**Long-term Clinical Follow-up of Patients with Familial Hypomagnesemia with Secondary Hypocalcemia**

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What is already known on this topic?

Hypomagnesemia with secondary hypocalcemia (HSH) is a rare autosomal recessive disease which is characterized by selective magnesium malabsorption related to a mutation on the transient receptor potential melastatin 6 (TRPM6) gene. Affected cases are usually diagnosed during infancy and usually present with seizures due to hypocalcemia and hypomagnesemia, due to irreversible neurological deficits and arrhythmias.

What this study adds?

Long-term follow-up data and treatment responses in six cases of HSH is presented. Of the four mutations identified in the TRPM6 gene, three were novel. Controversial topics in HSH are discussed, including short stature and testicular hypofunction. In addition, the genetic and clinical features of all Turkish patients previously reported are reviewed.

**Abstract**

**Objective:** Familial hypomagnesemia with secondary hypocalcemia (HSH) is a rare autosomal recessive disease caused by a mutation in the transient receptor potential melastatin 6 (TRPM6) gene and is characterized by selective magnesium malabsorption. Affected cases are usually diagnosed during infancy and usually present with seizures due to hypocalcemia and hypomagnesemia. Irreversible neurological deficits and arrhythmias can be observed without appropriate treatment. The aim was to evaluate the long-term follow-up of patients with genetically confirmed HSH.

**Methods:** A total of six patients with HSH, two of whom were siblings, were included. Age at diagnosis, clinical, laboratory and follow-up data on admission were recorded. All 39 exons of the TRPM6 gene and flanking exon-intron junctions from genomic DNA were amplified and sequenced in all cases.

**Results:** The median (range) follow-up duration was 12.1 (7.6-21.7) years. All cases were diagnosed in infancy. 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.

**Conclusion:** Of the four different TRPM6 mutations in this small cohort, three had not been previously reported. The long-term prognosis of HSH appears to be good, given early diagnosis and good treatment compliance. This long-term follow-up and prognostic data and the three novel mutations will contribute to the published evidence concerning this rare condition, HSH, and it is hoped will prevent negative outcomes.

**Keywords:** Hypomagnesemia, hypocalcemia, TRPM6 mutation
Introduction

Familial hypomagnesemia with secondary hypocalcemia (HSH) is a rare, autosomal recessively inherited disease, due to transient receptor potential melastatin 6 (TRPM6) gene mutation. HSH is seen in the early infancy period and may be characterized by hypocalcemia secondary to hypomagnesemia and symptoms of neuromuscular excitability, such as generalized seizures, muscle cramps and agitation (1). TRPM6 functions as a cation channel with high permeability to magnesium (Mg) ions (Mg$^{2+}$) and the activity of the TRPM6 protein is regulated by intracellular Mg$^{2+}$ levels (2). It is expressed in intestine and renal distal convoluted tubules. TRPM6 mutations cause hypomagnesemia by intestinal and renal Mg wasting. Hypocalcemia in HSH is secondary to parathyroid hormone (PTH) resistance and decreased PTH release because of hypomagnesemia (3,4). Mg plays essential roles in normal cell physiology throughout the body. It is difficult to distinguish the clinical manifestations of HSH from other causes of hypocalcemia such as hypoparathyroidism. If hypomagnesemia cannot be detected and treated rapidly, fatal convulsions, irreversible neurodevelopmental deficits and life-threating arrhythmias may develop. No genotype-phenotype correlation between mutations in TRPM6 and the severity of HSH have been identified.

In this study, clinical features and long-term follow-up data of six patients with HSH who had TRPM6 mutation are presented.

Methods

Patients

The clinical files of six HSH patients from five different families and who were followed-up in our clinic since 1998 were evaluated retrospectively. Primary hypomagnesemia was diagnosed biochemically and the low serum Mg$^{2+}$ levels present a requirement for high dose Mg$^{2+}$ treatment. Exclusion criteria were secondary hypomagnesemia, such as being an infant of diabetic mother, intestinal malabsorption, and clinical conditions such as short bowel syndrome and exposure to various drugs, such as proton pump inhibitors, antibiotics, diuretics, and chemo-therapeutic agents. The levels of serum electrolytes, serum creatinine (Cr), alkaline phosphatase, PTH, 25 (OH) vitamin D and urinary Mg$^{2+}$, Ca, P, Cr of the parents were also evaluated.

