

Case report

TREATMENT DIFFICULTIES IN HYPOMAGNESEMIA SECONDARY TO THE TRANSIENT RECEPTOR POTENTIAL MELASTATIN 6 GENE: A CASE REPORT WITH NOVEL MUTATION

Short Title: Treatment Difficulties in the mutation of Transient Receptor Potential Melastatin 6 Gene

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What's known on this topic? Hypomagnesemia is one of the causes of hypocalcemia. Enteral replacement is the key in the treatment but the treatment should be individualized for each patient. Normalization of hypomagnesemia is not always easy and should not be the aim of the treatment.

What this study adds? The genetic analysis revealed a novel frame shift variant in the transient receptor potential melastatin 6 genes. The magnesium levels varied during the treatment with different preparations of medication. The treatment should be individualized.

ABSTRACT

Background: Hypomagnesemia is a rare cause of seizures in childhood. But should be in mind in recurrent and intractable seizures and hypocalcemia the communities where consanguineous marriages are common. Familial hypomagnesemia with secondary hypocalcemia is a rare genetic cause of hypomagnesemia due to the variant in the transient receptor potential melastatin 6 genes. **Here, a 3 year-old boy who has been identified a novel variant in this gene and had difficulties in enteral hypomagnesemia treatment was presented.**

Case Report: We presented a 3 year-old boy having recurrent seizures since 2 years old and diagnosed as epilepsy and treated with multiple antiepileptic drugs. But then, he was diagnosed as rickets due to severe hypocalcemia an outer center. The patient was hypotonic and neurodevelopmentally poor. Our prominent laboratory finding was hypomagnesemia with secondary hypocalcemia. The genetic analysis revealed a novel variant in transient receptor potential melastatin 6 gene.

After the parental treatment of intravenous magnesium sulfate and calcium, the treatment was switched to enteral magnesium medications. Because of persistent hypomagnesemia and the gastrointestinal side-effects, different oral preparations were used. The patient was stable on an oral maintenance dose of magnesium oxide with borderline blood magnesium levels without hypocalcemia.

Conclusion: Hypomagnesemia is one of the causes of hypocalcemia. Enteral replacement is the key in the treatment but the treatment should be individualized for each patient. Normalization of hypomagnesemia is not always easy and should not be the aim of the treatment.

KEYWORDS: hypocalcemia; hypomagnesemia; TRPM6; transient receptor potential melastatin 6

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INTRODUCTION

Familial Hypomagnesemia with Secondary Hypocalcemia (HSH) is a rare autosomal recessive disorder that presents in infancy with neurological symptoms of magnesium (Mg^{2+}) dependent hypocalcemia (1,2). Variants in the gene for the distal convoluting tubules and colon specific apical Mg^{2+} channel, the transient receptor potential melastatin 6 (*TRPM6*), cause the most profound genetic hypomagnesemia (3). Until now, several variants of *TRPM6* have been rarely reported in children (4). However, some reports have superficially mentioned about the difficulties in maintaining the serum Mg^{2+} levels in these patients (3,4). The treatment complexities including the target serum Mg^{2+} levels and the options of the preparations to be elected were usually ignored in the reports. Therefore, herein we present a patient with resistant seizures who was diagnosed as HSH due to a novel variant in *TRPM6* gene to discuss the importance of checking Mg^{2+} in seizures and to join issue with the treatment strategies.

CASE REPORT

A 3-year-old Afghan boy was admitted to our hospital due to recurrent seizures since the age of 2 years-old. He had the history of fever induced seizure for the first time at the age of 4 months. The cognitive and motor development was normal until the age of one, **but thereafter neurodevelopmental decline was reported.** He had been having generalized tonic-clonic seizures since 2 years old. The diagnosis of epilepsy was made in another center because of the recurrent seizures and multiple antiepileptic drugs were started. He has been following on levetiracetam, clonazepam, valproic acid, and pyridoxine treatments. The patient was admitted to our hospital for further evaluation for recurrent seizures and hypocalcemia from Afghanistan. He was born at full-term gestation after an uncomplicated pregnancy including an absence of polyhydramnios with a birth weight of 3500 gr from a consanguineous family (first degree cousins). His prenatal and natal history was uneventful. His family history was unremarkable. Her family history was negative for epilepsy and neurological abnormalities, as well as any known renal, thyroid, or parathyroid disease. Physical examination revealed his growth parameters were within normal limits (**Height: 95 cm (25-50p), Weight: 15 kg (50-75p)**). He did not show any dysmorphic or neurocutaneous features. He was conscious and had a speech delay. Bilateral horizontal nystagmus was prominent. He was hypotonic with normal reflexes. The rest of physical examination was normal. Laboratory data included a serum magnesium level of 0.12 mmol / L (normal range: 0.7-0.86 mmol/L), calcium 4.7 mg / dL, phosphorus 6.2 mg / dL, alkaline phosphatase 222 U / L, parathyroid hormone: 6 pg/ml (normal range: 11-67 pg/ml), 25-OH Vitamin D3 60.1 ng/ml, sodium 139 mEq / L, potassium 4.24 mEq / L, albumin 3.2 g / dL, uric acid 5.3 mg / dL. The urine fractional excretion of magnesium was 12% (**normal range:<4%**) in the patient with normal urine calcium / creatinine. Laboratory examinations including acute phase reactants, serum glucose, and albumin levels, liver and renal function tests were normal. The renal ultrasound did not show any medullary nephrocalcinosis. EEG showed slow background activity without any epileptiform discharges and MRI of brain showed mild diffuse cerebral and cerebellar atrophy (Figure 1).

