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Case Report

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Familial Hypomagnesemia with Secondary Hypocalcemia

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Abstract

Familial hypomagnesemia with secondary hypocalcemia (FHSH) is a rare autosomal recessive disorder of magnesium metabolism. It occurs due to decreased intestinal absorption of magnesium and renal magnesium wasting with secondary parathyroid insufficiency leading to hypocalcemia. If adequate magnesium is not supplemented orally, then children continue to develop recurrent seizures secondary to hypocalcemia that can lead to stagnation of development of milestones and even regression of milestones. As it is customary to look for hypocalcemia in infants with seizures, most pediatricians detect hypocalcemia in these children and treat it symptomatically. Etiological work up of hypocalcemia is usually not done. Many a times hypomagnesemia as a cause of hypocalcemia is missed and even if picked up on investigation, it is not adequately treated because of lack of oral magnesium formulations.

1. Introduction

Hypomagnesemia can lead to convulsions. Magnesium is mainly associated with neuromuscular conduction and cardiovascular tone, and its deficiency can reduce the release of acetylcholine in neuromuscular junctions and nerve terminals, playing an important part in antagonizing peripheral nerve function. Symptoms like increasing nerve excitability similar to Novel TRPM6 Mutation Cause HSH that associated with hypocalcemia, appear when magnesium is deficient in the body. When hypomagnesemia accompanies hypocalcemia, the symptoms of convulsions are more severe. Hereditary hypomagnesemia with secondary hypocalcemia is a rare autosomal recessive disease due to homozygous or compound heterozygous mutations in the TRPM6 gene. HSH as a disorder of significantly decreased serum magnesium levels, usually <0.7 mmol/L, accompanied by secondary hypocalcemia. In patients with HSH, muscle weakness, tetany that does not respond well to antispasmodic medications, and polyuria are common in their infantile period. HSH needs to be differentially diagnosed to distinguish it from epilepsy. Currently, approximately 100 cases are documented, and no dominant inherited or incomplete penetrance was observed in affected families.

2. Case Report

A 4-month-old girl born of a non-consanguineous marriage presented with multiple episodes of generalized tonic clonic convulsions for the past one month. These episodes were associated with up-rolling of eyes and clenching of fists. There was no associated urinary or bowel incontinence. According to the parents, there was no post-ictal confusion. The patient would go to sleep after the episode and wake up normally without any residual symptoms. The seizures had an increasing frequency since the past 2 weeks. Upon presentation to the hospital emergency, physical examination was normal.

Electroencephalogram (EEG) showed no epileptiform discharges and brain MRI was unremarkable. There were no dysmorphic features and no neurocutaneous or meningeal abnormalities.

Neurological examination was also unremarkable with normal tone and reflexes of all 4 limbs. The laboratory workup showed severely low magnesium and mildly decreased calcium levels. She had no evidence of parathyroid abnormality and both calcium to creatinine ratio and magnesium excretion were normal. Stool analysis was not done. Ultrasound examination of the abdomen and pelvis revealed no signs of nephrocalcinosis. Given the severe hypomagnesemia and mild hypocalcemia, the patient was given two boluses of intravenous magnesium sulfate and intravenous calcium gluconate infusion. She was hospitalized in the pediatric unit to investigate the underlying causes of the recurrent seizures. The clinical and laboratory findings suggested that the electrolyte imbalance was the most likely cause for her presentation.

Numerous pediatric subspecialties were consulted to investigate the underlying cause of hypomagnesemia and secondary hypocalcemia. Intestinal loss was determined to be an unlikely cause of hypomagnesemia as there was no history of laxative use and no signs or symptoms of malabsorption. At this point, the diagnosis of FHSH as the cause of magnesium homeostasis disruption was suspected. Two Pathogenic variants, Deletion (Exons 20-23) (homozygous), were identified in TRPM6. The TRPM6 gene is as-

sociated with autosomal recessive familial hypomagnesemia with secondary hypocalcemia(MedGenUID: 355596). The patient was retained in the pediatric ICU for further monitoring and electrolyte replacement. Levetiracetam was given to keep the patient seizure free. Patient was discharged on high dose oral magnesium and calcium supplements.

