediatric (11%)[3] patients admitted to the intensive care unit. It has been suggested that hypomagnesemia may be a predictor of poor outcome in the critically ill[4]. This condition has been frequently noted in the neonatal period,

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owing to maternal causes such as decreased intake due to vomiting, overuse of laxatives, and neonatal causes, for instance, intrauterine growth retardation, birth asphyxia and exchange transfusion.

Hypomagnesemia may result from one or more of three mechanisms causing magnesium malabsorption, increased renal loss, and redistribution of Mg from extracellular fluids to cells. Most Mg-deficient patients have a low or an inappropriately normal PTH level, impaired PTH secretion, and action leading to hypocalcemia. This association is characterized by recurrent convulsions in the late neonatal period or early infancy, and is an uncommon cause of neonatal seizure. However, it is an important condition to recognize because magnesium administration restores the magnesium deficit, reverses the hypocalcemia, and prevents further seizures. The present study described the first, reported case of a Thai girl presenting with primary hypomagnesemia and hypocalcemia, and the 7-year follow-up. It also reviewed the literature pertaining to the clinical presentations and outcome of primary hypomagnesemia.

CASE REPORT

A female infant was born at full term with a birth weight of 3.6 kg after an uneventful pregnancy. She was the only child of non-consanguineous parents with no apparent medical problems during the neonatal period. She was breast fed and grew normally up to 10 weeks of age before developing frequent generalized convulsions. Initial investigations at a local hospital including serum electrolytes and lumbar puncture, and an ultrasonography of the head showed unremarkable results.

She was referred to Chiang Mai University Hospital at 3 months of age with uncontrolled seizures despite two weeks of phenobarbital and valproic acid treatment. A physical examination showed a well nourished infant with weight, height and occipitofrontal circumference of 6.47 kg, 60 cm and 40.5 cm, respectively. She had normal developmental milestones, and no abnormal neurological signs. Investigations showed normal results of urinalysis, complete blood count, serum BUN, Cr, electrolytes, phosphorus, alkaline phosphatase, albumin, total calcium, and a low level of magnesium that ranged from 0.35-1.02 mEq/L (normal range 1.4-1.7)[1]. Convulsions were controlled and serum Mg returned to normal level within 24 h after treatment with 50 per cent $MgSO_4$ and calcium gluconate. A cranial computerized tomographic scan showed normal attenuation of the brain parenchymal without abnormal enhancement, enlarged cortical sulci, cisterns, subarachnoid spaces or ventricles without mass effect or shifting of the midline structures. An EEG showed epileptiform discharges over the right centro-parieto-temporal area and she was, therefore, treated by multiple anticonvulsants with some improvement. She was finally discharged with carbamazepine and clonazepam. No magnesium supplementation was given, as hypomagnesemia was considered to be transient.

She was readmitted at 5 months of age because of repeated generalized convulsions for two weeks. There was no history of vomiting or diarrhea. Investigations showed a normal level of serum sodium, potassium, albumin, alkaline phosphatase, phosphorus of 5.3 mEq/L, and low serum total of calcium and magnesium. The Ca was 3.4 mEq/L, Mg 0.24 mEq/L. The serum parathyroid hormone (N terminal) was 30.6 pg/ml (normal range 14-21). Twenty-four hour urinary calcium and magnesium excretion, and urine Mg/Cr ratios are shown at a low level in Table 1 with negative urine metabolic screening. Stool examination showed no fecal fat. There was dramatic improvement in the level of calcium, magnesium and convulsion when a standard dosage of parenteral $MgSO_4$ and calcium gluconate was administered, and she was discharged with both medications to be taken orally. She had normocalcemia while calcium supplementation was tapered off. Oral magnesium sulfate could not be continued regularly because of its bitter taste and caused of frequent loose stools. Therefore, hypomagnesemia (Table 1) and occasional convulsions developed intermittently. Several following admissions showed only moderate hypomagnesemia and a low urinary excretion of magnesium (Table 1). The serum magnesium level was higher if $MgSO_4$ was given in three or four divided doses rather than twice a day. Oral magnesium sulfate caused black staining of the teeth (Fig. 1) if given for a long period. Due to the adverse effects of oral magnesium sulfate and the availability of magnesium oxide, it was switched to the latter when the patient was 5 yr 9 m of age. She then obtained better compliance with magnesium oxide because it was more palatable and her bowel movement returned to normal. The black staining of her teeth gradually disappeared, convulsions ceased, and

Table 1. Demonstrated serum level and urinary excretion of magnesium and calcium at each admission.