Laboratory examination revealed the characteristic combination of **severe hypomagnesemia, hypoparathyroidism, and profound hypocalcemia.** Clinical and laboratory findings together indicated the diagnosis of HSH as responsible for disruption in Mg^{2+} utilization. **The genetic analysis of the patient revealed a novel homozygous frame-shift variant in the *TRPM6* gene (NM017662.4: c.5473_5474insGCTTC (p.H18225Rfs*18) (p.His1825Argfs*18). This is a frameshift variant and due to ACMG (American College of Medical Genetics and Genomics) criteria this variant was classified as pathogenic. This is a null variant and causes a severe damage in gene function. *TRPM6* gene sequence analysis was performed by using MiSeq next generation sequencing (NGS) platform, a FDA approved diagnostic system (Illumina, San Diego, CA, USA). Sequences were aligned to the hg 19 genome within MiSeq Reporter software (Illumina Inc.). Visualization of the data was performed with IGV 2.3 (Broad Institute) software (Figure 2). Informed consent was obtained from the parents for genetic analysis. The parents were heterozygotes for the same variant.**

Intravenous Mg^{2+} sulfate was administered at 50 mg/kg along with intravenous calcium for three days after which the serum magnesium increased and calcium levels got normalized. The treatment was switched to oral Mg^{2+} sulfate 4x2000 mg (\square 533 mg/kg/d). But abdominal pain and diarrhea was significant. As well as the levels of blood Mg^{2+} decreased to 0.2 mmol/L and convulsions have occurred without hypocalcemia. The treatment then switched to oral Mg^{2+} citrate and soon after Mg^{2+} carbonate because of the persistent hypomagnesemia and the gastrointestinal side-effects. Finally, Mg^{2+} oxide sachets were started and blood **Mg^{2+} reached 0.78 mmol / L with high dose of Mg^{2+} oxide (3x2 sachets - \square 150 mg/kg/d) (Figure 3).** Antiepileptic treatment was reduced. His muscle tone, cognitive development, and motor development improved. He has been stable on an oral maintenance dose of 2000 mg of Mg^{2+} oxide daily with borderline blood Mg^{2+} levels without hypocalcemia.

DISCUSSION

We presented a case of HSH and a novel variant in *TRPM6* gene was shown. The patient's treatment was individually arranged according to the blood Mg^{2+} levels and the potential side effects of the Mg^{2+} containing medications. The patient benefitted from the Mg^{2+} replacement in neurodevelopmental status and showed prominent progress.

HSH is a rare autosomal recessive disorder that affects the Mg^{2+} permeable ion channel encoded for by *TRPM6* gene on chromosome 9q22 (3). This gene is expressed in the distal segment of the intestine and the distal convoluted renal tubule. So the primary defect is impaired intestinal absorption of Mg^{2+} with secondary defect in its renal conservation. The clinical presentation is usually in the early childhood period with hypocalcemia refractory to calcium supplementation. The secondary hypocalcemia often observed is probably caused by inhibition of the parathyroid gland by the hypomagnesemia, resulting in low levels of parathyroid hormone and finally leading to hypocalcemia (1,4-5). The condition is treatable but failure to diagnose early can lead to intractable seizures with irreversible cerebral damage and mental retardation (1). Some reports have revealed initial evaluations for neonates and infants presenting with seizures do not always include assessment for serum Mg^{2+} abnormalities (3,6). As far as the treatment is depended on lifelong high-dose supplementation of Mg^{2+} and the genetic diagnosis is relevant; this disorder should be included in the differential diagnosis of any infant presenting with seizures and hypomagnesemia. **Our patient was being followed for intractable epilepsy as well as rickets for two years. Neurodevelopmental delay and recurrent seizures increased the suspicion of neurometabolic disorders with the family history of consanguinity. The detail of checking Mg^{2+} levels in a severe hypocalcemic patient was overlooked.**

