ORIGINAL RESEARCH PAPER

Endocrinology

TRPM6 GENE MUTATIONS IN TWO SIBLINGS OF GENETIC HYPOMAGNESEMIA WITH HYPOCALCEMIA AND HYPOPARATHYROIDISM

KEY WORDS: Hypocalcemia, hypomagnesemia, hypoparathyroidism, TRPM6 gene

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ABSTRACT

Hypomagnesemia can cause neuromuscular irritability, seizures and cardiac arrhythmias. Mutations in the gene of transient receptor potential cation channel subfamily M member 6 *(TRPM6)* cause the most profound genetic hypomagnesemia. We described two siblings with *TRPM6* mutations. First case was applied with seizure at 5-month old and she had hypomagnesemia, hypocalcemia and hypoparathyroidism. Second case had also seizure with hypomagnesemia, hypocalcemia on newborn period. The molecular analysis confirmed the genetic cause of hypomagnesemia in cases by identifying the pathological homozygous variants c.2667+1G>A in *TRPM6*. To conclude, magnesium levels should also be checked in cases with hypocalcemia and hypoparathyroidism, genetic causes should be considered in case of hypomagnesemia and molecular analysis should be prioritized for early diagnosis.

INTRODUCTİON

The transient receptor potential cation channel subfamily M member 6 (TRPM6) gene provides instructions for making a protein that acts as a channel, which allows charged ions of magnesium (Mg2+) to flow into cells; the channel may also allow small amounts of calcium ions (Ca2+) to pass through cells (1-3). This gene is predominantly expressed in the kidney and colon, and encodes a protein containing an ion channel domain and a protein kinase domain for the distal convoluted tubule (DCT) and colon-specific apical Mg2+ channel (1-3). Magnesium is essential to the proper functioning of numerous cellular processes, including production of cellular energy, maintenance of DNA building blocks, protein production, and cell growth and death. Additionally, Mg2+ is needed for the production of parathyroid hormone (PTH) that regulates serum calcium levels. Magnesium and calcium are also required for the normal functioning of nerve cells that control muscle movement (motor neurons) (4). Hypomagnesemia can cause neuromuscular irritability, seizures and cardiac arrhythmias (1-4). Mutations in *TRPM6*, cause the most profound genetic hypomagnesemia. A defect in the TRPM6 channel impairs epithelial Mg2+ resorption in the colon and DCT, thereby inhibiting uptake and stimulating wasting of Mg2+, causing hereditary hypomagnesemia with secondary hypocalcemia (HSH) (1,5). HSH is a rare autosomal recessive disease (1,5), hereby we presented the clinical follow-up of two HSH siblings due to a mutation in the TRPM6 gene. We highlighted the need for checking serum magnesium levels in all cases of hypocalcemia and hypoparathyroidism and giving priority to molecular analysis espesially in inbred or familial cases.

Case 1

The 5-month old girl baby was admitted to another hospital with afebrile seizure. In the initial laboratory examination, hypocalcemia with hypoparathyroidism were detected whereas serum magnesium level did not be checked. The treatment for hypocalcemia was started to the baby. Serum calcium level was 7 mg/dl, iCa was 2 mg/dl and PTH was 6.7 pg/ml. The electroencephalography (EEG) was normal but cerebellar atrophy was determined in cranial Magnetic Resonance Imaging (MRI). Although the baby was treated with sodium valproate, fenobarbital, calcium and calcitriol, persistent seizures continued and in the second evaluation, hypomagnesemia was detected. The oral magnesium citrate was added to the treatment with 75 mg/kg/day dosage in 3 divided doses. The patient was referred to our endocrinology clinic with the diagnosis of hypomagnesemia, hypocalcemia and hypoparathyroidism. She followed with the diagnosis of hypomagnesemia and hypocalcemia until she had a brother with the same diagnosis and had a molecular definitive diagnosis. The last assesment was done at the age of 8 years and 10 months. The patient has mild neuromotor retardation. She takes risperidone and magnesium treatment. Her seizures are under control and her serum magnesium level is normal with these therapies (Table 1).