Results

Five male cases and one female case from five different families, diagnosed with primary hypomagnesemia, were included in the study. All patients presented with afebrile convulsions from between one and nine months of age at first admission. Consanguineous marriage was present in three families, one of which contained two affected siblings.
The clinical and laboratory findings of the subjects at the time of diagnosis and follow-up are presented in Table 1. The follow-up period of the subjects ranged from 7.5 to 21.6 years.

All cases were diagnosed with hypomagnesemia on admission, except one case (F4). This patient was admitted with a seizure at 3.5 months of age and the initial diagnosis was hypoparathyroidism because serum Mg was not assessed. Anticonvulsant treatment (phenytoin, phenobarbital) was started due to persistence of seizures despite calcitriol treatment. Hypomagnesemia was eventually diagnosed at seven months of age with the

Table 1. Laboratory, genetic and follow-up features of cases with familial hypomagnesemia with secondary hypocalcemia

|                     | F1.1     | F1.2     | F2         | F3         | F4         | F5         |
|---------------------|----------|----------|------------|------------|------------|------------|
| Age on admission (months) | 9        | 1        | 1.5        | 3          | 5.5        | 5          |
| Age on diagnosis (months)  | 9        | 1        | 1.5        | 3          | 7          | 5          |
| Gender               | Male     | Male     | Male       | Female     | Male       | Male       |
| Symptoms on admission| Seizures | Seizures | Seizures   | Seizures   | Seizures   | Seizures   |
| Serum Ca on admission (2.1-2.55 mmol/L) | 1.68     | 1.82     | 1.92       | 1.62       | 1.42       | 1.55       |
| PTH on admission (pg/mL) (n = 9-67) | 4.9      | 3.8      | 5.5        | 6.5        | 9.1        | 8.7        |
| Serum Mg on admission (0.66-1.07 mmol/L) | 0.23     | 0.16     | 0.21       | 0.18       | 0.13       | 0.17       |
| Age at last control (years) | 22       | 15.3     | 8.4        | 7.8        | 9.4        | 22         |
| Height SDS at last control | -0.93    | -0.92    | 0.8        | 2.32       | -0.22      | -0.43      |
| Follow-up period (years) | 21.2     | 15.2     | 8.3        | 7.6        | 8.9        | 21.7       |
| Magnesium doses at last control (mg/kg/day) | 12.5     | 13.6     | 13.5       | 31.5       | 24         | 13         |
| Neurodevelopmental status | Mild-moderate MR | SLD | Normal | Normal | Normal | ADHD |
| Serum Mg at final control (0.66-1.07 mmol/L) | 0.62     | 0.59     | 0.51       | 0.71       | 0.72       | 0.59       |
| Serum Ca at final control (2.1-2.55 mmol/L) | 2.25     | 2.52     | 2.37       | 2.52       | 2.42       | 2.52       |
| FeMg (%) (n = 3-5%) | 2.1       | 1.9      | 1.2        | 5.1        | 5.9        | 1.8        |
| Urinary Ca/Cr       | 0.1      | 0.06     | 0.19       | 0.04       | 0.06       | 0.036      |
| Nefrocalsinosis     | No       | No       | No         | No         | No         | No         |
| Parental consanguinity | Yes  | Yes   | Yes        | Yes        | No         | No         |
| Affected gene       | TRPM6    | TRPM6    | TRPM6      | TRPM6      | TRPM6      | TRPM6      |
| Mutation             | c.3158A>G (p.Tyr1053Cys) | c.3158A>G (p.Tyr1053Cys) | *c.841(+1) G>A | *c.1751A>G (p.His584Arg) | *c.841(+1) G>A | *c.3514C>T (p.Arg1172*) |
| Localization        | Exon 23  | Exon 23  | IVS7 donrsplice site | Exon 16 | IVS7 donrsplice site | Exon 25 |
| Mutation/mother     | c.3158A>G (p.Tyr1053Cys) (het) | c.3158A>G (p.Tyr1053Cys) (het) | *c.841(+1) G>A (het) | *c.1751A>G (p.His584Arg) (het) | *c.841(+1) G>A (het) | *c.3514C>T (p.Arg1172*) (het) |
| Mutation/father     | c.3158A>G (p.Tyr1053Cys) (het) | c.3158A>G (p.Tyr1053Cys) (het) | *c.841(+1) G>A (het) | *c.1751A>G (p.His584Arg) (het) | *c.841(+1) G>A (het) | *c.3514C>T (p.Arg1172*) (het) |