Previous reports of HSH have demonstrated how well-timed diagnosis and rapid Mg^{2+} replacement accelerate normal development (3). One case series described considerably impaired neurodevelopment in two affected members of the same family who failed to receive supplementation (7). In a report, a patient who had HSH with *TRPM6* variant was followed-up over the 29 years and demonstrated normal physical and mental development with treatment. The reported patient showed normal developmental milestones, she completed her education including getting a university science degree and went on to follow an academic career as an adult (3). The diagnosis age of the patients in the literature differentiates from neonatal period to 4 years old. The neurological outcome is reported to be related to the age at diagnosis and also the compliance to the treatment (5). Hypomagnesemia itself leads to lethargy, nystagmus and convulsions and also without suitable treatment it can lead to cerebral atrophy like in our case (8, 9). **Short follow-up of our patient proved the neurodevelopmental progress in our patient with the treatment.**

Oral or intravenous Mg^{2+} supplementation is the only existing treatment for hypomagnesemia of genetic origin. In the acute symptomatic situation of severely hypomagnesemic patient, intravenous Mg^{2+} supplementation is so critical (1). The optimal rise in serum Mg^{2+} concentration often improves symptoms, such as seizures and secondary hypocalcemia, despite the fact that normal blood Mg^{2+} values are rarely reached (2,10). Extended correction of the hypomagnesemia is generally delayed because of the gastro-intestinal side effects frequently associated with oral Mg^{2+} supplementation. Paradoxically, higher doses of oral Mg^{2+} is damaging to intestines and results in diarrhea and also deepening hypomagnesemia (1,11). Another issue to discuss is the type of oral preparations, since some preparations have reported to have a better bioavailability than others (1,10). In a recent report, Mg^{2+} chloride or Mg^{2+} glycerophosphate was suggested rather than Mg^{2+} oxide or Mg^{2+} sulfate for oral Mg^{2+} supplementation (1). **In a study conducted in mice, the different Mg^{2+} preparations (Mg^{2+} acetyl taurate; Mg^{2+} malate; Mg^{2+} magnesium glycinate; Mg^{2+} citrate) were shown to be effective in increasing Mg^{2+} levels in different tissues like brain and muscle (12). In that study, blood Mg^{2+} levels were increased in all doses of Mg^{2+} acetyl taurate, malate, and glycinate, whereas Mg^{2+} citrate increased blood magnesium levels at high doses. Mg^{2+} citrate was reported to lead to a dose dependent increase in blood, brain, and muscle tissues (12). But we report the highest serum Mg^{2+} levels without apparent side effects with Mg^{2+} oxide supplementation. This points out that the treatment should be based on the individual follow-up and personal decisions. The treatment options should be optimized in the light of the future studies that are held in tissue dependent issues in humans.**

On the other hand, milder clinical phenotypes should be faced by different variants. **No definitive genotype-phenotype correlation has been established before. The most reported symptoms on admission were recurrent and intractable myoclonic or generalized tonic clonic seizures (4).** Mg^{2+} transport in the intestine occurs by both an active transcellular system which is defective in HSH and a passive paracellular pathway, which increases with rising intraluminal Mg^{2+} concentrations (1-4). Therefore, lifelong enteral high-dose Mg^{2+} is required in HSH to prevent symptoms and achieve at least subnormal serum Mg^{2+} levels. Habitually, the optimal doses have been modified with serial serum electrolyte monitoring. Previously reported cases have shown serum Mg^{2+} levels remain in the subnormal range (0.5–0.6 mmol/L) even with significant increases in supplemented dose (3). The published data suggests to follow-up normocalcaemia and the absence of features of neuroexcitability as the target of therapy (3, 8). **There is no preparation of choice for oral Mg^{2+} replacement and this should be guided by the individual's follow-up and also differences in the genetic variations.**

TRPM6 variant is a profound cause hypomagnesemia secondary hypocalcemia. With appropriate treatment, the seizures and neurocognitive development of the patients can be controlled. Rapid diagnosis and treatment of this rare disorder can significantly improve the quality of life of affected individuals.

Hypomagnesemia is one of the causes of hypocalcemia. **A diagnosis of primary HSH should be taken into consideration in all pediatric patients presenting with generalized seizures or tetany.** This is intensely valuable in those communities where consanguineous marriages are common. Enteral or parenteral Mg^{2+} replacement is key intervention in managing this condition and the aim should be to normalize serum calcium and control the symptoms. The treatment of hypomagnesemia is not always easy and can be depended on the dose and the content of the medication. Individual decisions are crucial in prompting the treatment.

