Case report

Hypomagnesemiaandsecondaryhypocalcemiawith a TRPM6 mutation : a rare pathologywithdifficultdiagnosis and management - a case report

Abstract :

Inherited or genetichypomagnesemiawithsecondaryhypocalcemia, a diseasetypicallypresentingwithepilepsy and characterized by lowbloodlevels of magnesium and calcium and metabolicbonedisease, iscaused by mutations in the TRPM6 genes.Variousfactors, such as lowdietaryintake and poor absorption of magnesium in the gut, affect magnesium balance.Hypomagnesemiawithsecondaryhypocalcemiais rare, and thereforethere are no large epidemiologicalstudiesreflecting the global distribution of these conditions. In dailyclinical practice, one can usuallyseeit in connectionwithneonates. According to the literature, mutations of TRPM6 account for about 40–50% of hypomagnesemia patients withsecondaryhypocalcemia. The aim of this article is to highlight the difficultiesassociatedwithdiagnosis and management.

Keywords: hypomagnesemia,hypocalcemia,TRPM6 mutation ,seizur

Introduction :

Inherited or genetichypomagnesemiawithsecondaryhypocalcemia, a condition commonlyassociatedwithepilepsy and marked by reducedmagnesium and calcium levels in the blood and metabolicbone issues, isattributed to mutations in the TRPM6 genes. Along withhypoparathyroidism, itsharessimilaritieswithgeneticallyinheritedrenalhypomagnesemia. Severalfactors, includinginadequatedietaryintake and impairedmagnesium absorption in the gastrointestinal tract, impact magnesiumequilibrium. In Western societies, insufficientdietarymagnesiumlevels are exceedingly rare, thoughmalnourishmentis a contributing factor to hypomagnesemia.[1]

Chronicinadequatemagnesiumintakeisoftenoverlooked, leading to deficiency. Magnesiumlevels can remain stable untildepletionoccurs. Insufficientintake or reabsorption can decreasemagnesiumlevels. Early recognition and magnesiumsupplementation are important. Low magnesiumlevels affect hormone regulation and can lead to hypoparathyroidism.[2]

Case presentation :

F.N.female infant born to a 2nd degree consanguineous parents, with history for seizures due to an unexplored hypomagnesemiaat the age of 3 months, hospitalized and treated with magnesium 30 mg/kg/day. She is being monitored for epilepsy under Depakine at the dose of 30 mg/kg/day. She presents a delay in psychomotor acquisitions with good height and weight development. There is no sign of diarrhea or chronic vomiting.

She was brought to consultation for apyretic generalized seizuresafter 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. Biologically, she had severe hypomagnesemia < 0.6 mg/dl (N=1.6 – 2.6 mg/dl), associated with severe hypocalcemia at 71 mg/dl; phosphoremia was within normal limits (52 mg/dl) as were ALP = 123 mg (N) and parathyroid hormone at 29 mg/l. Potassium levels were normal and renal function was preserved, there was no acidosis. Urinaryionogram 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 aTRPM6 mutation.

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 seizuresclinically and an increase in magnesium levels to 1.07 mg/l with a correlated normalization of calcemia. The patient was discharged with oral magnesium (30 mg/kg/day of elemental magnesium) as treatment, with a possible IV magnesium in the event of diarrhea, vomiting or inability to feed.

Discussion :

Hypomagnesemiawithsecondaryhypocalcemiais rare in neonates. It isdefined as lowmagnesiumlevelsbelow 0.7 mmol/L and low calcium levelsbelow 2.05 mmol/L. Poor diet, malnutrition, malabsorption, and genetic mutations contribute to itsprevalence. Many cases go undiagnosed due to subtlesymptoms and regionaldifferences. Mutations of TRPM6 account for 40-50% of cases. Limited global epidemiological data exists. More researchisneeded to understandmagnesium and calcium metabolism. Supplementation and improvedoutcomes can lessen the burden on healthcaresystems.[3]Low magnesiumlevelsdirectlycontribute to low calcium levels in the patient. Hypocalcemiais a result of hypomagnesemia in this case. Magnesiumdeficiencyworsens calcium deficiency, makinghypocalcemiastronglylinked to lowmagnesiumlevels. Severehypomagnesemia can cause seizures and severe muscle cramps. The clinicalsymptomsmainlyinvolve the heart, leading to earlycardiovascularmortality. Thesesymptomsinclude muscle problems, cardiacarrhythmia, heartfailure, and troponinelevation. Carpopedalspasmis a common manifestation of hypocalcemia as it progresses. Severechronichypermagnesemiasuppressesparathyroid hormone synthesis and can lead to hypocalcemicseizures and tetany. Severehypomagnesemia and hypocalcemia are oftenaccompanied by severearrhythmia, heartattack, and heartfailure, indicatingadvancedkidneyfailure. This greatlyreduces the life expectancy of patients withchronickidneydisease.[4]

TRPM6 is a long TRPM proteinencoded by the TRPM6 gene. It ishighlyexpressed in the kidney and colon and has lower expression in other tissues. TRPM6 plays a criticalrole in the duodenum by compensating for the loss of TRPM7. Studies focus on mineral ion uptake in the kidneys.[5]

