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Familial Hypomagnesemia with Secondary Hypocalcemia: A Challenging Medical Affair

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Familial or genetic hypomagnesemia with secondary hypocalcemia is a disease typically presenting with epilepsy and characterized by low blood levels of magnesium and calcium and metabolic bone disease, and is caused by mutations in the TRPM6 genes. Various factors such as low dietary intake and poor absorption of magnesium in the gut, affect magnesium balance. Hypomagnesemia with secondary hypocalcemia is rare, and therefore there are no large epidemiological studies reflecting the global distribution of these conditions. We report in this article a case of a female infant with a diagnosis of congenital hypomagnesemia with secondary hypocalcemia. In daily clinical practice, one can usually see it in connection with neonates. According to the literature, mutations of TRPM6 account for about 40–50% of hypomagnesemia patients with secondary hypocalcemia.

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Keywords: Hypomagnesemia; hypocalcemia; TRPM6 mutation; seizure.

1. INTRODUCTION

Genetic hypomagnesemia with secondary hypocalcemia is a condition commonly associated with epilepsy and marked by reduced magnesium and calcium levels in blood and metabolic bone issues, and is attributed to mutations in the TRPM6 genes. Along with hypoparathyroidism, it shares similarities with genetic renal hypomagnesemia. Several factors, including inadequate dietary intake and dysfunctional magnesium absorption in the gastrointestinal tract, impact magnesium equilibrium. In Western societies, insufficient dietary magnesium levels are exceedingly rare, though malnourishment is a contributing factor to hypomagnesemia (Han et al., 2022).

Chronic inadequate magnesium intake is often overlooked, leading to deficiency. Magnesium levels can remain stable until depletion occurs. Insufficient intake or reabsorption can decrease magnesium levels. Early recognition and magnesium supplementation are important. Low magnesium levels affect hormone regulation and can lead to secondary hypoparathyroidism (Na et al., 2021).

2. CASE PRESENTATION

F.N. female infant born to a 2nd degree consanguineous parents, from a pregnancy carried to term and vaginal delivery. At birth, The APGAR score was 10/10, and the birth weight was 3500 g. She presented at the age of 3 months multiple seizures, for which she was hospitalized in order to do a metabolic check, which shows a hypomagnesemia, treated with magnesium 30 mg/kg/day. She is being monitored for epilepsy under sodium valproate at the dose of 30 mg/kg/day for 1 year. She presents a delay in psychomotor acquisitions with good height and weight development. There is no sign of diarrhea or chronic vomiting. EEG ralentissement du rythme de fong IRM normale ECG normale.

She was brought to consultation for apyretic generalized seizures after magnesium treatment was stopped. The clinical examination found an apyretic, eupneic infant and no signs of dehydration, with normal blood pressure and blood sugar levels; the neurological examination found axial hypotonia. EEG shows slowing of background rhythm, and in contrast, cerebral MRI and EKG were normal. Biologically, she had severe hypomagnesemia < 0.6 mg/dl (N=1.6 – 2.6 mg/dl), associated with severe hypocalcemia at 7.1 mg/dl (N=8.8 – 10.4 mg/dl); phosphoremia was within normal limits at 52 mg/l (N=35 – 65 mg/l) as were ALP = 123 IU/l (N= 134 – 518 IU/l) and parathormone PTH at 29 ng/l (N= 11 – 65 ng/l). Potassium levels were normal and renal function was preserved, there was no acidosis. Urinary ionogram revealed hypomagnesuria (< 5.37 mg/dl) with hypocalciuria (< 20 mg/l), creatininuria was low (= 355 mg/l). The fractional excretion (FE) of magnesium calculated was 16% confirming the renal origin of hypomagnesemia. Renal ultrasound did not find nephrocalcinosis. The diagnosis of hereditary hypomagnesemia was suspected in the absence of secondary causes, and the notion of 2nd degree consanguinity. In a genetic study, we have found a compound heterozygous variant in TRPM6 gene, containing a novel non-canonical splicing-site variant c.5058-26A > G and a heterozygous deletion in exons 27–33 (chr9q21.13: 77357467–77376734).