Admission	Age	Serum			Urine		
		Ca/Ca^{+}	P (mEq/L)	Mg (mEq/L)	Mg (mg/d)	Mg/Cr (mg/mg)	Ca/Cr (mg/mg)
1st	3 m	9.4/-	3.9	0.35-1.02	-	-	-
2nd	5 m	4.3/0.45	5.3	0.24	-	-	-
	5.2 m	4.9/-	6.8	0.4	1.23	0.05 (N 0.1-0.48)(5)*	0.047 (N 0.03-0.08)(5)*
3rd	10 m	9.8	4.6	1.14	-	-	-
4th	1 yr	9.6/-	4.8	0.98	-	-	-
5th	1 yr 1 m	9.8/-	4.8	1.25	-	-	-
6th	5 yr 9 m	9.9/4.6	4.4	0.86	0.88	0.005 (N 0.06-0.21)(5)**	0.13 (N 0.01-0.03)(5)**
7th	6 yr 9 m	9.7/4.7	4.6	1.27	6.92	0.028	-
		9.3/-	4.2	0.93	3.05	0.010 (N 0.06-0.21)(5)**	-

* normal value for age 1/12-1 yr
** normal value for age 5-7 yr

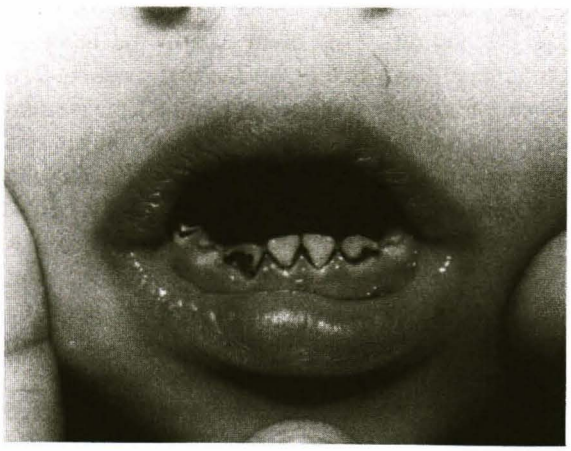

Fig. 1. Demonstrated black staining of the teeth during $MgSO_4$ supplementation.

the serum magnesium level increased to a range of 1.02-1.33 mEq/L that required an elemental magnesium dosage of 15-30 mg/kg/day.

She was followed-up on a regular basis, and was growing normally at 6 yr 9 m of age with a weight of 23 kg and height of 110 cm, both of which were within the ranges of normal Thai children. Aggressive behavior and a poor attention span were noted. Neurological examination showed an unremarkable result. An IQ test evaluated by WISC-R showed a verbal IQ of 70 and performance IQ of 68, with a full-scale score of 68, which recorded a level of mild mental retardation.

DISCUSSION

Hypomagnesemia was documented in this reported case of a Thai girl who presented with generalized convulsions in early infancy that responded to magnesium supplementation. The clinical manifestations recurred because of discontinued or inadequate dosage of medication with the presence of a very low urinary magnesium excretion of less than 10 mg/d, or urine Mg/Cr that ranged from 0.005 to 0.01 mg/mg. These findings indicated no renal magnesium wasting(1). Any defect should be of intestinal origin, but no study was made of magnesium intestinal absorption at this time. Nevertheless, this reported case had no history of vomiting or diarrhea or evidence of malabsorption or malnutrition. This was indicated by no fecal fat and normal body weight and height. This patient had persistent hypomagnesemia with one episode of hypocalcemia if medication was discontinued or inconsistent. The majority of Mg-deficient hypocalcemic patients have a low or an inappropriately normal PTH level, however, some have elevated levels(6), as in this patient. The presence of normal or elevated serum PTH levels in the face of hypocalcemia, suggest an end organ resistance to PTH action. These heterogeneous serum PTH values may be explained by the severity of Mg depletion. The clinical course and biochemical abnormalities are typical of primary hypomagnesemia, and the defect seems to be selective intestinal malabsorption, which is by-passed by an increasing magnesium dosage that is greater than the normal requirement. In this case, serum Mg failed to reach a normal level

despite treatment with a high dosage of oral Mg supplementation, which is an observation that has been reported previously[7-10] and may be due to inconsistency of magnesium supplementation.