Case 2

Second case was the sibling of the first case. The three-week old boy was admitted with seizure. He had serum magnesium level of 1.29 mg/dL (1.6-2.6). The EEG was normal and in MRI corpus callosum was bulged, 4th and lateral ventricles were slightly enlarged. The oral magnesium citrate (110 mg/kg/day in 3 divided doses) was started to the baby. The last assesment was done at age of 23 months, he had mild hypotonia during in the first year of life and he started walking after physiotherapy in 22 months. Hypomagnesemia was thought to be genetic in these siblings due to similar clinical presentation. There was a consanguinity between parents (first-cousin marriage). The molecular analysis confirmed the genetic cause of hypomagnesemia in these siblings by identifying the pathological homozygous variants c.2667+1G>A in TRPM6 gene, so these siblings had diagnosis of HSH.

DİSCUSSİON

In this article, we described the clinical phenotype and follow-up of two siblings with HSH due to a mutation in the TRMP6 gene. Previous reports state that the onset of the disease is in early infancy at an average age of 4.9 weeks (4-12 weeks), similar to these reports, our 2nd case presented in early infancy however, our 1st case was admitted at 5 month-old. Also, similar to previously reported cases, our cases presented with seizures, a symptom which is the most common manifestation of primary hypomagnesemia in children (7-9). Oral magnesium was successful in our cases to achieve a Mg2+ level providing a convulsion-free state. Although some cases who had the longest disease duration has been reported to have no serious complications, failure to thrive and mental retardation are the most frequently reported complications of the HSH (6,10). These complications have been attributed to non-compliance to treatment and/or to refractory convulsions due to delayed diagnosis (6,10). Although our 2nd case had early diagnosis, both of siblings had pathological MRI findings and stated delayed or problematic neurodevelopmental outcome. A characteristic feature of the condition is an extremely low level of serum magnesium (in most cases below 0.4 mmol/l) (6). Similar to literature, 2nd case had serum magnesium as 1.29 mg/dl (0.4 mmol/L). The pathological homozygous variants c.2667+1G>A in *TRPM6* of our cases have been reported before (8). However, to our knowledge, estimated incidence is low and number of known patients of TRPM6 gene mutation is only multiples of 10 (1). Until now, 11 Turkish patients with 8 different mutations were reported (6). We wanted to report our cases on the basis of limited number of HSH and added new Turkish cases to the literature.

CONCLUSİON

HSH is sometimes misdiagnosed as primary hypoparathyroidism, due to the initial presenting symptoms of hypocalcemia and concomitant low or inappropriate normal PTH. The clinical symptoms of hypomagnesemia are not easily distinguished from the symptoms of hypocalcemia. To conclude, magnesium levels should also be checked in cases with hypocalcemia and hypoparathyroidism. Early diagnosis is decisive to avoid neurological problems that can lead to permanent neurological injury or even sudden death as a consequence of arrhythmias. The genetic causes should be considered in case of hypomagnesemia and molecular analysis should be prioritized for early diagnosis.

Table 1. Laboratory of cases under treatment with additional results

Laboratory results	References	Case 1	Case 2
Glucose	65-100 mg/dL	92	75
Ca	8.6-10.2 mg/dL	8.9	9.6
P	2.7-4.5 mg/dL	4.8	5.1
ALP	35-105 U/L	260	375
PTH	15-68.3 pg/mL	45.3	36.3
Vit D3	> 20 pmol/L	27.3	44.9
Mg	1.6-2.6 mg/dL	1.8	1.8
Total cholesterol	<200 mg/dL	157	135
LDL	<100 mg/dL	96	88
HDL	> 40 mg/dL	47	36
Triglycerides	< 150 mg/dL	70	53
Urea	5-18 mg/dL	9	6
Creatinine	0.3-1 mg/dL	0.52	0.4
Blood gases		Normal	Normal
Urinal ultrasonography		Normal	Normal
Eye examination		bilateral anterior segment and fundus are natural	bilateral anterior segment and fundus are natural
Molecular analysis of TRPM6 gene		Pathological homozygous variants c.2667+1G>A	Pathological homozygous variants c.2667+1G>A

ALP: Alkaline phosphatase, Ca: Calcium, HDL: High density lipoprotein, LDL: Low density lipoprotein, Mg: Magnesium, P: Phosphorus, PTH: Parathormone, Vit D3: 25-hydroxyvitamin D

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