CNNM2 genetic variant induced hereditary renal hypomagnesemia: A case report

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Abstract

A 12 year and 2 month aged girl visited the General Hospital of Ningxia Medical University due to headache and dizziness for the past two years. The presented symptoms include headache and dizziness, numbness and weakness in the limbs and hypophrenia. Exome sequencing was conducted and revealed that the patient is a heterozygotic carrier of a novel CNNM2 genetic variant (c.806C>T; p.S269L), which is likely to be pathogenic. In light of the patients’ clinical symptoms and genetic testing results, she was diagnosed with hereditary renal hypomagnesemia. Potassium and magnesium aspartate tablets were prescribed followed by dose adjustment in the next half year, resulting in her serum magnesium ranged from 0.52 to 0.57mmol/L.

Keywords: Genetic variants, kidney, magnesium reabsorption, children, hereditary disease

INTRODUCTION

The hereditary renal hypomagnesemia is a rare disease that caused by genetic variant-induced dysfunction of magnesium reabsorption in the kidney [1]. Magnesium is one of the most crucial cations in the human body, constituting a variety of enzymes that are involved in DNA synthesis, protein interaction and oxidative phosphorylation [2]. In addition, study has shown that magnesium possesses inhibitory effect on excitability of central nervous system, skeletal muscle and cardiomyocytes [3]. CNNM2 gene encodes Cyclin M2, which has been demonstrated playing an important role in modulating homeostasis of magnesium as well as neurodevelopment [4]. Genetic variations in CNNM2 gene, mostly novel missense variants and rarely nonsense,
frameshift or copy number variations, have been associated with multiple autosomal dominant disorders[5]. Here, we reported a heterozygotic carrier of a CNNM2 variant (c.806C>T) presenting hypomagnesemia symptoms.

CASE PRESENTATION

A 12-year-old girl, visited the General Hospital of Ningxia Medical University in September 2022 due to her “two years’ headache and dizziness. The symptoms started two years ago, including headache and dizziness, numbness and weakness in the limbs, foreign body sensation in the abdomen, retching with mucus and amnesia, but no blurred vision, convulsion or abnormality in hearing was observed. Before emergence of these symptoms, she was in general healthy. As the first child in the first delivery of her mother, she was naturally delivered after a full-term pregnancy and raised with normal diet. However, later the patient was observed with lower height and slower language development than the average. Furthermore, she was graded low at her primary school due to a poor learning performance. So far in her life, no history of infectious diseases, food allergies or familial hereditary diseases was recognized. While not being a child of consanguineous marriage, her mother suffered from angioneurotic headache during her pregnancy. Recently, her father also had dizziness.

Patient health examination: body temperature 36.2, heard rate 73 times/min, respiratory rate 18 breaths/min, blood pressure 102/71mmHg (1mmHg=0.133kPa), body weight 41kg (P_{25}-P_{50}), height 141cm (<P_{3}). The patient is very conscious with normal mental reaction, moderately nourished and can answer questions in correct directions. She has normal appearance, no skin rash or abnormalities in heart, lung and abdomen. In addition, she has normal muscle force in the limbs and no irregular findings was observed after testing on her nervous system.

Laboratory analysis: no irregular findings was observed after the following tests– routine examination in blood, urine and faeces; liver and renal function; arterial blood gas analysis; electrolyte analysis; electrocardiogram; electroencephalogram; ultrasonic cardiogram; transcranial Doppler; cranial magnetic resonance imaging. Patient serum magnesium: 0.52 mmol/L (0.7-1.0 mmol/L is considered as standard level). Her father and mother had been tested for serum magnesium in our hospital, and their serum magnesium were normal (0.83 mmol/L and 0.90 mmol/L, respectively). Other causes of hypomagnesemia such as diuretics, proton pump inhibitors, diarrhea, and diabetes mellitus were excluded.

Genetic test: After receiving a consent from the patient’s parents, whole exome sequencing was conducted for the whole family through BerryGenomics (transcript number: NM_017649.5). One de novo variant was identified in CNNM2 gene, exon 1 (c.806C>T, p.S269L) and the patient is a heterozygotic variant carrier (Figure 1 and 2). Moreover, according to the American College of Medical Genetics and Genomics (ACMG), Clinical Genome Resource (ClinGene) as well as the search on public available databases related to genetic associations with headache, limb weakness, vomiting and dizziness, c.806C>T in CNNM2 gene is indicated as a likely pathogenic variant.

