

Magnesium Matters: Clinical and Endocrine Lessons from Paediatric Case Studies

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Abstract

Hypomagnesemia in children is an uncommon but potentially life-threatening electrolyte disorder associated with significant neurological and endocrine manifestations. Due to its close physiological relationship with calcium metabolism and parathyroid hormone regulation, magnesium deficiency often presents with refractory hypocalcaemia, leading to delayed diagnosis. We report two children who presented with recurrent drug-resistant seizures and persistent hypocalcaemia despite adequate calcium and vitamin D supplementation. Further biochemical evaluation revealed profound hypomagnesemia, prompting investigation for an underlying genetic cause. Genetic analysis confirmed congenital familial hypomagnesemia due to a pathogenic mutation affecting intestinal magnesium absorption, consistent with a TRPM6-related disorder. Correction of magnesium deficiency resulted in cessation of seizures and normalization of calcium homeostasis, emphasizing the critical role of magnesium in neuromuscular stability. Both children were initiated on lifelong oral magnesium supplementation and showed sustained clinical improvement on follow-up. These cases highlight the importance of considering hypomagnesemia in children presenting with refractory seizures and persistent hypocalcaemia. Early recognition of congenital familial hypomagnesemia is essential to avoid misdiagnosis, prevent unnecessary investigations, and ensure timely initiation of targeted therapy, thereby reducing long-term neurological morbidity.

Keywords: Hypomagnesemia; Hypocalcemia; TRPM Cation Channels Mutation; Genetic Diseases; Epilepsy.

1. Introduction

Hypomagnesemia in children is an infrequent but clinically important electrolyte abnormality, reported in less than 1% of the general paediatric population, though its prevalence is higher among hospitalized and critically ill children. Normal serum magnesium concentrations in children range from approximately 1.7 to 2.4 mg/dL (0.7–1.0 mmol/L). Magnesium is integral to neuromuscular excitability, myocardial conduction, cellular energy metabolism, and calcium–parathyroid hormone (PTH) homeostasis. Consequently, magnesium deficiency may manifest with seizures, tetany, cardiac arrhythmias, and endocrine dysfunction. A key diagnostic challenge is that hypomagnesemia often presents with secondary hypocalcaemia and hypoparathyroidism, which remain refractory to calcium and vitamin D therapy until magnesium levels are restored.

The etiology can be broadly classified into renal and gastrointestinal losses, which represent the two principal mechanisms of magnesium depletion. Renal magnesium wasting occurs due to either inherited or acquired defects in tubular reabsorption. Among inherited causes, disorders such as Gitelman syndrome and Bartter syndrome are well-recognized, while rarer conditions including Familial hypomagnesemia with hypercalciuria and nephrocalcinosis and mutations affecting magnesium transport pathways also contribute. Acquired renal losses are more commonly encountered in clinical practice and are frequently associated with the use of medications such as diuretics, aminoglycosides, amphotericin B, and calcineurin inhibitors, as well as conditions like osmotic diuresis and renal tubular injury.

In contrast, gastrointestinal losses primarily result from impaired magnesium absorption or excessive intestinal loss. Chronic diarrhea remains the most common cause, while malabsorptive disorders such as Celiac disease and Inflammatory bowel disease, along with conditions like short bowel syndrome and pancreatic insufficiency, significantly contribute to hypomagnesemia. Reduced dietary intake and chronic alcoholism further exacerbate magnesium deficiency, particularly in vulnerable populations. Distinguishing between renal and gastrointestinal etiologies is

essential, as it guides diagnostic evaluation and management, with urinary magnesium excretion serving as a key differentiating tool.

Congenital hypomagnesemia represents a rare subset of disorders caused by inherited defects in renal tubular reabsorption or intestinal magnesium absorption. Among these, congenital familial hypomagnesemia, most commonly associated with mutations in the *TRPM6* gene, typically presents in infancy or early childhood with recurrent seizures and severe neuromuscular irritability.

Diagnostic evaluation relies on biochemical profiling, including serum and urinary magnesium estimation, with fractional excretion of magnesium (FeMg) serving as a valuable tool to differentiate renal magnesium wasting from extrarenal causes. FeMg <2%, suggests an extra-renal (intestinal) cause. However, as noted in recent literature, an FeMg <4% in the setting of severe hypomagnesemia does not entirely rule out renal wasting, as the filtered load of magnesium is significantly reduced. Srinivasan et al. reported a similar finding (FeMg of 2.4%), indicating that high suspicion for *TRPM6* mutations should persist even when FeMg values are borderline. Advances in molecular genetics have further enabled definitive diagnosis through targeted gene sequencing, facilitating early recognition and appropriate counseling.