For her treatment, she received 02 boluses of magnesium (magnesia sulfate): 150 mg/kg over a period of 24 hours. The evolution is marked by a stopping of seizures clinically and an increase in magnesium levels to 1.07 mg/l with a correlated normalization of calcemia. The patient was discharged with oral magnesium triple complex (30 mg/kg/day of elemental magnesium) as treatment, with a possible IV magnesium in the event of diarrhea, vomiting or inability to feed.

3. DISCUSSION

Hypomagnesemia with secondary hypocalcemia is a rare autosomal recessive disorder (OMIM# 602014) found in childhood (Schlingmann et al., 2002). It is defined as low magnesium levels below 0.7 mmol/L and low calcium levels below 2.05 mmol/L. Poor diet, malnutrition, malabsorption, and genetic mutations contribute to its prevalence. Many cases go undiagnosed due to subtle symptoms and regional differences. Mutations of TRPM6 account for 40-50% of cases. Limited global epidemiological data exists. More research is needed to understand magnesium and calcium metabolism. Supplementation and improved outcomes can lessen the burden on healthcare systems (Gao et al.,2022). Low magnesium levels directly contribute to low calcium levels in the patient.

Hypocalcemia is a result of hypomagnesemia in this case. Magnesium deficiency worsens calcium deficiency, making hypocalcemia strongly linked to low magnesium levels. Severe hypomagnesemia can cause seizures and severe muscle cramps. The clinical symptoms mainly involve the heart, leading to early cardiovascular mortality. These symptoms include muscle problems, cardiac arrhythmia, heart failure, and troponin elevation. Carpopedal spasm is a common manifestation of hypocalcemia as it progresses. Severe chronic hypermagnesemia suppresses parathyroid hormone synthesis and can lead to hypocalcemic seizures and tetany. Severe hypomagnesemia and hypocalcemia are often accompanied by severe arrhythmia, heart attack, and heart failure, indicating advanced kidney failure. This greatly reduces the life expectancy of patients with chronic kidney disease (Bayramoğlu et al.,2021).

TRPM6 is a long TRPM protein encoded by the TRPM6 gene. It is highly expressed in the kidney and colon and has lower expression in other tissues. TRPM6 plays a critical role in the duodenum by compensating for the loss of TRPM7. Studies focus on mineral ion uptake in the kidneys (Adella et al., 2024).

TRPM6 senses intracellular magnesium levels and store depletion, affecting magnesium ion absorption. Knockouts of the TRPM6 gene may not cause medical phenotypes. Dominant mutations in TRPM6 gene result in calcium homeostasis variations. TRPM6 gene mutations cause non-heritable magnesium disorders. Defects in TRPM6 gene disrupt magnesium ion homeostasis in intestines and kidneys, impacting sodium chloride reabsorption (Vargas-Poussou et al., 2023).

The TRPM6 gene on chromosome 9 has 26 exons. It aids magnesium reabsorption in the kidney and intestinal transport alongside TRPM7. Mutations in TRPM6 cause autosomal recessive hypomagnesemia, leading to low parathyroid hormone levels and refractory hypomagnesemia in children. Pathogenic variants typically involve large deletions and gene conversion, resulting in complete loss of gene expression and protein function (Bobrowicz et al., 2024).

Five TRPM6 mutations (c.1846C > T, c.287G > A, c.2436+2T > C, c.2455+2T > G, c.2065+1G > A) were not found in human population databases. These variants reduce TRPM6 activity and cause low magnesium efficiency. Exon-skipping treatment may help hypomagnesemia patients with TRPM6 mutations. TRPM6 mutations lead to absence of TRPM6-encoded protein and impaired function, resulting in symptoms related to ion transport. Autosomal dominant inheritance is suggested for hypomagnesemia with secondary hypocalcemia (Uddin et al., 2024).

