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Primary Hypomagnesemia with Secondary Hypocalcemia in an Infant-Case Series.

KEYWORDS

Hypocalcemia , Refractory seizures, Hypomagnesemia.

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ABSTRACT Familial hypomagnesemia with secondary hypocalcemia is a genetic disorder of magnesium metabolism that presents with refractory seizures in infancy. **Case characteristics**: We herein report an infant with familial hypomagnesemia who presented as medically-refractory seizures and .Interestingly she had lost previous sibling because of lack of correct diagnosis. **Intervention**: Child was given oral magnesium supplementation and the seizures got controlled. **Conclusion**: Familial hypomagnesemia should be considered in any baby with refractory hypocalcemic seizures.

Introduction:

The association of hypomagnesaemia with hypocalcemia is known for the past few years and in majority of these instances, disturbances of magnesium (Mg) homeostasis is secondary to an obvious cause. Primary hypomagnesaemia due to disorder of magnesium metabolism (1) though rare, has been reported. In these infants who are hypomagnesaemia and hypocalcaemia, symptoms and biochemical disturbances respond only to administration of magnesium salts. Hypomagnesemia is now reported in neonates and during early infancy ––(13) as a result of specific malabsorption of magnesium. Previously, only male infants were reported to be affected but now there have been a few documented cases in females. Here, we report one such infant who was followed up from the age of 4 weeks to 8 months.

Case 1: A breast fed female infant, second issue born of a second degree consanguineous marriage, was delivered by LSCS (Indication – previous LSCS) at term with a normal birth weight. The antenatal period was unremarkable. .She was referred at the age of 28 days of life for repeated attacks of multifocal clonic seizure of two days duration baby was treated with inj.Calcium gluconate, inj. Phenobarbitone at the referring hospital.. At the time of admission examination, the child had normal weight, height and head circumference. There were no neurocutaneous markers with normal neurological examination.

On 36th day of life baby had recurrence of multi focal clonic seizures requiring up to 40mg/Kg of Inj.Phenobarbitone. Work up revealed hypocalcemia (calcium: 6.4 mg/dL ionized calcium: 3.2mg/dl) with normal levels of phosphorous, alkaline phosphatase, electrolytes, arterial blood gases and albumin. Renal and liver function tests were normal. Serum parathormone level was slightly low 4.64 pg/mL (Range: 6-55). As his serum calcium remained low despite intravenous calcium for two days, serum magnesium levels analysed and it was found to be very low 0.65mg/dL; range (1.6-2.4).

In view of the severe hypomagnesemia the possibility of primary hypomagnesemia with secondary hypocalcemia. Baby was treated with IM Magnesium and IV calcium gluconate following which the serum magnesium and calcium levels came into 1mg/dl and 9.2mg/dl, with cessation of seizures.

Multifocal tonic clonic seizures recurred on D53 which was controlled with IM Magnesium sulphate. The serum magnesium and Calcium level is had again dropped which had resulted in recurrence of seizures. Subsequently oral supplements of Magnesium sulphate and calcium were started and baby was discharged on day 60 of life. One week after discharge he was seizure free and Sr. Magnesium and Calcium levels were normal

Other investigations: CBC-Normal, CRP –Negative, Blood culture –NO growth. Imaging- x- ray chest, skeletal survey-normal.USG-Abdomen cranium,-normal. MRI Brain –normal. Urinary PH-6.0, Urinary specific gravity -1.020. Urinary spot magnesium< 0.4, urinary spot calcium -0.3, urinary creatinine -7.1.UMS, TMS-Negative.CSF analysis-normal.Sodium-140, potassium-5, urea -16, creatinine-0.6, choloride-114, HCO3-10.Mother worh up revevled PTH-105.3 (15-65),Vitamin D-10.49 (30-100) ng /ml ,Calcium .phosphorus .ALP-Normal.USG -Neck & Abdomen –Normal. Blood Group –B Positive.