Ethics

Informed Consent: Informed consent was obtained from the parents for genetic analysis and for the report of the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Meltem Akcaboy, Saliha Senel, Design: Cigdem Kasapkara, Cigdem Genc Sel, Data Collection and Processing: Çigdem Genc Sel, Gulin Karacan Kucukali, Senay Erdeve, Ulkuhan Oztoprak, Analysis and Interpretations: Serdar Ceylaner, Literature Search: Meltem Akcaboy, Saliha Senel, Husniye Yucel, Cigdem Kasapkara, Cigdem Genc Sel, Gulin Karacan Kucukali, Senay Erdeve, Ulkuhan Oztoprak, Writing: Meltem Akcaboy, Husniye Yucel.

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Figure 1. Cerebral and cerebellar atrophy in T2-Weighted cranial Magnetic Resonance images.

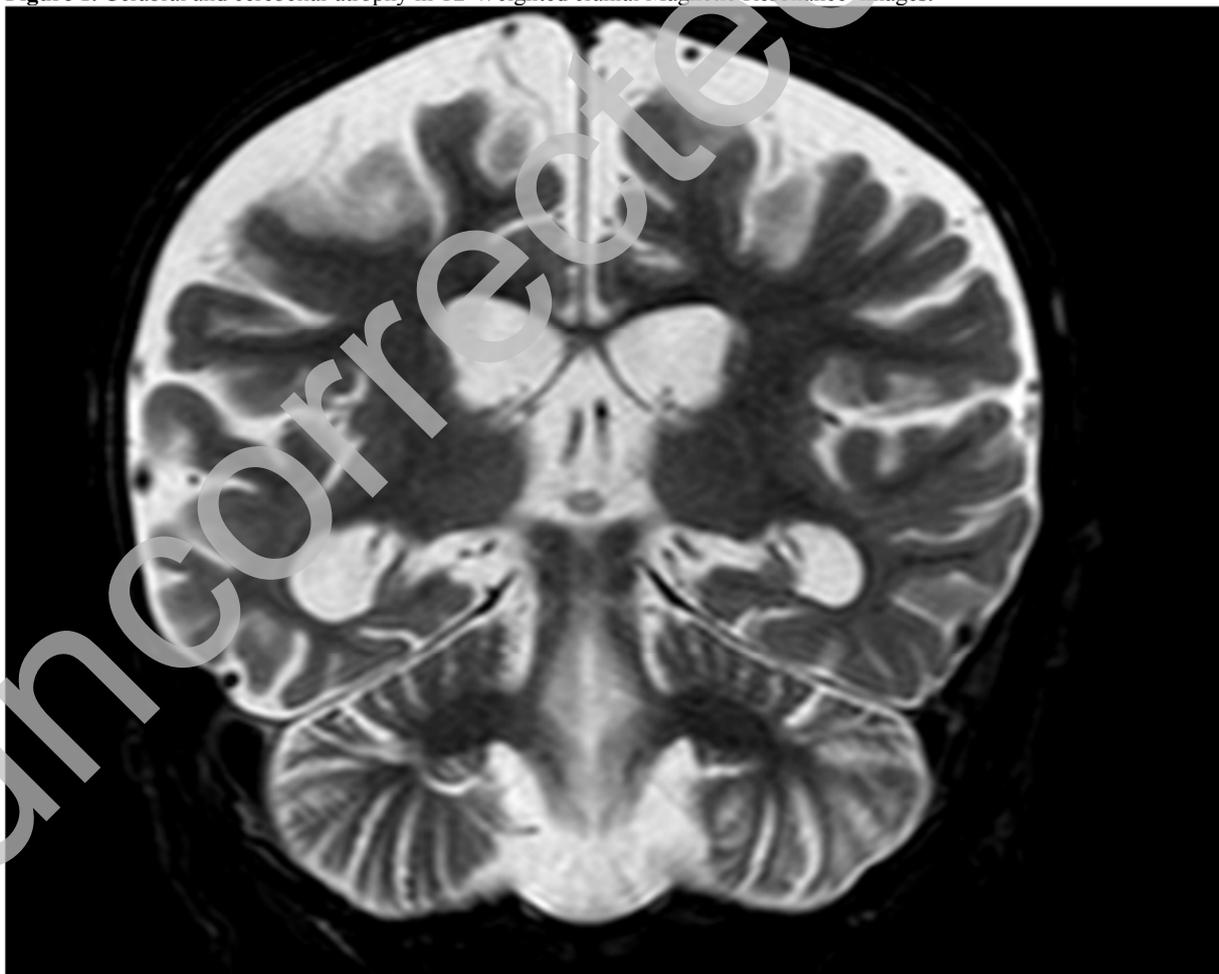


Figure 2. The figure of the pathogenic variant in the transient receptor potential melastatin 6 genes.