*No association with the disease has been reported before.
Ca: calcium, Mg: magnesium, PTH: parathormone, SDS: standard deviation score, Cr: creatinine, FeMg: fractional magnesium excretions, MR: mental retardation, SLD: specific learning difficulty, ADHD: attention deficit/hyperactive disorder
observation of hypomagnesemia and recurrent resistant seizures despite calcitriol and anticonvulsant therapy.

On admission the range of serum Mg$^{2+}$ levels was 0.13-0.23 mmol/L, serum Ca levels were 1.42-1.92 mmol/L, and PTH levels were 3.8-9.1 pg/mL. Following Mg$^{2+}$ treatment, serum Ca and PTH levels returned to normal levels during follow-up of all patients.

Oral Mg$^{2+}$ treatment doses were adjusted to sustain normocalcemia, according to the tolerance of the cases. Dose was not increased in patients with diarrhea. Treatment doses ranged between 12.5 and 31.5 mg/kg/day. In two cases (F3, F4), serum Mg$^{2+}$ concentrations were maintained at the reference intervals with oral treatment and were subnormal in four cases (0.51-0.59 mmol/l). However, no symptoms were observed. Fractional Mg$^{2+}$ excretion was between 1.2% and 5.9%. Hypercalciuria and nephrocalcinosis were not detected in any case.

None of the patients had short stature at the last follow-up. Height standard deviation (SD) scores ranged from -0.93 to 2.36 SD. In one case, who was diagnosed at nine months of age (F1.1), mild-to-moderate mental retardation was observed while his brother had a specific learning difficulty (F1.2). In another case (F5) attention deficit and attention deficit/hyperactivity disorder (ADHD) was diagnosed. Neurodevelopmental status of all patients, except F1.1 and F1.2, were consistent with their ages.

**Mutation Analysis**

Four different mutations were detected in the TRPM6 gene in six cases out of five families (Table 1). A homozygous missense mutation, which has been identified previously in a Turkish family on Exon 23 was detected in F1.1 and F1.2. [c.3158A>G, (p.Tyr1053Cys)]. Both of the parents were heterozygous carriers of this mutation. Two patients from non-consanguineous families (F2 and F4) had the same splice-site mutation, which had not been previously described (IVS7 splice-site, c.841 (+1)G>A). This mutation affected an essential splice site. The parents of these patients were heterozygous for the same mutation. A missense mutation [c.1751A>G, (p.His584Arg)] on Exon 16 was detected in patient F3. This variant was reported in the ExAC database (exac.broadinstitute.org) as a rare variant at a frequency of 29/120000 and classified as a variant of unknown significance. However, this variant was predicted to be disease causing by *in silico* analysis in Mutation Taster. Furthermore, the parents of these patients were heterozygous for the same variant. In F5, a nonsense mutation on exon 25 [c.3514C>T, (p.Arg1172)] reported in the ExAC database as a rare variant with a frequency of 1/120000, was detected. This mutation is predicted to cause a premature stop codon to be formed; the parents were heterozygous for this mutation. Therefore, this mutation, which was not previously reported in any patient, was accepted as a pathogenic variant (Figure 1).
The clinical and laboratory findings, including serum Ca, serum Mg²⁺, alkaline phosphatase, PTH, 25 (OH) vitamin D and urinary Mg²⁺, Ca, P, and Cr, of the heterozygous parents were evaluated and were found to be unremarkable.