Case 2: A breast fed male infant, second issue born of a second degree consanguineous marriage, delivered by labour natural at term with a normal birth weight. Antenatal period was unremarkable and was presented to us 15 days of life multiple episode of seizure of one day duration. There was history of previous female sibling death due to recurrent seizure. On examination, baby had normal weight, height and head circumference. There were no neurocutaneous markers and neurological examination baby was drowsy, lethargy and mild hypotonia. Work up revealed hypocalcemia (calcium: 5.9 mg/dL ionized calcium: 2.8mg/dl) with normal levels of phosphorous, alkaline phosphatase, electrolytes, arterial blood gases and albumin. Renal and liver function tests were normal. Serum parathormone level was low 3.84 pg/mL (Range: 6-55). As his serum calcium remained low despite intravenous calcium for two days, serum magnesium levels analysed and it was found to be very low 0.75mg/dL; range (1.6-2.4).

In view of the severe hypomagnesemia the possibility of primary hypomagnesemia with secondary hypocalcemia. Baby was treated with IM Magnesium and IV calcium gluconate following which the serum magnesium and calcium levels came into 2.2mg/dl and 10.4mg/dl, with cessation of seizures.

Discussion:

Deficiency of magnesium can lead to convulsive disorder with permanent neuro-logic impairment. In adults, chronic magnesium depletion has been linked with hypertension, arrhythmias, atherosclerotic vascular disease, metabolic bone disease, renal stones and sometimes sudden death. Symptomatic hypomagnesemia is frequently encountered in children where it may be secondary to chronic diarrhea, protein energy malnutrition, hypo-parathyroidism, primary aldosteronism, renal tubular acidosis, hyper-calcemic states and a result of drugs like loop diuretics, aminoglycosides, cephalosporin, post intestinal resection or long term treatment with intravenous fluids. In the neonates,

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transient hypomagnesemia is known to occur in babies of toxaemic and diabetic mothers or in IUGR babies or with transient hypoparathyroidism or maternal hypomagnesemia due to celiac disease. None of these conditions could account for the disturbances of magnesium and calcium metabolism in this patient.

Primary hypomagnesemia with secondary hypocalcemia is a rare genetic disorder (4)characterized by recurrent tetany (5)or convulsions in early infancy, or both, which are refractory to calcium supplementation but respond to magnesium treatment. In cases reported in literature, manifestations of primary hypomagnesemia were seen in early infancy ranging from the fifteenth day of life till the fourth month. It was initially believed that primary hypomagnesemia had X-linked recessive inheritance as it was reported only in male siblings (6). In view of the disorder being reported in female siblings in the last few years, autosomal recessive inheritance is now considered. Our patient had previous male siblings who had died of intractable convulsions between the ages of 3 months also suggesting autosomal recessive inheritance.

Mutations in the TRPM6 (hypomagnesemia with secondary hypocalcemia) gene for the DCT- and colon-specific apical Mg2+ channel, TRPM6, cause the most profound genetic hypomagnesemia]. A measured serum Mg2+ low as 0.2 mg/dl are may be immeasurable levels, is not uncommon in these patients. Consequently, patients often present with seizures within the first months of life . A defect in the TRPM6 channel impairs epithelial Mg2+ resorption in the colon and DCT, thereby inhibiting uptake and stimulating wasting of Mg2+, causing significant hypomagnesemia . The secondary hypocalcemia often observed is probably caused by inhibition of the parathyroid gland by the hypomagnesemia, resulting in low levels of parathyroid hormone and eventually leading to hypocalcemia.(7)

This patient had significant hypocalcemia with hypomagnesemia. It was of interest to note that therapy with calcium as well as with magnesium alone resulted in improvement and caused elevation of serum calcium, which did not rise when only calcium was administered. Magnesium is the second most common cation in the body. Probably, till the tissue stores are depleted the clinical symptoms do not become manifest, hence the unpredictable relationship between spasms and the serum levels.

Though magnesium metabolic balance studies and radioactive magnesium absorption studies could not be carried out in this patient, family history and rest of the investigations, follow up studies and the dramatic therapeutic response to magnesium therapy excluded other causes

On follow up of at 8 months of age baby was on oral magnesium sulphate, asymptomatic, neurologically normal .Blood sample has been stored for gene mutation analysis (TRPM6)to be done later.,

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