Understanding ions transport pathways is crucial for understanding absorption in the body. This section focuses on TRPM6's role in absorption, discussing how mutations affect its function and lead to hypomagnesemia. Magnesium enters enterocytes via TRPM6, which has two mechanisms for transporting magnesium ions. TRPM6 is part of the transient receptor potential ion channels family, associated with cellular response to layer sensing. Studies suggest that defects in TRPM6's sensing ability mediate magnesium reabsorption. Mutations in TRPM6 are found in Bartter syndrome type II patients, leading to low serum magnesium levels and increased urinary magnesium excretions. Fractional excretion of magnesium remains normal (Ayu et al., 2024).

Loss of function of TRPM6 causes decreased absorption of magnesium in kidney cells. Despite this, most adults do not excrete magnesium in urine. Lower levels of ionized calcium are detected by thyro-parathyroid receptors, leading to increased production of active vitamin D. This helps absorb calcium and phosphate in the intestines. Plasma ionized calcium and magnesium levels are not correlated, so the increase in parathyroid hormone secretion may not balance the loss of dietary calcium. Hypomagnesemia patients require more dietary calcium to prevent bone loss, despite greater urinary magnesium loss. Chronic hypomagnesemia is usually secondary to treatable conditions like steatorrhea, diabetes, and familial hypoparathyroidism, rather than causing major symptoms (Pietropaolo et al., 2020). International diagnostic criteria for hypomagnesemia: serum magnesium levels <0.7 mmol/L, plasma magnesium concentration <0.85 mmol/L. Severe hypomagnesemia (<0.6 mmol/L) can cause secondary hypocalcemia. Clinicians must identify patients with low serum magnesium levels and hypocalcemia. Diagnosis of hypomagnesemia with secondary hypocalcemia requires parental consanguinity, differential diagnosis, patient history, and clinical examination. It is recommended to firstly rule out specific renal hypomagnesemia causes before

starting magnesium supplement treatment (Tinawi, 2020).

Urine electrolytes are necessary to diagnose hypomagnesemia and hypocalcemia, including primary hypomagnesemia with low magnesium reabsorption, such as familial hypomagnesemia. Different genotypes indicate various types of hypomagnesemia with or without hypercalciuria. Ratios of urinary calcium/creatinine and 24-hour urinary magnesium excretion can help identify familial hypocalcemia and hypomagnesemia. Serum tests like fractional magnesium excretion and urinary magnesium clearance-based tests are effective for detecting renal disorders (Pepe et al., 2020).

For this case, the difficulty of management resides in treating multiple symptoms of this disorder : gastrointestinal and particularly seizures which, if not managed properly, can have a negative in neuro psychological development of the child. The follow-up is crucial with regular biological check-ups (3 to 6 months) with EEG and MRI done annually.

Hypomagnesemia, caused by SLC12A3 gene mutations or splicing errors, is more severe than isolated hypocalcemia. Immediate intervention is necessary, with oral magnesium supplementation for mild symptoms and intravenous magnesium for severe symptoms. Correcting electrolyte abnormalities in TRPM6 mutations requires careful consideration, with more aggressive supplementation based on clinical symptoms (Han et al., 2024). Increase magnesium and calcium intake for patients. Provide supplementation if requirements are not met. Consider magnesium parenteral preparation for hospitalized patients with gastrointestinal issues, fasting for seizure investigation, or persistent hyperemesis. Evaluate for hypomagnesemia in these patients. Monitor serum levels for treatment effectiveness and compliance. The long-term complications of hypomagnesemia and hypocalcemia have been reported, including nephrocalcinosis and epiphyseal hypoplasia. Careful and long-term observation is needed for these electrolyte abnormalities. Effective treatment and genetic studies can improve the condition. Regular monitoring of electrolytes and the central nervous system is important. Long-term follow-up is necessary for patients with TRPM6 mutations (Dokurel et al., 2024).

