

# Diagnostic dilemmas in primary hypomagnesaemia - a treatable metabolic disorder in children

## Abstract

Primary hypomagnesaemia is a treatable metabolic cause of refractory seizures in children. We report an Indian family with three siblings who presented with refractory seizures during neonatal period. A novel mutation of TRPM6 gene was identified. Early detection and adequate magnesium therapy improved clinical outcome and long term prognosis of proband. Focus of presenting this case report is to convey a vital key message that primary hypomagnesaemia in addition to being a fully treatable metabolic disorder only when intervened early also needs uninterrupted, balanced, lifelong magnesium therapy both as oral diet and drugs supplements to prevent both mortality and morbidity.

**Keywords:** primary hypomagnesaemia, TRPM6, refractory seizures, neonatal period, clonic spasms, epileptogenic foci

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## Introduction

Magnesium, an essential cofactor required for normal intracellular metabolic activities related to energy storage and utilization within human biological systems has vital roles through TRPM6 gene in neuronal development and functioning.<sup>1,2</sup> Hypomagnesaemia defined as serum magnesium levels <1.8 mg/dl or <0.74 mmol/L may be primary due to hereditary causes or secondary to systemic disorders like intestinal malabsorption or polycythemia.<sup>1,3,4</sup> We report an Indian family with hereditary hypomagnesaemia and secondary hypocalcaemia (HSH) to highlight importance of early diagnosis and timely administration of adequate lifelong magnesium supplements to improve clinical outcome and long term prognosis.

## Case report

A 4 years old male child was referred to Pediatric endocrine and metabolic clinic for evaluation of primary etiology of refractory seizures since infancy. During clinical examination child was noted to have florid caries teeth, dysarthria, positive Trousseau sign, weak handgrips, generalized hypotonic and brisk deep tendon reflexes. Salient highlights of past history included the following in that child was third born to second degree consanguineous parents with history of two elder male siblings deaths in infancy due to undiagnosed refractory seizures. The index child presented with a sudden onset of multifocal, clonic spasms at 45 days of age and was treated with anticonvulsant phenobarbitone at 5 mg/kg/day. As relief was only partial, a complete evaluation was done. Blood sugar, electrolytes, liver functions, blood urea and creatinine were normal. As calcium levels were low at 5mg/dl (normal 8.5 to 10mg/dl) 10% calcium gluconate was administered at 5ml/kg/day.

Electroencephalographs recorded nonspecific epileptogenic foci. Ultrasound of the abdomen for renal cystic lesions or nephrolithiasis, magnetic resonance imaging of brain and abdomen to rule out basal ganglia abnormalities and focal space occupying lesions were reported as normal.<sup>4</sup> Tandem mass spectrometry screening performed on dried whole blood spots and gas chromatography mass spectrometry in

both plasma and urine samples ruled out amino acids and organic acid disorders. As seizures recurred and predominantly as carp pedal spasms, magnesium levels were done which revealed low values at 0.4 mg /dl (normal 1.7 to 2.6 mg/dl). Therapy with intramuscular magnesium sulphate as 50% solution at 0.2ml/kg/ dose/8 hourly restored normal magnesium values and seizures were controlled. Infant was discharged later with advice to continue both calcium and magnesium supplements in view of persistent hypocalcaemia with hypomagnesaemia.

As child was asymptomatic and neurodevelopment milestones were normal for age, inadvertent omission of calcium and magnesium supplements resulted in recurrence of carp pedal spasms at around 4 years of age. Hence a complete metabolic reevaluation was done. Biochemistry revealed persistent hypocalcaemia with total calcium varying from 4.8 to 7mg/dl, ionized calcium low at 0.41mg/dl (normal 4.8 to 5.52 mg/dl) with normal albumin. Magnesium was low varying from 0.4 to 0.9 mg/dl, phosphorus levels were normal to high (normal 4.5 to 6.5mg/dl), 25 hydroxyl vitamin D was low at 21ng/ml (normal above 30ng/ml) with reduced parathormone (PTH) levels at 5pg/ml (normal >32pg/ml) respectively. Serum creatinine levels were normal at 0.3 mg/dL (normal 0.3 to 0.7mg/dL). Urinary spot values of magnesium, sodium, chloride and calcium were 0.3 mEq/l, 180 mEq/l, 65 mEq/l and 35mEq/l respectively (normal spot urine magnesium >2mEq/l, sodium <40mEq/l, chloride <40mEq/l, calcium< 3mEq/l). Urinary calcium/creatinine ratio was 0.50 (normal<0.22) indicative of hypercalciuria. Fractional excretion of magnesium (Fe Mg) was above 4 % (normal< 2 %) (Table 1).<sup>4,5</sup>

