

TRPM6 Gene Mutation Responsible for Familial Hypomagnesemia with Secondary Hypocalcemia

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Abstract

This case report describes a five years old Emirati boy, who had a history of convulsions (twice) at the age of two weeks, associated with reduced activity and excessive startling response. His investigation showed hypomagnesemia with normal calcium level, normal parathyroid hormone and no urinary loss of Magnesium (Mg). Mutations in the TRPM6 gene, a member of the transient receptor potential family of cation channels, was identified by the genetic study. This gene, located on chromosome 9, is expressed in the intestinal epithelium and renal cells. TRPM6 gene plays a crucial for magnesium homeostasis which is subsequently linked to the rare metabolic disorder; Familial hypomagnesemia with secondary hypocalcemia.

Keywords: Hypomagnesemia; TRPM6 gene; Hypocalcemia

1. Introduction

Familial hypomagnesemia with secondary hypocalcemia (FHS) is a rare autosomal recessive disorder of intestinal and renal magnesium (Mg^{2+}) transport, resulting in profound hypomagnesemia. Severe magnesium deficiency result in parathyroid failure and parathyroid hormone resistance, which consequently leads to secondary hypocalcemia [1]. The disease manifests as early as the neonatal period with generalized convulsions refractory to anticonvulsant medications or signs of increased neuromuscular excitability, such as muscle spasms or tetany [2]. The disease may be fatal or lead to severe neurologic sequelae if untreated promptly. Treatment includes immediate administration of magnesium, usually intravenously, followed by life-long high-dose oral magnesium [3].

2. Case Presentation

A five years old boy presented to our hospital at the age of one month with a history of convulsions twice in a week prior to admission. Semiology of Convulsion was stiffening of both arms associated with circum-oral cyanosis lasted for 15 to 20 seconds. It was also associated with excessive startling response. He was hospitalized in another hospital on the same day of convulsion, lab investigation showed low serum magnesium level of 0.07 mg/dl (Normal range: 1.7-2.2 mg/dl). Hence, he received magnesium correction and discharged after 5 days on no medication (magnesium level on discharge was 0.83 mg/dl). Two days later, serum magnesium level dropped to 0.3 mg/dl, but without convulsion. He was brought to our emergency; magnesium level was repeated and was admitted for IV magnesium correction. He was feeding well and passing normal stool and urine. Patient was born at 36 weeks gestation by LSCS as the third child to first-degree cousin parents, with unremarkable perinatal history. His birth weight was 1.9 kg. He was on exclusive breast-feeding. His other two siblings are healthy. Family history was unremarkable, with no convulsive, metabolic or genetic disorders.

On examination (upon admission at one month of age), he was pink, active & no dysmorphic features. Vital signs: Heart rate 142/min, Respiration 30/min, Blood Pressure 92/48 mmHg. Growth parameters: Weight 3 kg (3rd centile), Height 50 cm (between 10th and 50th centile), Head Circumference 36.5 cm (between 50th and 90th centile). Neurological examination was unremarkable with normal tone and reflexes and spontaneous movement of all four limbs. Other systemic examination was normal. The child was admitted for management and full investigative work-up was carried out.

2.1 Investigations

Serum sodium, potassium and glucose were normal. Magnesium level was low (0.67 mg/dl) with no urinary loss of Mg²⁺ (Mg²⁺ random urine 1.1 mg/dl, and Magnesium in 24 hours urine was 0.3 mg/24 hours (normal range 60-210), his serum Calcium was normal (9.6 mg/dl) with normal Calcium random urine (16 mg/dl), his Phosphate was normal as well (4.5 mg/dl) with normal Phosphate random urine (0.3 mg/dl). His Parathyroid hormone was also normal 6.5 pg/ml (normal range 6.2-29 pg/ml).