4. CONCLUSION

Familial hypomagnesemia with secondary hypocalcaemia is a rare genetic disorder that is very difficult to diagnose and manage. Mutation of the TRPM6 gene should be suspected in all cases of severe hypomagnesemia detected at an early age in consanguineous families.Early diagnosis and treatment is important to prevent irreversible neurological damage.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

As per international standards, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

Adella, A., Gommers, L. M., Bos, C., Leermakers, P. A., de Baaij, J. H., & Hoenderop, J. G. (2024). Characterization of intestine-specific *TRPM6* knockout C57BL/6 J mice: Effects of short-term omeprazole treatment. *Pflügers Archiv-European Journal of Physiology*, 1-11.

Ayu, A. (n.d.). Disorders of magnesium metabolism: Hypomagnesemia and hypermagnesemia. *iiardjournals.org*.

Bayramoğlu, E., Keskin, M., Aycan, Z., Savaş-Erdeve, Ş., & Çetinkaya, S. (2021). Long-term clinical follow-up of patients with familial hypomagnesemia with secondary hypocalcemia. *Journal of Clinical Research in Pediatric Endocrinology*, *13*(3), 300.

Bobrowicz, M., Pachucki, J., & Popow, M. (2024). Hypomagnesemia leading to

parathyroid dysfunction, hypocalcemia, and hypokalemia as a complication of long-term treatment with a proton pump inhibitor. *Endokrynologia Polska*.

Dokurel Cetin, I., Betül Gerik-Çelebi, H., Demiral, M., & Çetin, O. (2024). Hereditary hypomagnesemia with secondary hypocalcemia caused by a novel mutation in *TRPM6* gene. *Journal of Pediatric Endocrinology and Metabolism*, *37*(2), 184-188.

Gao, X. (2022). Palmitoylation and regulation of divalent cation transport by *TRPM7* and *TRPM6*.

Han, Y., Zhao, Y., Wang, H., & Huo, L. (2022). Case report: Novel *TRPM6* mutations cause hereditary hypomagnesemia with secondary hypocalcemia in a Chinese family and a literature review. *Frontiers in Pediatrics*.

Na, D., Tao, G., Shu-Ying, L., Qin-Yi, W., Xiao-Li, Q., Yong-Fang, L., ... & Yan-Yi, Y. (2021). Association between hypomagnesemia and severity of primary hyperparathyroidism: A retrospective study. *BMC Endocrine Disorders*, *21*, 1-8.

Pepe, J., Colangelo, L., Biamonte, F., Sonato, C., Danese, V. C., Cecchetti, V., ... & Cipriani, C. (2020). Diagnosis and management of hypocalcemia. *Endocrine*, *69,* 485-495.

Pietropaolo, G., Pugliese, D., Armuzzi, A., Guidi, L., Gasbarrini, A., Rapaccini, G. L., ... & Trapani, V. (2020). Magnesium absorption in intestinal cells: Evidence of cross-talk between EGF and *TRPM6* and novel implications for cetuximab therapy. *Nutrients*, *12*(11), 3277.

Schlingmann, K. P., Weber, S., Peters, M., Niemann Nejsum, L., Vitzthum, H., Klingel, K., Kratz, M., Haddad, E., Ristoff, E., Dinour, D., & Syrrou, M. (2002). Hypomagnesemia with secondary hypocalcemia is caused by mutations in *TRPM6*, a new member of the *TRPM* gene family. *Nature Genetics*, *31*(2), 166-170.

Tinawi, M. (2020). Disorders of magnesium metabolism: Hypomagnesemia and hypermagnesemia. *Archives of Clinical and Biomedical Research*.

Uddin, M. S., Alradhi, A. Y., Alqathani, F. M. N., Alessa, O. S., Alshammari, A. N. M., Tripathy, R., & Alomari, M. A. (2024). A rare case of neonatal hypomagnesemia with secondary hypocalcemia caused by a novel homozygous *TRPM6* gene variant. *The American Journal of Case Reports*, *25*, e942498-1.

Vargas-Poussou, R., Claverie-Martin, F., Prot-Bertoye, C., Carotti, V., van der Wijst, J., Perdomo-Ramirez, A., ... & de Baaij, J. H. (2023). Possible role for rare *TRPM7* variants in patients with hypomagnesemia with secondary hypocalcemia. *Nephrology Dialysis Transplantation*, *38*(3), 679-690.

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