Isolated intestinal magnesium malabsorption or primary hypomagnesemia is a rare condition, and was first reported by Paunier in 1965[11]. There are now at least seventy-three cases reported according to the world literature[8,10,12-21]. Both sexes can be affected, but it is more common and severe in males. The initial preponderance of affected males among Arab cases[12] and the basis of a single case of X-autosome translocation t(9;X)[22], suggested that this condition was an X-linked recessive disorder. However, the identification of several affected females has suggested an autosomal recessive inheritance[12,23] that is determined by mutation in a gene located on chromosome 9 (9q12-q22.2)[24].

The age of presentation is usually between 1 and 16 weeks, although older patients of up to 36 years have been reported[12]. The most common presentation is generalized seizures that respond to parenteral magnesium treatment. The consistent laboratory findings were hypomagnesemia, mostly below 1 mEq/L and associated with hypocalcemia. The serum phosphorus varied from a low to high level and hypokalemia was observed in a few patients. The serum magnesium level can be maintained at near normal with oral magnesium supplements at an average (SD) dosage of 38 (22) mg elemental magnesium/kg/d[10]. This dosage is much higher than the recommended daily maintenance supplementation (4-10 mg/kg/d)[25]. The major adverse effects of oral magnesium supplement is diarrhea, which requires an appropriate preparation of magnesium.

Primary hypomagnesemia is caused by selective malabsorption of magnesium from the gastrointestinal tract[26]. The fraction of magnesium absorbed from the gut in a majority of these patients is about 10 per cent (5.6-33%) of the magnesium ingested, while the control subjects absorb about 50-60 per cent.

Patients with primary hypomagnesemia require continuous magnesium supplementation for life. There are a few reports on the long-term outcome[10,11], but a normal neurodevelopmental outcome was achieved in those who were treated with the appropriate long-term dosage of magnesium. The prognosis in terms of life expectancy is relatively good, as long as magnesium supplements are maintained.

Therefore, in patients with primary hypomagnesemia, delay in establishing a diagnosis or noncompliance with recommended treatment leads to convulsions with permanent neurological damage[10], as shown in the presented patient, or even death. In a family with one child with primary hypomagnesemia, a follow-up of all subsequent children at 4 weeks of age is encouraged, as even in affected infants, the serum Mg level may be near normal in the first week after birth[17].

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ภาวะ primary hypomagnesemia ในเด็กไทย : รายงานผู้ป่วยที่ได้ติดตามการรักษาเป็นระยะเวลา 7 ปี และทบทวนวารสาร

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รายงานผู้ป่วยเด็กหญิงไทยที่ได้รับการวินิจฉัยเป็น primary hypomagnesemia และมีอาการชักตั้งแต่อายุ 10 สัปดาห์ ตอบสนองดีต่อการให้แมกนีเซียมซัลเฟต ตรวจพบมีระดับแมกนีเซียมในเลือดอยู่ระหว่าง 0.35–1.02 mEq/L และมีการขับแมกนีเซียมออกมาในปัสสาวะน้อยกว่า 10 มก/วัน หรือ urine Mg/Cr มีค่าระหว่าง 0.005–0.01 เนื่องจากแมกนีเซียมซัลเฟตมีรสขม และทำให้มีการถ่ายอุจจาระบ่อย ผู้ป่วยจึงกินยาได้ไม่สม่ำเสมอ และมีภาวะ hypomagnesemia เกิดขึ้นเป็น ๆ หาย ๆ ตามด้วยภาวะ hypocalcemia หนึ่งครั้ง และมีอาการชักเกิดขึ้นในบางครั้ง หลังจากเปลี่ยนการรักษาไปเป็นแมกนีเซียมออกไซด์ ผู้ป่วยสามารถรับยาได้ดีขึ้น การถ่ายอุจจาระกลับเป็นปกติ ผู้ป่วยต้องได้รับการรักษาอย่างต่อเนื่อง โดยใช้ elemental magnesium ขนาด 15–30 มก/กก/วัน โดยมีระดับของแมกนีเซียมในเลือดอยู่ระหว่าง 1.02–1.33 mEq/L และไม่มีอาการชัก ได้ติดตามผู้ป่วยเป็นระยะเวลา 7 ปี พบมีการเจริญเติบโตของร่างกายอยู่ในเกณฑ์ปกติ และมีภาวะปัญญาอ่อนระดับความรุนแรงเล็กน้อย พร้อมทั้งได้ทบทวนวารสารเกี่ยวกับโรคนี้

คำสำคัญ : ภาวะแมกนีเซียมต่ำในเลือด, ภาวะแคลเซียมต่ำในเลือด, อาการชัก, แมกนีเซียมซัลเฟต, แมกนีเซียมออกไซด์

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