# Familial Hypomagnesemia with Secondary Hypocalcaemia Due to TRPM6 Gene Mutation in A Pediatric Patient

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**Abstract**

***Familial hypomagnesemia with secondary hypocalcemia (FHSH) is a rare genetic autosomal recessive disorder caused by mutations in the TRPM6 gene, which encodes for the receptor which serves as an active channel that transports Mg2+ and Ca2+ ions. It results in hypomagnesemia and secondary hypocalcemia. Typical symptoms begin in the neonatal period with seizures and tetany that are resistant to antiepileptic medications. This is a treatable condition, and the treatment involves magnesium and calcium supplementation. If left untreated, prolonged hypomagnesemia can lead to long-term disability. Here we report a case of a 50-day-old term female infant, born to non-consanguineous parents, who presented with recurrent generalized seizures starting at 40 days of age. Initial evaluation revealed severe hypocalcemia with persistent seizures despite calcium and antiepileptic therapy. Further workup showed marked hypomagnesemia with hyperphosphatemia. Seizures responded only after magnesium supplementation. Genetic testing confirmed a TRPM6 gene mutation, establishing the diagnosis of primary hypomagnesemia with secondary hypocalcemia. The patient achieved complete seizure control and normal milestones of development with appropriate magnesium replacement therapy.***

***Key words: TRPM6 mutation, hypomagnesemia, hypocalcemia, neonatal seizure***

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## Background

Familial hypomagnesemia with secondary hypocalcemia (FHSH) is a rare genetic disorder, inherited in an autosomal recessive pattern. It is caused by mutations in the TRPM6 gene, located on chromosome 9q22, that encodes transient receptor potential melastatin 6 (TRPM6). This receptor serves as an active cation channel that transports Mg2+ and Ca2+ ions.[1,2] The main defect in FHSH is the reduced absorption of magnesium, along with renal wasting, resulting in extreme hypomagnesemia.[3] Hypocalcemia occurs secondarily due to hypomagnesemia.[4,5] Magnesium (Mg) is the fourth most abundant mineral in the human body. It acts as a cofactor for enzymes, regulating a number of essential functions such as muscle contraction, neuromuscular conduction, blood sugar regulation, myocardial contraction, and blood pressure control [6,7].

FHSH clinically manifests in newborns with symptoms of neuromuscular hyperexcitability, including tetany and seizures that are unresponsive to typical anti-seizure

medications.[8,9] If left untreated, prolonged hypomagnesemia can result in developmental delays, intellectual disability, failure to thrive, and severe heart muscle issues. Diagnosis involves genetic testing to identify mutations in the TRPM6 gene responsible for FHSH.[10]

Immediate treatment involves intravenous magnesium administration to alleviate symptoms and restore normal calcium levels, followed by long-term oral magnesium supplementation. Timely recognition and management are crucial to prevent mortality and long-lasting neurological complications. Here we report the case of a female infant with a mutation of the TRPM6 gene, detailing her initial presentation and subsequent care.

**Case presentation**

A 50-day-old female baby, the first issue of non-consanguineous parents, was referred to a tertiary hospital due to uncontrollable seizures for the past 10 days. She was born via normal vaginal delivery at term, with a birth weight of 2.8 kg in 2023, after an uneventful pregnancy. Initially, she was breastfed. She appeared to be well until the age of 40 days, when she began to experience several attacks of generalized convulsions, each lasting about 5-10 minutes. She was admitted to a private hospital on the same day. Physical examination revealed a normal but irritable baby.

Investigations at a local hospital, which included a complete blood count, urinalysis, serum electrolytes, blood sugar, cerebrospinal fluid examination, ultrasound of the brain, and CT scan of the brain, were all within normal limits except for the serum calcium level, which was 6.28 mg/dL. Standard antiepileptic therapy and parenteral calcium were administered, resulting in a partial response. She continued to have 1-2 seizure episodes every day, each lasting 5-10 minutes.

Upon admission to a tertiary care hospital, her serum calcium level was 5.06 mg/dL (normal range: 8.8-10.2 mg/dL), serum magnesium was 0.97 mg/dL (normal range: 1.30-2.70 mg/dL), and serum inorganic phosphate (PO4) was 6.15 mg/dL (normal range: 2.4-5.1 mg/dL). An electroencephalogram revealed nonspecific changes in the background activity. After initial treatment with parenteral calcium and magnesium, followed by oral magnesium chloride 50% solution at 0.5 ml daily, the seizure frequency gradually decreased and eventually disappeared completely over the next few days.

During the early stages of follow-up, she had occasional tonic seizures with low serum magnesium levels. Shortly after the dosage of magnesium chloride was increased to 0.5 ml twice daily, serum magnesium and calcium levels were maintained within normal ranges, and no further seizures were observed. No evidence of malabsorption was found. Whole exome sequencing was sent to MedGenome Labs Ltd, India, and the report revealed pathogenic mutations in the TRPM6 gene.

She is on regular follow-up. Till reporting, she continued to receive a daily oral supplement of magnesium as a 50% magnesium chloride solution in divided doses without any side effects. At the age of 2 years, she had a normal height and weight for her age. The neurological examination and electroencephalogram were normal.4

| Gene (Transcript) | Location | Variant | Zygosity | Disease (OMIM) | Inheritance | Classification |
|---|---|---|---|---|---|---|
| TRPM6(-) (ENST0000036 0774.6) | Exon 28 | c.4792_4793delins TA (p.Thr1598Ter) | Homozygous | Familial hypomagnesemi a with secondary hypocalcemia (OMIM#602014) | Autosomal recessive | Likely Pathogenic (PVS1,PM2) |

## Discussion

Primary hypomagnesemia with secondary hypocalcemia is a rare genetic disease that was first described by Paunier and colleagues in 1968.[11]

The disease stems from a TRPM6 gene mutation affecting Mg and Ca transport. TRPM6, expressed in the small intestine and distal tubule, contributes to hypomagnesemia through impaired Mg reabsorption and renal wasting. This hypomagnesemia further leads to lowered calcium levels by inhibiting parathyroid hormone synthesis and release due to significant hypomagnesemia.[2]

During prenatal development, magnesium is provided through free exchange across the placenta. Following birth, magnesium levels gradually decline until hypomagnesemia becomes clinically noticeable within a few weeks. In the presence of hypomagnesemia, the kidneys work to conserve magnesium by reducing the fractional excretion of magnesium to below 0.5-1% (normal range is 3-5%).[12]

The primary manifestations of Familial Hereditary Hypomagnesemia with Secondary Hypocalcemia (FHSH) typically involve neurological symptoms such as seizures, tetany, tremors, and restlessness. Our patient experienced seizures in early infancy at 40 days old, a presentation consistent with previously documented cases.[13,14]

Familial hypomagnesemia with secondary hypocalcemia (FHSH) is a treatable condition. Our patient received initial treatment with intravenous magnesium and calcium, followed by oral magnesium supplements, which is consistent with other documented cases.[15] Early diagnosis and treatment can prevent long-term disability. Although FHSH is rare, genetic testing should be considered when there is a strong clinical suspicion, as the condition is treatable.

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