

Hypomagnesemia with Secondary Hypocalcemia Linked to a Novel TRPM6 Gene Mutation

Amel Tej^{1*}, Bernd Dworniczak², Asma Marzouk¹, Najla Soyah¹, Samia Tilouche¹, Moez Gribaa³, Jihène Bouguila¹, Lamia Boughamouira^{1,4}

¹Pediatric Department, Farhat Hached, Sousse, Tunisia

²Department of Human Genetics, Westfaelische Wilhelms Universität, Münster, Germany

³Department of Human Genetics Farhat Hached, Sousse, Tunisia

⁴Medical faculty Ibn Jazzar, University of Sousse, Sousse, Tunisia

Email: *ameltej@yahoo.fr, Bernd.Dworniczak@ukmuenster.de, marzoukasmajaziri@gmail.com, soyahnajla@yahoo.fr, samiatilouche@yahoo.fr, moez_gribaa@yahoo.fr, jbouguila@yahoo.fr, lamia_boughamouira@yahoo.fr

How to cite this paper: Tej, A., Dworniczak, B., Marzouk, A., Soyah, N., Tilouche, S., Gribaa, M., Bouguila, J. and Boughamouira, L. (2016) Hypomagnesemia with Secondary Hypocalcemia Linked to a Novel TRPM6 Gene Mutation. *Open Journal of Pediatrics*, 6, 290-294.

<http://dx.doi.org/10.4236/ojped.2016.64040>

Received: August 24, 2016

Accepted: November 18, 2016

Published: November 21, 2016

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Abstract

Hypomagnesemia with secondary hypocalcemia (HSH) is a rare inherited disorder, characterized by extremely low levels of serum magnesium associated with symptomatic hypocalcemia. HSH manifests in the new born period with neurological symptoms, including generalized seizures, which are refractory to anticonvulsant treatment. In this disorder, the basic abnormality is the defective intestinal absorption of magnesium. Mutations in TRPM6, the gene encoding the transient receptor potential cation channel subfamily member 6 have been found to be responsible for this disease. We report on a four-month-old Tunisian girl who presented with convulsions. Laboratory evaluation yielded extremely low serum magnesium levels, low calcium levels, and abnormal PTH levels. The diagnosis of HSH was confirmed by mutation analysis which identified the novel mutation c.1307A >G in exon 11 of TRPM6 (Lys436Arg). Our patient was homozygous for this mutation. Prenatal diagnosis was done during second pregnancy. DNA from trophoblast biopsy showed the same mutation as the proband.

Keywords

Magnesium, Hypomagnesemia, Hypocalcemia, Convulsion, TRPM6

1. Introduction

Hypomagnesemia with secondary hypocalcemia (HSH) is an autosomal recessive disease that results in electrolyte abnormalities shortly after birth [1] [2]. Affected individuals presented generalized convulsions or signs of increased neuromuscular excita-

bility [3] [4]. The low serum magnesium which characterizes this disorder is related to defective intestinal magnesium absorption [4] [5]. Impaired synthesis and secretion of parathyroid hormone (PTH) as a consequence of profound hypomagnesemia have been suggested to be responsible for the observed hypocalcemia [6] [7]. Restoring the concentrations of serum magnesium to normal values by high-dose magnesium supplementation can overcome the apparent defect in magnesium absorption and in serum concentrations of calcium [8]. Delay in diagnosis resulted in permanent neurologic damage [6].

We report a Tunisian girl affected by HSH. Through her case report, we elucidated the importance to recognize hypomagnesemia as the primary cause of neurologic symptoms and we detailed approaches to diagnosis and treatment of HSH.

2. Case Report

A four-month-old girl of Tunisian origin presented with generalized convulsions without fever or trauma. She was born at term and there was no specific finding in medical history. The parents were second degree cousins. Physical examination noted a wide anterior fontanelle. Laboratory results revealed normal blood glucose and electrolytes. However, serum Mg^{+2} and Ca^{+2} were low being 1.6 mmol/l and 0.23 mmol/l respectively. Serum PTH was 18 pg/ml (10 - 65 pg/ml), serum phosphorus level: 1.43 mmol/l, PAL: 247UI/l, 25OHvitD: 34.6 ng/ml (20 - 40 ng/ml). The patient showed no clinical or radiological evidence for rickets but was treated accordingly. Two months later, she was referred to our hospital because of recurrent seizures. CSF analysis revealed pneumococcal meningitis. Despite Clonazepam and a well conducted antibiotic therapy, seizures persisted. Electroencephalogram and magnetic resonance imaging did not show any specific findings. Blood examination revealed hypocalcemia (1.92 mmol/l) with hypomagnesemia (0.22 mmol/l). Serum PTH was 25 pg/ml (10 - 65 pg/ml). Blood glucose, electrolytes, renal function tests, levels of urinary ions and calcium excretion were normal. Fractional magnesium excretion (FE Mg^{+2}) was 1.4%. There was no nephrocalcinosis on renal ultrasonography. A normal serum level of calcium and magnesium was restored with intra venous calcium gluconate and magnesium sulphate, leading to control seizures. After cessation of parenteral magnesium sulphate, we started oral supplementation. However, the serum magnesium level rapidly decreased from 0.74 mmol/l to 0.34 mmol/l within three days, while serum level of calcium remained in normal limits. To keep our patient symptom free and normocalcaemic, a high dose of enteral magnesium was required. In fact, she received 145 mg/kg/j (6 mmol/kg/j) of magnesium pidolate which increased serum magnesium level to 0.68 mmol/l. A gastrointestinal cause of hypomagnesemia was suspected. As the clinical picture and the laboratory results in serum and urine pointed toward hypomagnesemia with secondary hypocalcemia, the TRPM6 gene was screened for mutations, which identified the novel mutation c.1307A >G in exon 11 of TRPM6 (Lys436Arg). In addition to the aminoacid exchange, the mutation affects the donor splice site of exon 11 of the TRPM6 gene. According to splice prediction programs, it is most likely that exon 11 of the TRPM6 gene

