CASE REPORT

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A Rare Cause of Seizures: Hypomagnesemia Type 1

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- IG, CPS: Bibliographical search, data collection, analysis and interpretation of results, drafting of the article.
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ABSTRACT

Hypomagnesemia type I is a rare autosomal recessive disorder characterized by severe hypomagnesemia, often accompanied by hypocalcemia. This disease is caused by mutations in the *TRPM6* gene (which encodes the respective channel), leading to reduced intestinal absorption of magnesium and increased renal excretion due to a defect in reabsorption in the distal convoluted tubule. It usually manifests itself in the first months of life, with symptoms of neuromuscular hyperexcitability and seizures, refractory to antiepileptic therapy. Treatment consists of administering high doses of magnesium throughout life. Here, we report a case of hypomagnesemia type I with a novel pathogenic variant of *TRPM6* in a 5-month-old girl who developed refractory seizures due to hypomagnesemia.

Keywords: Child; Hypocalcemia/genetics; Magnesium Deficiency/genetics; Mutation; Seizures/etiology; TRPM Cation Channels/genetics

INTRODUCTION

Seizures are the most common pediatric neurologic disorder. Most times seizures during childhood are benign and self-limiting (febrile seizures) but there is a multiplicity of etiologies to take into consideration particularly in the setting of refractory seizures.[1] In this regard it is of utmost importance to know that renal diseases may have neurological presentations, such as refractory seizures, and the diagnosis can be challenging.[2] The kidney plays an important role in the homeostasis of multiple electrolytes, including magnesium (Mg^{2+}). It is well known that alterations in Mg^{2+} homeostasis can be a cause of muscular hyperexcitability and seizures.[3]

Mg^{2+}, a cofactor in more than 300 enzyme systems, is involved in phosphate transfer, muscle contractility and neuronal transmission. It is the second most common intracellular cation whose physiological concentration in a healthy individual is around 0.7-1 mmol/L (1.7-2.4 mg/dL).[3] Homeostasis of Mg^{2+} is tightly regulated and is dependent of the balance between intestinal absorption and renal excretion. The kidney is the main site of Mg^{2+} balance: 80% of the total serum Mg^{2+} is ultrafiltered and subsequently reabsorbed in consecutive segments of the nephron. The transient receptor potential melastatin type 6 (TRPM6) protein, both expressed in the kidney and intestine epithelia, plays an essential role in active Mg^{2+} (re)absorption.[3-5]

The malfunctioning of the TRPM6-dependent Mg^{2+} influx pathway provides an explanation for severe hypomagnesemia seen in patients with type 1 hypomagnesemia, also known as familial hypomagnesaemia with secondary hypocalcemia (HOMG 1).[5,6] Hypocalcemia is a consequence of parathyroid failure and parathyroid hormone resistance as a result of the severe magnesium deficiency. HOMG 1 is a rare autosomal recessive genetic disorder (OMIM #602014) that typically manifests in the first months of life with signs of increased neuromuscular excitability (muscle spasms or tetany) or generalized seizures, refractory to the antiepileptic drugs. The treatment consists of life-long administration of high-doses of magnesium. Left untreated, HOMG 1 can be fatal or lead to severe neurologic damage.[7,8]

The authors hereby report a case of HOGM 1 highlining the importance of the study of electrolytes in the setting of seizures and the central role of the kidney in magnesium homeostasis.

CASE REPORT

We report a case of a 5-month-old girl, born at term, with no reported complications. She was the second child of consanguineous young parents (first degree cousins), with an irrelevant medical history. Birth weight and length evolution were regular and she was reported to have a normal psychomotor development. Neonatal screenings were also normal.

By the age of 5 months, she presented at the emergency department with a generalized tonic-clonic seizure. She was afebrile, had

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no intercurrent illness (past or present) and parents denied the consumption of suspicious substances. She was admitted for diagnostic work-up and antiepileptic treatment.

Seizures failed to respond to diazepam and phenobarbital. Physical examination was unremarkable including neurological examination. Initial diagnostic work-up was normal - full blood count, electrolytes (sodium, potassium, chloride), glucose, C reactive protein, liver and kidney function tests. Cranial tomography showed a benign subdural effusion and mild enlargement of the ventricular system (compatible with benign macrocephaly). Lumbar puncture was normal. Electroencephalogram showed bilateral temporal slow waves, without alteration of the baseline rhythm. Initial metabolic work-up (serum and urinary amino acids, organic acids, pyruvate and ammonia) was normal. Therapy was started with oral pyroxidine 75 mg/day and oral phenobarbital 3.5 mg/kg/day, considering the hypothesis of cryptogenic epilepsy. However, despite therapeutical serum levels of phenobarbital, seizures did not subside and persisted for more than 48 hours. Laboratory investigations were repeated but this time Mg^{2+} and calcium levels were evaluated. Blood analysis disclosed severe hypomagnesemia (0.25 mmol/L, reference values 0.7-1 mmol/L), with normal potassium, chloride, calcium, phosphorus, acid-base balance, blood glucose, kidney and liver function tests. Fractional magnesium excretion ($FEMg^{2+}$) was 0.9% (reference values 3%-4%) Hypomagnesemia correction was started with intravenous Mg^{2+} (magnesium sulfate 50% 0.8 mmol/kg/day), with cease of seizures and adequate serum levels of Mg^{2+} and $FEMg^{2+}$ of 8.9%. Antiepileptic drugs were discontinued. Parathormone levels were normal. Cranial, renal and vesical ultrasound, as well as cardiovascular exams (electrocardiogram and echocardiogram), showed no alterations. Electroencephalogram was repeated and it showed no alterations. Mg^{2+} replacement was switched to oral (60 mg/kg/day) and intramuscular (75 mg/kg 2-3 times per week) after ten days. The child remained asymptomatic even though serum values of Mg^{2+} were low (0.42-0.6 mmol/L) and she was discharged home.