At follow-up, two months after her discharge, the magnesium level stayed within the normal range of 0.68 mmol/L, and she continued to be seizure-free.

3. Discussion

Primary hypomagnesemia with secondary hypocalcemia (HSH) is an autosomal recessive disorder characterized by neuromuscular symptoms in infancy due to extremely low levels of serum magnesium and moderate to severe hypocalcemia [1]. Homozygous mutations in the magnesium transporter gene transient receptor potential cation channel member 6 (TRPM6) cause the disease. HSH can be misdiagnosed as primary hypoparathyroidism. Magnesium constitutes the majority of intracellular cations and is absorbed through the small and large intestine via two distinct transport pathways [2]. It is also absorbed through the kidneys with the majority (60-70%) absorbed via the thick ascending limb of Henley (TAL). The balance of gastrointestinal absorption and renal excretion influences magnesium hemostasis. Magnesium is necessary for the function of numerous enzymes and the regulation of several ion channels, and the stabilization of negatively charged molecules [3]. Affected individuals have a defect in the magnesium permeable ion channel encoded for by the transient receptor potential mela statin 6 (TRPM6) gene on chromosome 9q22. This gene is expressed in the intestine and the kidney, but the defect primarily affects the intestine, leading to serum hypomagnesaemia. Presentation is usually in the neonatal period with hypocalcemia refractory to calcium supplementation. The condition is treatable but failure to diagnose early can lead to intractable seizures with irreversible cerebral damage and mental retardation, or even death. Recent reports have suggested initial investigations for neonates presenting with seizures do not always include assessment for serum magnesium abnormalities. Calcium supplementation alone in these scenarios will fail to be effective and result in significant morbidity or mortality. Genetic diagnosis of HSH is now possible but treatment remains lifelong high-dose magnesium supplementation. This condition should be included in the differential diagnosis of any neonate presenting with seizures [4].

Magnesium is a critical cofactor for numerous enzyme systems and its deficiency may result in varied clinical manifestations. In adults chronic magnesium depletion has been linked with hypertension, arrhythmias, atherosclerotic vascular disease, and metabolic bone disease. However, since these complications can result from other chronic illnesses in adults, the exact role of hypomagnesaemia is undefined. Children with primary hypomagnesaemia are commonly reported as presenting with tetany or convulsions, or both [5]. Treatment usually consisted of acute intravenous magnesium supplementation leading to relief of clinical symptoms and normokalaemia, followed by lifelong oral magnesium supplementation. Serum magnesium levels remained in the subnormal range despite adequate therapy. This is best explained by a disturbed magnesium conservation in the distal convoluted tubule, which emerged in all patients upon magnesium supplementation. Delay of diagnosis resulted in permanent neurologic damage in three patients [6]. Asymptomatic patients should be treated with oral magnesium supplements. Parenteral magnesium should be reserved for symptomatic patients with severe magnesium deficiency (< 1.2 mg/dL). Establishment of adequate renal function is required before administering any magnesium supplementation. The median (range) follow-up duration was 12.1 (7.6-21.7) years. Four different mutations, three of which had not been previously reported, were detected in the TRPM6 gene. Treatment compliance was good and there were no severe complications in the long-term follow-up of cases. However, mental retardation, specific learning difficulty and attention deficit/hyperactive disorder were observed as comorbidities [7].

4. Conclusion

Familial hypomagnesemia with secondary hypocalcemia (FHSH) is a rare autosomal recessive disorder characterized by profound hypomagnesemia associated with hypocalcemia. It is caused by mutations in the gene encoding transient receptor potential cation channel member 6 (TRPM6). It usually presents with neurological symptoms in the first months of life. We report a case of a neonate presenting with recurrent seizures and severe hypomagnesemia. The genetic testing revealed a novel variant in the TRPM6 gene. The patient has been treated with high-dose magnesium supplementation, remaining asymptomatic and without neurological sequelae. Early diagnosis and treatment are important to prevent irreversible neurological damage

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

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Patient consent

Written informed consent has been obtained from the patients' mother for publication of the submitted article.

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