Management of hypomagnesemia based on prompt magnesium repletion, using intravenous therapy in acute symptomatic cases followed by long-term oral supplementation in congenital forms. Early diagnosis and sustained treatment are crucial to prevent recurrent symptoms, repeated hospitalizations, and long-term neurodevelopmental sequelae. This case underscores the importance of routine magnesium assessment in paediatric metabolic and endocrine emergencies, particularly in children presenting with refractory seizures or unexplained hypocalcaemia.

THE CASE:

Case 1:

A 10-month-old male infant presented with recurrent seizures since the neonatal period. He was the first child of non-consanguineous parents, born at term by normal vaginal delivery with a birth weight of 3.0 kg. Antenatal, perinatal, and neonatal periods were uneventful, with no history of birth asphyxia, neonatal sepsis, or hypoglycemia. Feeding history and developmental milestones were appropriate for age, and there was no family history of seizures, metabolic disorders, renal disease, or unexplained infant deaths.

The first seizure episode occurred at 26 days of life and was characterized by generalized tonic-clonic movements with up-rolling of eyes and postictal drowsiness, lasting 2–3 minutes without fever or precipitating factors. Initial investigations revealed hypocalcemia, hypomagnesemia, and severe vitamin D deficiency, for which calcium, vitamin D, and antiepileptic therapy were initiated. Electroencephalography demonstrated multifocal epileptiform discharges with intermittent epileptic bursts. The child subsequently remained seizure-free, and antiepileptic drugs were discontinued after a normal repeat EEG at 6 months of age.

Within one month of treatment withdrawal, the infant developed recurrent generalized tonic-clonic seizures similar to previous episodes. Examination revealed normal anthropometric parameters, stable vitals, and no dysmorphic features or focal neurological deficits. Repeat biochemical evaluation demonstrated persistent hypocalcemia with significant hypomagnesemia. Parathyroid hormone (PTH) levels were inappropriately normal for the degree of hypocalcemia, while vitamin D levels were sufficient, suggesting hypocalcemia secondary to magnesium deficiency. These findings prompted further metabolic and genetic evaluation.

Table 1

Investigation Range	Normal	Result
Ser. Na (mEq/L)	135–145	136
Ser. K (mEq/L)	3.5–5.5	4.2
Ser. Ca (mg/dl)	9–10.6	8.14
Ionic Ca (mg/dl)	4.8–5.52	4.08
Mg (mg/dl)	1.7–2.1	0.6
PO4 (mg/dl)	4.5–8.3	5.66
Parathormone (PTH) (pg/ml)	8.5–112.3	36.1
Vit-D (ng/ml)	>30	61.9
Urine Mg (mg/dl)	0.10–0.48	0.84
Urine Creatinine (mg/dl)	2–36	28.4
Urine Calcium/Creatinine Ratio	0.60	0.24

FRACTIONAL EXCRETION of MAGNESIUM–

$$= \frac{\text{Urinary Magnesium} \times \text{Plasma Creatinine}}{\text{Plasma Magnesium} \times \text{urinary creatinine} \times 0.7} \times 100$$

$$\text{FeMg} = \frac{0.87 \times 0.44}{1.32 \times 20.9 \times 0.7} \times 100$$

$$= 1.9$$

Table 2: Genetic Testing

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
TRPM6 (-) (ENST00000360774.1)	Exon 17	c.2020C>T (p.Gln674Ter)	Homozygous	Hypomagnesemia with secondary hypocalcemia-1	Autosomal recessive	Pathogenic

Table 2 shows Genetic testing confirmed a diagnosis of Hypomagnesemia with secondary hypocalcemia-1 (OMIM) with an autosomal recessive inheritance.

Treatment: Child started on Tab. Magnesium oxide 10mg/kg/day and Magnesium and calcium supplementation corrected electrolyte abnormalities, enabling seizure cessation and antiepileptic withdrawal. Child is now growing well and cognitively normal.

Case 2:

A 5-year-old male child presented with recurrent seizures since infancy. He was born to non-consanguineous parents following an uncomplicated full-term pregnancy and normal vaginal delivery. The neonatal period was uneventful, and developmental milestones were normal. There was no significant family history.

The child had first seizure at 4 months of age, characterized by generalized tonic–clonic movements, upward rolling of eyes, and loss of consciousness lasting 1–3 minutes, followed by postictal drowsiness. Initial evaluation revealed hypocalcemia, and treatment with intravenous calcium, oral calcium supplementation, and antiepileptic drugs was initiated. Serum magnesium was not assessed at that time.

Despite treatment, the child continued to experience recurrent seizures. Multiple evaluations documented persistent hypocalcemia, although the underlying etiology remained unidentified for several years. At 5 years of age, he was referred to our center for evaluation of refractory hypocalcemic seizures.

On examination, the child was hemodynamically stable with age-appropriate growth parameters and no dysmorphic features or neurocutaneous markers. Neurological examination during the interictal period was normal.

Laboratory results showed marked hypocalcemia and hypomagnesemia (Table 3). Similar to Case 1, the PTH level was within the normal range, and the Vitamin D level was sufficient (Table 3), supporting the diagnosis of hypocalcemia secondary to magnesium deficiency.