The child started regular follow-up in a Pediatric Nephrology consultation. Mg^{2+} levels remained low (0.4-0.61 mmol/L) with $FEMg^{2+}$ levels between 0.39%-2.27%, despite frequent adjustments in Mg^{2+} intake (maximum dose of 60 mg/kg/day). A karyotype and molecular study of claudin-16 were performed in the beginning of follow-up as part of the diagnostic workup, with no alterations. Parents and sister were evaluated and had no hypomagnesemia or alterations in urinary electrolyte's excretion. A throughout history also unveiled no dietary restrictions and no gastrointestinal complaints.

The child remained asymptomatic with an adequate psychomotor development throughout time but at the age of 10 years old noncompliance with therapeutic was detected. At that time blood analysis revealed apart from severe hypomagnesemia (0.28 mmol/L), mild hypocalcemia (2.09 mmol/L, reference values 2.19-2.51 mmol/L), with decreased parathormone levels (8.9 pg/mL, reference values 2-87.6 pg/mL). Genetic workup was expanded with molecular study (sequencing and research of large chromosomal rearrangements by MPLA) of the epidermal growth factor and *TRPM6* genes. Molecular analysis of the *TRPM6* gene disclosed homozygosity for c.3031C>T(p.Arg1011*) pathogenic variant, molecularly confirming the diagnosis of HOMG1. Both parents are heterozygotes for the mutation.

The patient is now 15 years old and remains asymptomatic. Even though she is supplemented with oral Mg^{2+} and compliant with the therapy, her magnesium levels remain low with no other electrolytes' imbalance. Abdominal pain was reported as secondary to therapy but did not interfere with daily activities.

DISCUSSION

There is a variety of causes of hypomagnesemia to take into consideration and multiple differential diagnosis of seizures in childhood. Although rare, HOMG1 needs to be placed as a diagnostic hypothesis in the setting of seizures in a child with severe hypomagnesaemia with/without hypocalcemia, as the case described emphasizes.

In newborns and infants with seizures, it is essential to pursue electrolytes' imbalance as part of the initial diagnostic workup.[1,2] In the reported patient, only serum sodium, potassium and chloride were evaluated at the start, which led to a delay in the recognition of hypomagnesemia and to a subsequent inappropriate management of the seizures, which could have led to serious consequences. Once hypomagnesemia was detected and managed in our patient, seizure activity seized, highlining the importance of considering all electrolytes' imbalance as potential causes of seizures.

As previously mentioned, there are multiple possible causes for hypomagnesemia: insufficient Mg^{2+} intake, abnormal Mg^{2+} gastrointestinal absorption, impaired renal conservation or redistribution of Mg^{2+} from the extracellular space to the intracellular space.[9] HOMG1, caused by the loss of TPRM6 function that leads to decreased intestinal Mg^{2+} absorption and renal reabsorption, was first described by Paunier and his colleagues in 1968.[7,8-12] It is an autosomal recessive disease, whose prevalence is unknown. Currently, less than 100 cases have been described in the literature. Both sexes are equally affected and there is no familial or racial association described, although parental consanguinity is often present, as in this case.[9-11] Over than 70 loss-of-function mutations in the *TRPM6* gene have been reported, but the likely pathogenic variant of the *TRPM6* gene c.3031C>T(p.Arg1011*) described in our case had not yet been reported in the medical literature nor has been identified in population databases.[8,12,13]

At the time of diagnosis, $FEMg^{2+}$ is usually low to normal when taking into account the reference range, but in reality in HOMG1, it is probably inappropriately high when considering the degree of hypomagnesemia. Then, when plasma levels of Mg 2+ increase and approach normal, $FEMg^{2+}$ increases disproportionately to the degree of hypomagnesemia. This situation reflects the renal concentration defect, as seen in this case.[8,12] Hypocalcemia is not always present at the time of diagnosis. It is caused by inhibition of the parathyroid hormone synthesis and release from the parathyroid gland in the presence of profound and prolonged hypomagnesemia.[7,9] As hypocalcemia can be a belated finding, as in our case, its absence should not lead us to dismiss HOGM1 diagnosis.

Acute treatment consists of administering intravenous Mg^{2+}, followed by lifelong oral Mg^{2+} supplementation at high doses. Studies have reported the need for high Mg^{2+} doses of 18-87 mg/kg/day.

However, despite high doses, Mg^{2+} plasmatic levels usually remain suboptimal (0.5-0.6 mmol/L) due to disturbed magnesium conservation in the distal convoluted tubule. Thus, the aim of treatment is primarily to prevent symptoms and to achieve normal calcium levels, in spite of achieving normal Mg^{2+} levels.[4,8,14] In our case, treatment objectives were achieved. There is no oral Mg^{2+} formulation of choice and it must be adapted to the patient's tolerance. Given the associated gastrointestinal effects, there is a need for occasional administration of parenteral Mg^{2+}.[7,10] Although the reported patient complained about abdominal pain, it was sporadic and did not require any therapeutic action.[8,11] In growing children, it is necessary to maintain regular monitoring of Mg^{2+}, calcium and parathormone levels and to make dose adjustments when needed.[12]

Besides the seizures, prolonged and untreated hypomagnesemia can lead to growth retardation, long-term neurodevelopmental disorders, severe cardiomyopathy or even death. Early diagnosis and treatment are essential for a good prognosis. Although rare, HOGM1 has a prognosis changing treatment: Mg^{2+} supplementation.[7,10,11]

This case unveils that it is of utmost importance to remember that neurological symptoms may be the first sign of a kidney disease.

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