Discussion

In this study, the long-term follow-up results of six genetically confirmed HSH patients are presented. Three novel mutations in the TRPM6 gene were identified, in addition to one known pathogenic mutation. The first presentation of all cases was afebrile seizures in the first year of life. Mild mental retardation, specific learning difficulty and ADHD were found as comorbidities. On long-term follow-up, growth was normal with Mg supplementation and maintenance of normal serum Ca levels.

Mg²⁺ is a cofactor for many enzymes and transporters, including phosphatases and phosphokinases. It is required for energy storage and use, and plays an important role in the synthesis of nucleic acids and proteins (5). Therefore, insufficient cellular Mg²⁺ concentrations affect many systems. Mg is strictly regulated by intestinal absorption and renal excretion and/or reabsorption. Intestinal absorption of Mg²⁺ occurs in the jejunum and the ileum. Most of the renal-filtered Mg²⁺ is absorbed by passive paracellular transport from the proximal tubule and the thick ascending loop of Henle. In the distal convoluted tubule, the fine tuning of Mg²⁺ equilibrium is made by active transcellular transport (6).

Hypomagnesemia in children may develop secondary to clinical conditions, such as intestinal malabsorption, short bowel syndrome, being the infant of a diabetic mother and the use of various drugs (proton pump inhibitors, antibiotics, diuretics, chemotherapeutic agents) and may also develop as a result of primary familial hypomagnesemia disorders (7). HSH is usually characterized by clinical findings, such as restlessness, tremor, muscle cramps, tetany, perioral cyanosis and generalized convulsions, in neonates or in the early infancy period. Mg levels are normal at delivery, the early infancy period. Mg levels are normal at delivery, and urinary Mg²⁺, Ca, P, and Cr, of the heterozygous parents were evaluated and were found to be unremarkable.

The standard treatment in HSH is high dose Mg²⁺. On diagnosis, intravenous or intramuscular administration can be preferred and maintenance therapy is high dose oral Mg²⁺. A significant variation of mean oral Mg dose (0.41-3.9 mmol/kg) has been reported between patients and centers (9,17). In the literature, it has been shown that serum Mg levels do not reach normal values in patients with HSH, with the exception of only three cases undergoing high dose Mg treatment (9,14). In line with the literature, in our study, oral Mg doses ranged between 0.51-1.28 mmol/kg (12.5-31.5 mg/kg). Normal serum Mg levels near the lower limit of the reference intervals were obtained in only two patients under Mg treatment.

Physiological fractional renal Mg excretion is 3-5 %, but this falls below 0.5-1 % in order to maintain serum Mg levels.
in the presence of hypomagnesemia (18,19). In the current study fractional renal Mg excretion was measured over 5% in two patients whose serum Mg levels were normal but close to the lower limit of the reference intervals. In patients with subnormal course of serum Mg levels, renal Mg excretion was over 1% (1.2–2.1%). Increased renal Mg excretion has a clear role in the pathogenesis of the disease and prevents the achievement of physiological serum Mg values, despite adequate treatment. In other words, the treatment should not provide normomagnesemia, but should provide normocalcemia, and if serum Ca is normal, Mg doses should not be increased.

It has been shown that the mutations previously identified in patients with HSH are not localized in a specific region and may be distributed across many areas of the TRPM6 protein (3,9,14). To date, 11 different mutations have been identified in 17 Turkish patients (Table 2) (9,14,15,20,21,22). The most common TRPM6 mutations in Turkish patients were c.5775A>G (in five cases from three non-consanguineous families), c.469G>T (in three cases from three family with), and c.3158A>G (in three cases from two non-consanguineous families). In our study, missense mutation (F1.1 and 1.2) was found in the twenty third exon, previously described in a Turkish case by Lainez et al (14). In addition, we demonstrated three novel mutations. The first mutation, c.841(+1)G>A, was found in the IVS7 splice site and was present in two unrelated patients (F2 and F4). The second novel mutation was c.5514C>T (p.Arg1172) in the twenty fifth exon. It was reported as a rare variant in the database, however it causes the formation of a premature stop codon and both parents were heterozygous carriers for the same mutation; therefore this mutation is accepted as pathogenic. The missense variant found in F3 was c.1751A>G (p.His584Arg) and both parents were heterozygous carriers for the same mutation. This variant was reported in ClinVar database as a variant of unknown significance. It may be pathogenic when evaluated together

