International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Familial Hypomagnesemia with Secondary Refractory Seizures in a Neonate Born to Consanguineous Parents

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Abstract: ***We report the case of an 80-day-old male neonate who presented with recurrent seizures since the 35th day of life, refractory to conventional antiepileptics. Genetic testing revealed a homozygous pathogenic variant in the TRPM6 gene, confirming the diagnosis of familial hypomagnesemia with secondary hypocalcemia (HOMG1). The child responded dramatically to magnesium supplementation with seizure freedom for 14 days at follow-up. This case highlights the importance of considering metabolic and genetic causes of neonatal seizures, particularly in consanguineous families, and contributes to the limited global literature on TRPM6-related hypomagnesemia.***

Keywords: Refractory seizures, hypomagnesemia, neonatal seizures, hypocalcemia, channelopathy, consanguinity.

1. Introduction

Neonatal seizures are one of the most common neurological emergencies, with an incidence of 1–3 per 1,000 live births [1]. While hypoxic-ischemic encephalopathy is the leading cause, metabolic and genetic etiologies account for a significant subset, especially when seizures are refractory to conventional antiseizure medications. One such rare cause is familial hypomagnesemia with secondary hypocalcemia (HOMG1), first described in the 1960s and later linked to mutations in the TRPM6 gene [2, 3].

TRPM6 encodes a magnesium-permeable cation channel expressed in the intestine and distal renal tubules. Dysfunction leads to defective intestinal absorption and renal conservation of magnesium, resulting in profound hypomagnesemia and secondary hypocalcemia. Affected neonates usually present between the third and sixth week of life with refractory seizures, irritability, and tetany [4, 5]. If left untreated, this condition can lead to permanent neurological impairment or death.

Here, we present a genetically confirmed case of TRPM6-related familial hypomagnesemia, occurring in a neonate born to consanguineous parents after 10 years of infertility treatment—highlighting both the clinical and genetic significance of this disorder.

2. Case Presentation

An 80-day-old male neonate was referred for evaluation of recurrent seizures since day 35 of life. Seizures were described as generalized tonic–clonic movements with bicycling of lower limbs, lasting 1–2 minutes, occurring several times daily. There was no history of fever, perinatal asphyxia, or infection.

- Birth history: The baby was born full term via vaginal delivery, cried immediately at birth, with a birth weight of 3.5 kg.
- Family history: Third-degree consanguineous parents. A family history of seizures was noted. The child was conceived after 10 years of infertility treatment, adding psychosocial relevance.
- Examination: Weight 4.2 kg, head circumference 38 cm, no dysmorphic features. Neurological examination was unremarkable between seizures.

Investigations:
Serum magnesium: markedly reduced.
Serum calcium: low–normal.
MRI brain: enlargement of subarachnoid spaces in bilateral frontoparietal regions, but otherwise normal myelination.
Genetic testing (whole exome sequencing):
Homozygous c.3924_3927del p.Glu1309Leufs (exon 26) in TRPM6, classified as Likely Pathogenic per ACMG criteria.

Management: The child was initiated on intravenous magnesium supplementation during acute seizures, later transitioned to oral magnesium sulfate (1.5 g/kg/day), with concurrent calcium, vitamin D, and multivitamin therapy. Antiepileptic therapy with phenobarbital was started but tapered after stabilization.

Outcome: The child remained seizure-free for 14 days on follow-up with normalization of magnesium levels.

3. Discussion

Pathophysiology: Magnesium plays a critical role in neuronal excitability by modulating NMDA receptors and calcium channels. In TRPM6-related hypomagnesemia, profound deficiency results in hyperexcitability and seizures [4, 6]. Secondary hypocalcemia is explained by impaired parathyroid hormone release and action in magnesium deficiency [5].

4. Review of Literature

Since the identification of TRPM6 in 2002, fewer than 100 cases of HOMG1 have been reported worldwide [2,3】. Most cases originate from Europe, the Middle East, and South Asia, where consanguinity is prevalent [3, 6]. Typical presentation occurs between the 3rd and 8th week of life with seizures

refractory to conventional antiepileptic drugs, often accompanied by tetany and neuromuscular irritability. Consanguineous parentage has been repeatedly described, reflecting the autosomal recessive inheritance [6].

Genetic studies reveal a spectrum of mutations including frameshift, nonsense, and missense variants, with significant allelic heterogeneity. No founder mutation has been identified, underscoring the genetic diversity of TRPM6 defects [2–4, 6]. Importantly, delayed diagnosis is associated with intellectual disability, motor delay, or even mortality, whereas early recognition and magnesium replacement leads to excellent prognosis [4,6, 7].

Novelty of the present case:

1) It represents one of the first genetically confirmed homozygous TRPM6 frameshift variants from India, thereby expanding the global mutational spectrum.
2) The child was born after a decade of infertility treatment in a consanguineous marriage, highlighting the psychosocial importance of genetic counseling in high-risk families.
3) Early diagnosis and initiation of magnesium supplementation resulted in complete seizure freedom, emphasizing the need for prompt biochemical evaluation in neonatal seizures unresponsive to antiepileptic drugs.

5. Conclusion

This case emphasizes the importance of recognizing familial hypomagnesemia with secondary hypocalcemia as a treatable cause of refractory neonatal seizures. Genetic confirmation is vital for diagnosis, prognosis, and counseling. In regions with high rates of consanguinity, awareness of such rare metabolic disorders is essential to prevent long-term neurological sequelae.

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