Table 3

Investigation	Normal Range	Result
Ser. Na (mEq/L)	135–145	139
Ser. K (mEq/L)	3.5–5.5	3.63
Ser. Ca (mg/dl)	9–10.6	6.6
Ionic Ca (mg/dl)	4.8–5.52	0.66
Mg (mg/dl)	1.7–2.1	0.5
PO4 (mg/dl)	4.5–8.3	7.6
PTH (pg/ml)	11–59	35.1
Vit-D (ng/ml)	>30	103.9
ALP (Iu/L)	130–335	276

Urine Calcium/Creatinine Ratio	0.02–0.41	0.17
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Genetic Study

Table 4 shows Genetic testing identified a mutation in the TRPM6 gene, Heterozygous, Autosomal recessive results in disease due to second undetected variant like Deep intronic variant, large deletion/ duplication or regulatory mutation.

Table 4: Genetic Testing

Gene (Transcript) #	Location	Variant	Zygoty	Disease (OMIM)	Inheritance	Classification
TRPM6 (-) (ENST00000360774.6)	Exon 8	c.941del Exon 8 (p.Val314GlyfsTer30)	Heterozygous**	Hypomagnesemia 1 intestinal (OMIM#602014)	Autosomal recessive**	Likely Pathogenic (PVS1,PM2)

Treatment: Child started on Tab. Magnesium oxide 8 mg/kg/day. Oral magnesium and calcium supplementation resolved seizures and improved clinical status. Child is now growing well and cognitively normal.

Discussion

Primary Hypomagnesemia with Secondary Hypocalcemia (PHSH) is a rare autosomal recessive disorder caused by pathogenic variants in the TRPM6 gene, which encodes a magnesium-permeable ion channel involved in active intestinal absorption and renal tubular reabsorption of magnesium. Defective TRPM6 function leads to profound magnesium depletion, resulting in impaired parathyroid hormone secretion and peripheral resistance to PTH, thereby causing secondary hypocalcemia.

Both children in the present report demonstrated the classical phenotype of TRPM6-related PHSH, with early-onset refractory seizures associated with severe hypomagnesemia and hypocalcemia. The onset of symptoms during early infancy corresponds to the period when transplacental magnesium transfer ceases and intestinal magnesium absorption becomes physiologically essential. Neurological manifestations, particularly recurrent seizures, remain the most common presenting feature and may be life-threatening if diagnosis is delayed.

A major learning point highlighted by our second case is the significant diagnostic delay. The child received prolonged treatment for hypocalcemic seizures for nearly five years before serum magnesium estimation was performed. This reflects a well-recognized challenge in clinical practice, where hypocalcemia is often emphasized while concomitant magnesium deficiency remains overlooked. Persistent or refractory hypocalcemia with inappropriately normal or low PTH levels should prompt mandatory evaluation of serum magnesium, particularly in infants and young children with recurrent seizures.

The biochemical profile observed in both cases—marked hypomagnesemia, secondary hypocalcemia, adequate vitamin D levels, and inappropriately normal PTH—is highly characteristic of PHSH. Correction of calcium levels could only be achieved after magnesium repletion, emphasizing the pivotal role of magnesium in calcium homeostasis and neuromuscular stability.

Differential diagnoses of inherited hypomagnesemia include CLDN16- and CLDN19-related familial hypomagnesemia with hypercalciuria and nephrocalcinosis, as well as Gitelman syndrome. However, the absence of nephrocalcinosis, renal dysfunction, hypokalemia, and metabolic alkalosis in our patients strongly favored TRPM6-related PHSH.

Management consists of aggressive magnesium replacement during acute presentations followed by lifelong oral magnesium supplementation. Although maintaining normal serum magnesium levels remains challenging due to ongoing renal magnesium wasting, adequate supplementation effectively prevents seizures and stabilizes calcium homeostasis. The recurrence of seizures in Case 1 following discontinuation of therapy further highlights the lifelong nature of treatment and the importance of adherence and regular follow-up.

These cases emphasize the importance of considering hypomagnesemia in all children presenting with refractory hypocalcemic seizures. Early diagnosis and prompt magnesium supplementation can prevent recurrent seizures, avoid unnecessary investigations, and significantly reduce long-term neurological morbidity. Increasing awareness of TRPM6-related PHSH among clinicians is essential for timely recognition and targeted management of this rare but treatable disorder.

Conclusion

These cases underscore the critical importance of a “magnesium-first” approach in the evaluation of neonatal and

infantile seizures. Refractory hypocalcaemia despite adequate vitamin D status and non-suppressed parathyroid hormone levels should prompt immediate assessment of serum magnesium and consideration of TRPM6-related primary hypomagnesemia to enable timely, targeted therapy and prevent long-term neurological sequelae.

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