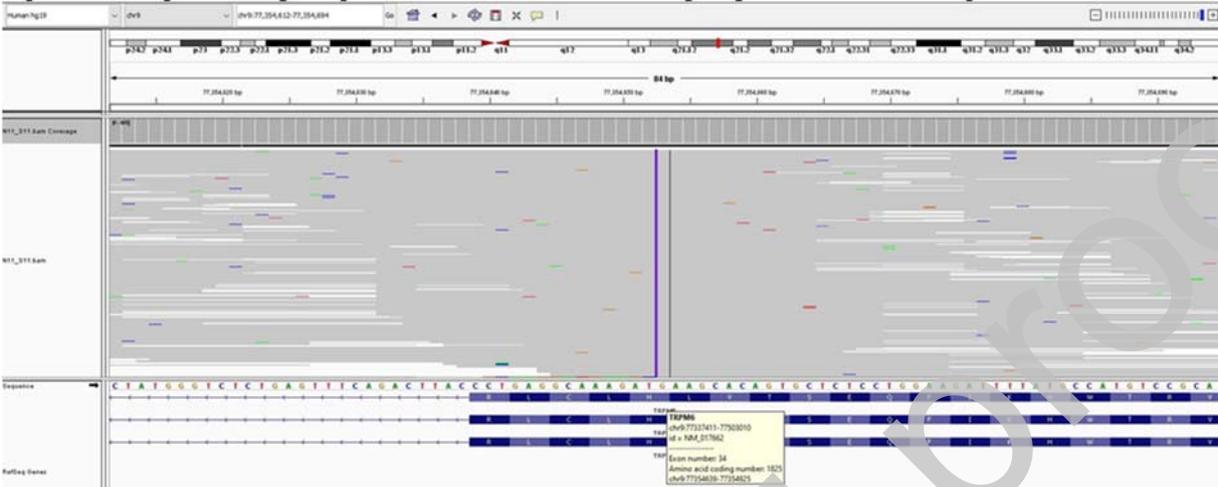
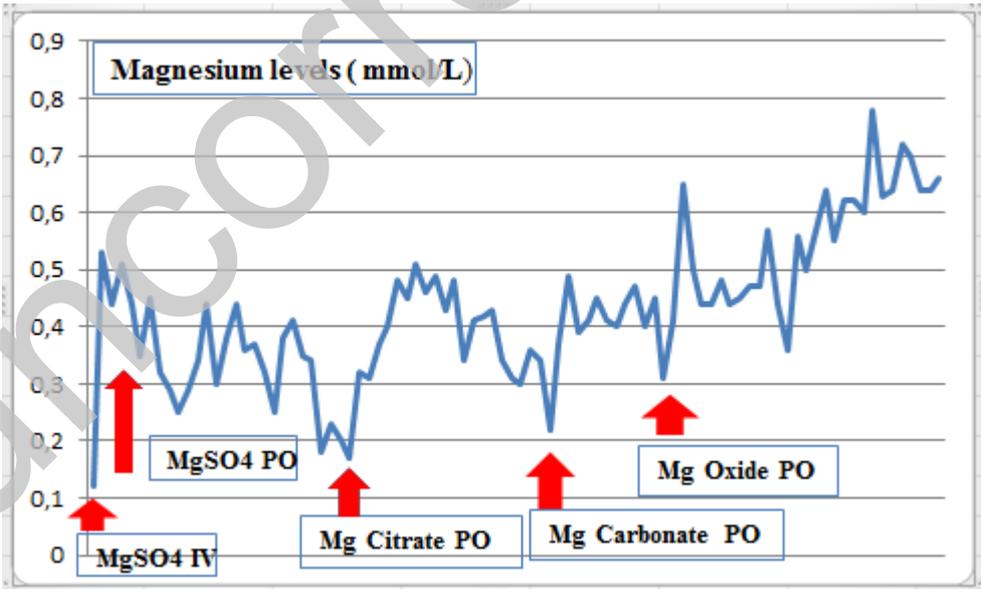


Figure 3. The blood magnesium levels by different magnesium preparations.



Mg: Magnesium; MgSO4: Magnesium sulphate; IV: intravenous; PO: per oral

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