TRPM6 sensesintracellularmagnesiumlevels and store depletion, affectingmagnesium ion absorption. Knockouts of the TRPM6 genemay not cause medicalphenotypes. Dominant mutations in TRPM6 generesult in calcium homeostasis variations. TRPM6 gene mutations cause non-heritablemagnesiumdisorders. Defects in TRPM6 genedisruptmagnesium ion homeostasis in intestines and kidneys, impacting sodium chloridereabsorption.[6]

The TRPM6 gene on chromosome 9 has 26 exons. It aidsmagnesiumreabsorption in the kidney and intestinal transport alongside TRPM7. Mutations in TRPM6 cause autosomal recessivehypomagnesemia, leading to lowparathyroid hormone levels and refractoryhypomagnesemia in children. Pathogenic variants typicallyinvolve large deletions and gene conversion, resulting in completeloss of gene expression and proteinfunction.[7]

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 lowmagnesiumefficiency. Exon-skippingtreatmentmay help hypomagnesemia patients with TRPM6 mutations. TRPM6 mutations lead to absence of TRPM6-encoded protein and impairedfunction, resulting in symptomsrelated to ion transport. Autosomal dominant inheritanceissuggested for hypomagnesemiawithsecondaryhypocalcemia.[8]

Understanding ions transport pathwaysis crucial for understanding absorption in the body. This section focuses on TRPM6's role in absorption, discussing how mutations affect itsfunction and lead to hypomagnesemia. Magnesiumentersenterocytes via TRPM6, which has twomechanisms for transportingmagnesium ions. TRPM6 is part of the transient receptorpotential ion channels family, associatedwith cellular response to layer sensing. Studiessuggestthatdefects in TRPM6's sensingabilitymediatemagnesiumreabsorption. Mutations in TRPM6 are found in Bartter syndrome type II patients, leading to lowserummagnesiumlevels and increasedurinarymagnesiumexcretions. Fractionalexcretion of Mg^{2+} remains normal.[9]

Loss of function of TRPM6 causes decreased absorption of magnesium in kidneycells. Despitethis, mostadults do not excretemagnesium in urine. Lowerlevels of ionized calcium are detected by thyro-parathyroidreceptors, leading to increased production of active vitamin D. This helpsabsorb calcium and phosphate in the intestines. Plasma ionized calcium and magnesiumlevels are not correlated, so the increase in parathyroid hormone secretionmay not balance the loss of dietary calcium. Hypomagnesemia patients require more dietary calcium to preventboneloss, despitegreaterurinarymagnesiumloss. Chronichypomagnesemiaisusuallysecondary to treatable conditions like steatorrhea, diabetes, and familial hypoparathyroidism, ratherthancausing major symptoms.[10]International diagnostic criteria for hypomagnesemia:serummagnesiumlevels<0.7 mmol/L, plasma magnesium concentration <0.85 mmol/L. Severehypomagnesemia (<0.6 mmol/L) can cause secondaryhypocalcemia. Clinicians must identify patients withlowserummagnesiumlevels and hypocalcemia (hypomagnesemiawithsecondaryhypocalcemia or HS). Diagnosis of HS requires parental consanguinity, differentialdiagnosis, patient history, and clinicalexamination. Rule out specific IMCD hypomagnesemia causes beforestartingmagnesiumsupplementtreatment.[11]

Urine electrolytes are necessary to diagnose hypomagnesemia and hypocalcemia, includingprimaryhypomagnesemiawithlowmagnesiumreabsorption, such as familial hypomagnesemia. Differentgenotypesindicatevarious types of hypomagnesemiawith or withouthypercalciuria. Ratios of urinary calcium/creatinine and 24-hour urinarymagnesiumexcretion can help identify familial hypocalcemia and hypomagnesemia. Serum tests like fractionalmagnesiumexcretion and urinarymagnesium clearance-based tests are effective for detectingrenaldisorders.[12]

Hypomagnesemia, caused by SLC12A3 gene mutations or splicingerrors, is more severethanisolatedhypocalcemia. Immediate intervention isnecessary, with oral magnesiumsupplementation for mildsymptoms and intravenousmagnesium for severesymptoms. Correctingelectrolyteabnormalities in TRP6 mutations requirescarefulconsideration, with more aggressivesupplementationbased on

clinicalsymptoms.[1] Increasemagnesium and calcium intake for patients. Providesupplementation if requirements are not met. Considermagnesiumparenteralpreparation for hospitalized patients with GI issues, fasting for seizure investigation, or persistent hyperemesis. Evaluate for hypomagnesemia in these patients. Monitor serumlevels for treatmenteffectiveness and compliance.The long-term complications of hypomagnesemia and hypocalcemia have been reported, includingnephrocalcinosis and epiphysealhypoplasia. Careful and long-term observation isneeded for theseelectrolyteabnormalities. Effective treatment and geneticstudies can improve the condition. Regular monitoring of electrolytes and the central nervous system is important. Long-term follow-up isnecessary for patients with TRPM6 mutations.[13]

Conclusion :

Congenitalhypomagnesemiawithsecondaryhypocalcaemiais a rare geneticdisorderthatisverydifficult to diagnose and manage. Mutation of the TRPM6 geneshouldbesuspected in all cases of severehypomagnesemiadetected at an earlyage in consanguineousfamilies.Earlydiagnosis and treatmentis important to preventirreversibleneurological damage

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