2.2 Management and progress

The patient received intravenous Magnesium Sulphate. Magnesium level increased to 1.1 mg. He was discharged after 3 days on oral Magnesium Glycerophosphate 0.6 mmol TID. Magnesium level at the time of discharge was 1.12 mg/dl and was advised to repeat serum magnesium after 3 days. 5 days later, he was readmitted as serum magnesium dropped to 0.68 mg/dl, although he was compliant with medications. He was given one dose of IM Magnesium Sulphate and oral magnesium dose was increased. His Magnesium level improved and he was discharged home after 3 days.

2.3 Differential diagnosis

In view of recurrent severe hypomagnesemia, we excluded non-hereditary or secondary causes of hypomagnesemia; as medications, hypoparathyroidism, intestinal causes (as chronic diarrhea, steatorrhea, malabsorption or inflammatory bowel), or renal disorders (Recovery after acute tubular injury). Gitelman and Bartter syndrome was excluded as investigations showed no alkalosis, hypokalemia, hypocalciuria, and hypermagnesuria. The possibility of primary hereditary cause of hypomagnesemia was considered. Surprisingly, normal serum calcium level as well as normocalciuria with normal parathyroid hormone level were noted. Thereafter, patient was regularly followed up in the Pediatric outpatient clinic. Oral magnesium dose was increased accordingly. During Pediatric clinic follow up patient remained well, achieving normal developmental milestones as per his age.

At the age of 3 years, Parent sought second opinion in Germany at University Children's hospital. A diagnosis of primary hypomagnesemia/secondary hypocalcemia was also raised; hence, a mutation analysis for TRPM6 gene was performed. TRPM6 gene mutation was confirmed. The coding region of TRPM6 including adjacent intron /exon boundaries was completely sequenced. One homozygous truncating mutation was identified. The insertion of a single nucleotide leads to a shift of the reading frame of translation and a premature stop codon at position 1017. The truncated TRPM6 protein is lacking the pore region, sixth transmembrane domain and entire c-terminus of the ion channel subunit (c.2998_2999ins T; p.S1000fs1017), and therefore is presumed to lead to a complete loss of function.

3. Discussion

Familial/ primary hypomagnesemia with secondary hypocalcemia (FHS) is a rare autosomal recessive disease. Affected patients have evidence of a defect in the magnesium permeable ion channel encoded for by the transient receptor potential melastatin 6 (TRPM6) gene on chromosome 9q22.1. This gene is expressed in the intestine and the apical membrane of the distal convoluted tubules (DCT) of the kidney. Subsequently there is a defect in intestinal absorption and impaired renal reabsorption of Mg^{2+} leading to serum hypomagnesaemia [4]. In the past FHS was thought to be an X linked recessive disorder until 1997 when the autosomal recessive inheritance was proven [5, 6]. To date, approximately 100 cases have been reported in the literature, where both sexes are equally affected [5, 6]. Affected individuals appear to have an isolated defect of intestinal magnesium absorption with normal or low renal magnesium excretion at diagnosis; the renal magnesium leak only becoming apparent once the serum magnesium concentration rises, indicating a reduced renal threshold for magnesium. This increase in fractional excretion of magnesium after adequate replacement is a valuable test to aid diagnosis [2]. In our case, urine magnesium level remained normal. FHS typically manifests during the first months of life with convulsions, muscle spasms or tetany. Relief of symptoms is achieved by administration of intravenous or intramuscular magnesium followed by life-long treatment with high-dose oral magnesium [2].

Our patient presented stiffening of both arms associated with circum-oral cyanosis lasting for 15 to 20 seconds. Hypocalcemia results from a secondary insufficiency of the parathyroid glands in the presence of profound

hypomagnesemia [7]. Surprisingly, our patient has normal serum calcium level at the time of diagnosis. Our patient has been followed regularly, with serial measurement of serum magnesium level and adjustment of the dose of oral magnesium accordingly. Currently, he is 5 years old, doing well with normal development, on regular Magnesium supplementation, with normal serum magnesium levels.

4. Conclusion

We report this case to alert the clinician towards this rare disease, since any delay in diagnosis may cause adverse neurodevelopmental outcome and sometimes may be fatal, the early treatment being very important for prognosis.

Declaration of Interest

None

Conflict of Interest

We declare that there is nothing to disclose and there is no conflict of interest

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