Pedigree analysis with consanguinity and similar history of refractory seizures in all three male siblings suggested familial disorder with autosomal recessive inheritance. Persistent serum magnesium levels below 0.4 mg/dL with renal fractional excretion of magnesium more than 4% and abnormal urinary concentrations of sodium, chloride and calcium were suggestive of primary renal magnesium wasting in the index child and which could have also been cause of refractory seizures in two other elder siblings.<sup>4</sup> TRPM6 gene pathology was considered. Till date around 48 pathogenic TRPM6

mutations have been published.<sup>6</sup> Molecular analysis of transitional receptor potential TRPM6 gene confirmed a large deletion in *TRPM6* gene which encodes transient receptor potential cation channel subfamily melastatin 6, a bifunctional protein with both channel and

kinase activity regulating entry and balance of magnesium ions in membranes of distal convoluted tubules of kidneys, large intestine, lungs and testes.<sup>2,4,6</sup>

**Table 1** Salient biochemical analytes values in serum urinary samples of patient

Test dates	Ca <sup>++</sup> in Serum/Urine S/U	Mg <sup>++</sup> in Serum/Urine S/U	PTH values	Vitamin D3	Urine Ca /Urine Creatinine	FE Mg %
2012	5.9	0.4	5.12	116	-	
2013	4.8/35	0.4/0.3	5.6	110	0.5	>4%
2014 JAN	9.7	0.9	11.4	429	-	-
2014 DEC	9.4/6.9	1.10/0.7	7.9	60	4.5	1.1 %
2015	9.6/2.7	1.8	21	303	-	-
2016	9.3	1.3	-	21.9	-	

**Abbreviations:** S/U-, Serum/Urine; Ca<sup>+</sup>, Calcium; iCa<sup>+</sup>, Ionised Calcium; Mg<sup>++</sup>, Magnesium; [All Measurements as mg/dl; PTH, Parathyroid hormone [pg/ml]; Vit D<sub>3</sub> 25[OH]D<sub>3</sub> [ng/ml]; U Ca/ UCr, Urinary Calcium/Urinary Creatinine; FE Mg%, Fractional Excretion of Magnesium in urine.

## Discussion

Primary hypomagnesaemia with secondary hypocalcaemia is a rare autosomal recessive disorder characterized by profound hypomagnesaemia associated with hypocalcaemia. Path physiology is related to impaired intestinal absorption of magnesium accompanied by renal magnesium wasting as a result of a reabsorption defect in distal convoluted tubule and increased renal clearance of magnesium.<sup>1,4,6,7</sup> Magnesium metabolic derangements particularly hypomagnesaemia affect predominantly neuromuscular and cardiovascular system and ventricular arrhythmias are most life threatening. Common signs are usually sudden jerks; carp pedal spasms, muscle cramps and refractory seizures. Both hyper and hypo magnesemia states can impair parathormone (PTH) secretion which also causes secondary hypocalcaemia.<sup>7</sup>

In this child TRPM6 gene mutation possibly caused a frame shift and premature truncation of the protein. It was also noted that child had persistent diarrhea as a significant side effect of oral magnesium therapy which may have added to inadequate intestinal absorption further compromising magnesium levels and recurrence of carpo pedal spasms.<sup>8,9</sup> After stabilization of acute phase follow up advice was prescribed specifically to provide daily magnesium requirements up to 350 mg/day both as drugs and diet to prevent diarrhea with a target to maintain serum magnesium above 1.2 mEq/l. Magnesium tablets were started in a sustained release form to provide daily dosage of 120 to 140 mg/day at 5 mg to 9.6mg/kg/day with oral magnesium rich diet formulated to provide 200 to 220 mg /day along with calcitriol as a source of vitamin D at 40 ng/kg/day and oral calcium supplements at 50 to 75 mg/kg/day respectively. We have followed patient for 5 years and presently child is seizure free with appropriate growth and development.

## Conclusion

Our report is presented to emphasize the fact that primary hypomagnesaemia is a treatable metabolic disorder requiring high index of suspicion and timely management is vital to prevent mortality and intellectual disability.<sup>2,3,9</sup> carefully balanced magnesium intake as uninterrupted lifelong therapy is most vital to improve both outcome and long term prognosis.

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