CASE REPORT

Familial Hypomagnesemia with Secondary Hypocalcemia Mimicking Neurodegenerative Disorder

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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 had cerebral atrophy on neuroimaging. Interestingly he had lost previous two siblings because of lack of correct diagnosis. **Intervention**: Child was given oral magnesium supplementation and the seizures got controlled. **Message**: Familial hypomagnesemia should be considered in any child with recurrent or refractory hypocalcemic seizures.

Keywords: *Calcium, Developmental delay, Drug- resistant seizures, Magnesium.*

Familial hypomagnesemia with secondary hypocalcemia (FHSH) is a rare autosomal-recessive disorder of magnesium metabolism [1]. It occurs due to decreased intestinal absorption of magnesium and renal magnesium wasting with secondary parathyroid insufficiency leading to hypocalcemia [2]. If adequate magnesium is not supplemented orally, then children continue to develop recurrent seizures secondary to hypocalcemia that can lead to stagnation of development of milestones and even regression of milestones. As it is customary to look for hypocalcemia in infants with seizures, most pediatricians detect hypocalcemia in these children and treat it symptomatically. Etiological work up of hypocalcemia is usually not done. Many a times hypomagnesemia as a cause of hypocalcemia is missed and even if picked up on investigation, it is not adequately treated because of lack of oral magnesium formulations.

CASE REPORT

Case 1: A 13-month-old boy born to second degree consanguineously married couple presented with recurrent generalised clonic seizures from one month of age. The seizures occurred in clusters every 2-3 weeks despite use of three antiepileptic drugs. Child presented at 13-months of age with status epilepticus (generalised clonic and complex partial type). Child had developmental delay affecting all domains (could just sit with support without pincer grasp and had monosyllables only). Family history was significant that her previous two children had died due to seizures at 2 month and 8 month of age, respectively. They were not investigated in detail but parents reported that their blood calcium levels were very low. Child was referred to us as a probable neurodegenerative disorder.

On examination, the child had normal weight, height and head circumference. There were no neurocutaneous markers or meningeal signs. He was excessively irritable and had bilateral horizontal nystagmus. There was mild hypotonia and reflexes were normal. Work up revealed hypocalcemia (calcium:5.2 mg/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 5.5 pg/mL (Range: 6-55). As his serum calcium remained low despite intravenous calcium for two days, serum magnesium levels were; these were low (0.4mg/dL; range:1.8-2.4). EEG showed slow background activity without any epileptiform discharges and MRI of brain showed mild diffuse cerebral atrophy. CT scan of brain did not reveal any calcifications. USG abdomen and pelvis was normal without any evidence of nephrocalcinosis. His urinary calcium was 397 mg/day (Normal: 25-300) and urinary magnesium was 9.5 mg/L (Normal: 110-210).

In view of severe hypomagnesemia, a possibility of FHSH was considered. Genetic studies for the mutation could not be done. Child was given intravenous magnesium at 50 mg/kg along with intravenous calcium for three days after which the serum magnesium and calcium levels got normalised. Child became seizure free and the nystagmus subsided. Antiepileptics were withdrawn and child was discharged on oral magnesium

sulphate (parental magnesium sulphate was given orally). Follow-up after a month showed that the baby was now seizure-free and had attained independent sitting, standing with support and cruising, along with bisyllable speech.

DISCUSSION

FHSH is an autosomal-recessive condition caused by mutations in the *Transient Receptor Potential Melastatin-6* (*TRPM6*) gene that is expressed in the intestine and the kidney and codes for a transient receptor potential cation channel [3]. Patients present with seizures, tetany, tremors or restlessness at 2-8 weeks of life due to severe hypomagnesemia and secondary hypocalcemia. It leads to lethargy, nystagmus and convulsions. If untreated it can lead to cerebral atrophy like in our case and can also be fatal [4]. Hypomagnesemia causes secondary hypocalcemia by impairing the release of PTH by the parathyroid gland and through blunting of the tissue response to PTH [2].

Hypomagnesemia may result from inadequate magnesium intake, increased gastrointestinal or renal losses, or redistribution from extracellular to intracellular space [1]. Gitelman and Bartter syndrome are the most common autosomal recessive conditions associated with hypomagnesemia. They must be ruled out by doing the urinary pH and serum electrolytes [4]. Various drugs like Amphotericin, diuretics and osmotic agents can also cause symptomatic hypomagnesemia.

Familial hypomagnesemia with hypercalciuira and nephrocalcinosis is an autosomal recessive disorder caused by a mutation in the gene *CLDN16* and it also presents with symptoms of renal magnesium wasting. This generally presents with high serum calcium levels along with nephrocalcinosis or nephrolithiasis on the ultrasound of the kidneys. Once the diagnosis of FHSH is made, the condition is treated by parenteral magnesium followed by long term term therapy of oral magnesium salt. Automatically the hypocalcemia gets corrected.

Hypomagnesemia which is a treatable condition in our particular case probably led to the death of previous two children despite the administration of oral calcium supplements to both the children. Recurrent seizures and use of high doses of antiepileptic drugs with repeated admissions may lead to developmental slowing. Hypomagnesemia itself can lead to lethargy thereby contributing to developmental delay.

Though genetic confirmation was not done in our case, a timely diagnosis and appropriate simple intervention lead to complete cessation of seizures and regaining of milestones. Our case report highlights the importance of considering FHSH as a possibility in any child with severe hypocalcemia with normal to low PTH levels especially when intravenous calcium injections fail to correct hypocalcemia. Parental preparation of magnesium sulphate can be used orally and works well as oral magnesium syrups are not available. We had 5 other similar cases in last two years presenting with refractory hypocalcemic seizures and developmental delay highlighting the importance of increasing the awareness of this rare condition among pediatricians.

FHSH, though very rare, is an eminently treatable condition and because it is an autosomal recessive disorder there is scope for genetic counselling.

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