is skipped from the mature mRNA. Skipping of exon 11 will cause a deletion (c.1208_1308del) resulting in a premature stop coding (pGly403AlafsX2). Both parents of Sabrina are each heterozygous for the above mentioned mutation. The mother of the proband is 25 years old and the father is 37 years old. Serum magnesium level was 0.44 mmol/l for the mother and 0.84 mmol/l for the father. None had a history of convulsions but the mother expressed paresthesia. At the age of 3 years, the patient suffered from mental impairment. She was under magnesium supplementation with sodium valproate. The main side effect of oral magnesium was diarrhea. When the drug compliance was poor, she presented seizures and she required, occasionally, intravenous infusion of magnesium. Prenatal diagnosis was done during second pregnancy. DNA from trophoblast biopsy showed homozygosity for c.1307A >G in exon 11 of TRPM6 (Lys436Arg).

3. Discussion

Hypomagnesemia with secondary hypocalcemia (HSH) is a rare autosomal-recessive disorder that appears in early infancy [1] [2]. HSH is quite rare in all races [3]. To our knowledge, this is the first Tunisian case identified with the novel mutation c.1307A >G in exon 11 of TRPM6. HSH is characterized by severe hypomagnesemia leading to low serum calcium levels [9]. The observed hypocalcemia is due to impaired synthesis and secretion of parathyroid hormone (PTH) as a consequence of profound hypomagnesemia [10] [11]. The low serum magnesium levels result from defective intestinal magnesium absorption and increased renal magnesium clearance [10] [12]. There was an association between HSH and mutations in the gene encoding the transient receptor potential channel melastatin 6 (TRPM6), which is involved in transepithelial magnesium transport and belongs to the transient receptor potential (TRP) family of cation channels [12]. Children with HSH are commonly reported as presenting with tetany, or convulsions, or both [2]. In the present case, the initial clinical manifestations were generalized hypocalcaemic seizures, as it was reported by Shalev *et al.* [2]. In fact, among 15 patients with HSH, the most common presenting events (67%) were generalized seizures at a mean age of 4.9 weeks [2].

The very low serum Mg^{2+} of our patient was considered, firstly, as a transient phenomenon. Recurrent convulsions with persistent hypocalcaemia and hypomagnesemia, despite treatment with vitamin D and calcium, led to exclude the diagnosis of nutritional rickets. Further investigations were done to exclude Gitelman and Bartter syndroms. The normal renal ultra sonography and urinary calcium excretion were not suggestive of familial hypomagnesemia with hypercalciuria and nephrocalcinosis. Acute intravenous magnesium infusion leading to relief of clinical symptoms and normocalcemia and requirement of high doses of oral magnesium to remain the serum magnesium in the subnormal range are suggestive of HSH. Shalev *et al.* affirmed that blood magnesium concentrations of their patients with HSH did not fully normalise despite high doses of enteral magnesium [2].

HSH was confirmed, in our patient, by genetic analysis which identified the novel

mutation c.1307A >G in exon 11 of TRPM6. On one hand this mutation is a missense mutation (Lys436Arg), on the other hand the mutation damages the donor splice site of exon 11 of the TRPM6 gene. By this, most likely exon 11 is skipped from the TRPM6 mRNA resulting in a non-functional transcript with a premature stop coding (pGly-403AlafsX2). Katayama *et al* reported that no genotype-phenotype correlation exists for HSH [12]. A good neurodevelopmental outcome could be achieved in affected children who were treated with the appropriate long term dosage of enteral magnesium [2].

Failure of early diagnosis of HSH or non compliance with treatment recommendations can be detrimental causing permanent neurological damage and even a death [2]. Our patient exhibited mental retardation. Pneumococcal meningitis, repeated convulsions and low drug compliance contributed to mental impairment.

Considering early diagnosis of HSH allows protection of the child, prenatal diagnosis was performed for the proband's mother during second pregnancy. As the expected new baby have the same mutation of her sister, careful clinical observation during newborn period with control of serum levels of magnesium may indicate the appropriate time for initiation of magnesium supplementation. Apa *et al* reported a new born with HSH who presented with atonic seizures that first occurred on the 20th day of life. This patient had a normal mental and motor development under treatment [6].

4. Conclusion

In conclusion, this case highlights the importance to distinct HSH from other disorders which also have hypomagnesemia as a symptom [10] [13]. Any delay in the diagnosis of this rare disease may affect neurodevelopmental outcome [2].

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