Diagnostics and treatment: given the clinical symptoms, the patient was diagnosed with renal hypomagnesemia. Potassium and magnesium aspartate tablets were prescribed (each tablet contains 11.8mg magnesium) in oral administration (0.5 tablet per time, three times per day). The patient was followed up for half a year and the dose was increased to 2.5 tablet per time, three times per day. Consequently, the serum magnesium ranged from 0.52 to 0.57mmol/L.

3. DISCUSSION

In 2011, Stuiver et al. for the first time reported that CNNM2 genetic variants can induce autosomal dominant or recessive hereditary renal hypomagnesemia, epilepsy disorders and hypophrenia [6]. To date, only 24 cases that develop CNNM2 variant induced hypomagnesemia, epilepsy and hypophrenia were reported [7]. Among these cases, some exhibited epilepsy disorders at younger ages, whereas the others didn’t present limb weakness, dizziness and headache until adolescence [8]. Here, we reported a heterozygotic carrier of a CNNM2 variant (c.806C>T) presenting symptoms including headache and dizziness, numbness and weak-
ness in the limbs, hypophrenia and hypomagnesemia. Evidence has shown that genetic variation in CNNM2 is closely related to patients’ clinical phenotypes [9]. While heterozygotic carriers of CNNM2 pathogenic variant can present hypomagnesemia, epilepsy and mild to moderate hypophrenia, homozygote of such variants might induce high degree of structural abnormality in brain and therefore cause severe hypophrenia. In case of epilepsy, common antiepileptic drugs such as phenobarbital and sodium valproate can be used for heterozygotic carriers, but not for homozygotic carriers since they commonly present intractable epilepsy. Importantly, Arjona and colleagues demonstrated that epilepsy is a consequence of developmental disorder of the brain instead of the loss of magnesium and such brain developmental disorder [9], including neurodevelopmental disorder, has been observed in CNNM2 knock-out zebrafish. Furthermore, magnesium complementary therapies cannot alleviate hypomagnesemia or properly control epileptic seizure[10]. Therefore, it is highly likely that epilepsy doesn’t result from CNNM2 variant induced hypomagnesemia, but from variant induced dysfunction of the brain [11]. So far, there is no guidelines for hereditary renal hypomagnesemia treatment [12]. In clinics, magnesium complementary therapies are commonly applied as direct methods to treat hypomagnesemia, yet have rarely reached satisfied outcomes. Similarly in this case, prescribing potassium and magnesium aspartate tablets and increasing the dose in the following half-year didn’t improve patient serum magnesium level. It has been showed that spironolactone, a medication that is primarily used to treat heart failure, increases the driving force for Mg$^{2+}$ entry into the cells of the distal convoluted tubule, and thus can be used as a magnesium-sparing agent in such rare disease[13]. We anticipate this and similar findings can complement current treatment options for hereditary renal hypomagnesemia and improve therapeutic outcomes in the near future.

4.CONCLUSION

In this study, we reported a girl patient presenting hypomagnesemia symptoms that is likely induced by a novel CNNM2 missense variant (c.806C>T). We further confirmed that magnesium complementary therapy has no significant effect on CNNM2 variant-associated hypomagnesemia. This novel variant increases the naturally occurring pathogenic variant pool in CNNM2 and is anticipated to help further understand the pathogenesis of hypomagnesemia, epilepsy and other related hereditary diseases.

Author contributions

**Jing Liu:** Data curation; writing – original draft. **Juanyin Zhang:** Data curation; writing – original draft. **Junli Liang:** Data curation; writing – original draft; writing – review and editing. **Haijin Ma:** Conceptualization; supervision.

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Key Clinical Message

This study identify a novel missense variant in CNNM2 gene that might contribute to hereditary renal hypomagnesemia.

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REFERENCES


Figure legends

Figure 1. Pedigree chart of the proband’s family. *CNNM2* c.806C>T is marked as black. Male and female are presented as square and circle, respectively. The arrow indicates the proband.

Figure 2. Exonic sequences of the patient and parents in *CNNM2* gene. The patient is a c.806C>T heterozygotic carrier, whereas her parents are wild-type on this locus.