Table 2. Clinical data and results of the TRPM6 mutational analyses of Turkish patient with familial hypomagnesemia with secondary hypocalcemia

| Turkish patients (references) | Gender | Age at diagnosis | Symptoms at manifestation | Initial serum Mg\(^{2+}\) (mmol) | Initial serum Ca\(^{2+}\) (mmol) | Oral/IM Mg\(^{2+}\) (mmol/kg/d) | Mg\(^{2+}\) under therapy (%) | FeMg (%) | Additonal finding | Mutation |
|-------------------------------|--------|------------------|---------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------------------|----------|------------------|----------|
| P1 (9)                        | F      | 2 mo             | Seizures                  | 0.21                          | 1.63                          | 1.03 (o)                      | 0.59                         | 2.6      | -                | c.1769G>G |
| P2 (9)                        | M      | 6 yr             | Seizures                  | ND                            | 1.29                          | 0.62 (o)                      | 0.57                         | 2.8      | MR               | c.2667 +G>A |
| P3 (9)a                       | M      | 3 mo             | Seizures                  | 0.09                          | 1.6                           | 0.54 (o)                      | 0.33                         | ND       | -                | c.5775A>G |
| P4 (9)a                       | M      | 4 mo             | Asymptomatic              | 0.16                          | 1.75                          | 0.94 (o)                      | 0.53                         | ND       | -                | c.5775A>G |
| P5 (9)                        | M      | 4 mo             | Seizures                  | 0.1                           | 1.45                          | 2.0 (o)                       | 0.50                         | 3.7      | -                | c.469G>T |
| P6 (9)                        | F      | 3 wk             | Seizures                  | 0.2                           | 1.72                          | 0.95 (o)                      | 0.52                         | ND       | -                | c.2667 +G>A |
| P7 (14)                       | F      | Infancy          | Seizures                  | 0.05                          | 1.78                          | 0.97 (o)                      | 0.50                         | ND       | MR               | c.3158A>G |
| P8 (14)                       | F      | 8 mo             | Seizures                  | 0.2                           | 1.6                           | 0.5 (o)                       | 0.53                         | ND       | -                | c.469G>T + |
|                              |        |                  |                           |                               |                               |                               |                               |          | 5261G>A         |          |
| P9 (21)                       | F      | 2 mo             | Seizures                  | <0.24                         | 1.5                           | 1.6 (o)                       | 0.57                         | 3.9      | -                | c.3447delT>p. |
|                              |        |                  |                           |                               |                               |                               |                               |          | F1149fs         |          |
| P10 (15)b                     | M      | 3 mo             | Seizures                  | 0.16                          | 1.8                           | 0.2 (o)/0.8 (im)              | 0.38                         | 0.1      | -                | c.3556C>T |
| P11 (15)b                     | F      | 3 mo             | Seizures                  | 0.08                          | 1.0                           | 0.4 (o)/0.9 (im)              | 0.45                         | 0.1      | Short stature    | c.3556C>T |
| P12 (15)                      | M      | 1 mo             | Seizures                  | 0.2                           | 2.4                           | 0.9 (im)                      | 0.41                         | 0.8      | -                | c.5775A>G |
| P13 (15)                      | M      | 1 yr             | Seizures                  | 0.14                          | 2.6                           | 0.8 (o)                       | 0.75                         | 2.7      | -                | c.1444-1G>T |
| P14 (15)a                     | M      | 1 mo             | Seizures                  | 0.5                           | 1.7                           | 0.6 (o)/3.7 (im)              | 0.58                         | 2.3      | Short stature    | c.5775A>G |
| P15 (15)c                     | F      | 3 mo             | Seizures                  | 0.5                           | 1.7                           | 0.5 (o)/7 (im)               | 0.66                         | 1.9      | -                | c.5775A>G |
| P16 (22)                      | M      | 1 mo             | Seizures                  | 0.16                          | 1.42                          | 0.7 (o)                       | 0.69                         | ND       | -                | 469G>T + |
| P17 (23)                      | M      | 8 mo             | Seizures + hypotonia       | 0.19                          | 1.67                          | 1.72 (o)                      | ND                           | 0.18     | -                | 3178A>T |

* 4, 5: siblings, F: female, M: male, yr: year, mo: month, wk: week, o: oral, im: intramuscular, ND: not defined, MR: mental retardation, Mg: magnesium, FeMg: fractional magnesium excretions, Ca: calcium
with the clinical features and segregation analysis of the patient, however functional analysis is required.

In a study, in which 28 HSH cases were evaluated regarding genotype-phenotype relationship, normal serum Mg levels were obtained by Mg treatment in two cases with a deletion in exon 32 or 33 (9). Since mutations in these exons only affect a small portion of the TRPM6 protein, it has been suggested that the channel function may be partially protected. However, it was reported, after functional analysis, that all mutations resulted in complete loss of function in the TRPM6 ion channel and no genotype-phenotype correlation was reported (9). In another study, the age of admission, serum Mg and Ca levels and oral Mg doses have been compared in 30 cases previously described in the literature. No relation was found between genotype and these clinical and laboratory parameters (10). In our study, clinical and laboratory findings of all patients with different mutations were similar. In addition, in one patient, normal serum Mg levels were obtained with Mg treatment, while Mg levels were subnormal in another patient with the same mutation, suggesting phenotypic variability despite genotypic homogeneity.

Mg treatment and close follow-up are essential to prevent clinical symptoms and to obtain normal Ca metabolism in HSH patients. In our case series, we observed that an early diagnosis, appropriate treatment and good treatment compliance the long-term (about 15 years) prognosis was good and no serious complications developed in HSH patients, similar to the study of Astor et al (16) which reported long-term (about 40 years) follow-up data.

**Study Limitations**

The main limitation of our study was the small number of patients. Additionally, functional analysis could not be performed although we identified new pathogenic mutations.

**Conclusion**

Evaluation of our cases with HSH revealed a homogenous clinical picture at manifestation with onset in the first year of life with generalized seizures. However there were heterogenous molecular findings, including four different TRPM6 mutations, of which three were novel. Early diagnosis, appropriate treatment and good treatment compliance are crucial for the prognosis. Enlightenment of the genetic etiology of autosomal recessive disorders like HSH is important, and can reveal mutations especially in populations where consanginous marriages are prevalent. Molecular studies in cases with HSH and their families will contribute to increase our knowledge about Mg homeostasis. Determination of the genetic mutation is also useful to know the prognosis and associated comorbidities.

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**Ethics**

**Ethics Committee Approval:** This study was approved by the Sultangazi Haseki Training and Research Hospital Local Ethical Committee (no: 2020-58, date: 14.05.2020).

**Informed Consent:** All participants and their parents received oral and written information concerning the study before providing signed consent.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: Elvan Bayramoğlu, Melikşah Keskin, Zehra Aycan, Şenay Savaş-Erdeve, Semra Çetinkaya, Concept: Elvan Bayramoğlu, Semra Çetinkaya, Design: Elvan Bayramoğlu, Semra Çetinkaya, Data Collection or Processing: Elvan Bayramoğlu, Melikşah Keskin, Zehra Aycan, Şenay Savaş-Erdeve and Semra Çetinkaya, Analysis or Interpretation: Elvan Bayramoğlu, Zehra Aycan, Semra Çetinkaya, Literature Search: Elvan Bayramoğlu, Melikşah Keskin, Zehra Aycan, Şenay Savaş-Erdeve and Semra Çetinkaya, Writing: Elvan Bayramoğlu, Semra Çetinkaya.

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