Familial Hypomagnesemia with Secondary Hypocalcemia Presenting as Refractory Seizures

Dear Editor,

A three-month-old baby boy presented with complaints of multiple episodes of right-sided focal seizures involving the right upper and lower limbs for 15 days. The semiology of seizures was tonic-clonic type lasting for five minutes associated with a preseizure aura of blank-staring look without any postictal urination or defecation. There were no episodes of fever. He was taken to numerous local practitioners and was admitted to one hospital, where the baby was treated for hypocalcemia. Two days after discharge, the baby again had multiple seizure episodes and was admitted to our hospital. During the seizure-free time, the baby was feeding well and was having regular activity and tone. The baby was born at 36 weeks gestation by vertex vaginal mode as the second child to third-degree consanguineous marriage with a birth weight of 1.75 kg and no significant Neonatal Intensive care unit (NICU) stay. He was on exclusive breastfeeding. He had a positive family history of the baby's aunt, a known case of generalized tonic-clonic seizures and was under medical treatment.

On examination, he appeared active with no dysmorphic features and stable vitals, along with normal anthropometry. Systemic examination was unremarkable with normal tone, reflexes, good activity, and no neurocutaneous markers or meningeal signs. On investigation, complete blood counts, C-

Reactive Protein (CRP), serum electrolytes, serum phosphorus, arterial blood gases, serum proteins, and blood sugar levels were within normal limits along with liver and renal function tests. Serum calcium (5.6 mg/dl) was at a lower level, following which serum magnesium was sent, which came low (0.5 mg/dl) with no urinary loss of Mg^{2+}. The serum parathormone (PTH) level was not done.

Lumbar puncture, Electroencephalogram (EEG), and Magnetic Resonance Imaging (MRI) scans of the brain were done, which were within the normal range. Ultrasonography (USG) abdomen and pelvis were normal without any pathology. Familial hypomagnesemia with secondary hypocalcemia (FHSH) was suspected due to lower magnesium levels, but genetic studies were not affordable by the parents, hence could not be done.

The serum magnesium levels were corrected by administering intravenous magnesium at the rate of 50 mg/kg slow Intravenous (IV) infusion (0.1 ml/kg of a 50% solution) every six hours three times and repeated serum magnesium levels were checked before starting every infusion along with the calcium supplementation for two days, after which the counts were repeated and were within normal limit with no episode of seizure during that period. The baby was discharged on an oral magnesium supplement (containing 75 mg elemental magnesium in a 5 ml solution) and off anti-epileptics. Follow-up after one month was seizure-free with serum calcium and magnesium levels within the normal limit.

Familial hypomagnesemia with secondary hypocalcemia, a rare autosomal recessive disorder, is associated with reduced intestinal magnesium absorption and enhanced renal wasting followed by hypocalcemia due to secondary parathyroid insufficiency.[1] It usually presents with recurrent seizures secondary to hypocalcemia, lethargy, and tetany, which are symptoms of hypocalcemia. Familial hypomagnesemia with secondary hypocalcemia

has a defect in the TRPM6 gene present on chromosome 9q22.1, which encodes for the magnesium permeable ion channel in the intestine and kidney, causing impaired intestinal and renal reabsorption of Mg2+, leading to serum hypomagnesemia.[2,3] In addition, hypomagnesemia causes secondary hypocalcemia by causing impairment to PTH released by the parathyroid glands and blunting its tissue response.[4]

The mechanism behind hypomagnesemia-causing seizures is not well understood. It has been proposed via rat models that a reduction in extracellular magnesium results in a lack of antagonism at the *N*-methyl-d-aspartate-type glutamate receptors, resulting in epileptiform discharges.[5] Familial hypomagnesemia with secondary hypocalcemia usually presents during the first months of life with convulsions, muscle spasms, or tetany, which subsides on calcium and magnesium supplementation.[6] In the absence of adequate magnesium supplementation, the baby presents with recurrent seizures secondary to hypocalcemia, which can result in the failure to thrive and global developmental delay or even regression of developmental milestones. As in our case, the patient's hypocalcemia was corrected by a local practitioner, but seizure episodes continued and subsided only after correcting the magnesium levels. Various conditions can result in hypomagnesemia, including increased intestinal or renal losses, inadequate magnesium intake, or redistribution from extracellular to intracellular space.[4] In order to establish the diagnosis of FHSH, other conditions presenting with hypomagnesemia should be excluded. A few of the most common autosomal recessive conditions associated with hypomagnesemia are Gitelman and Bartter syndrome, easily ruled out by serum electrolyte and urinary pH.[6] The secondary causes of hypomagnesemia include medications, hypoparathyroidism, chronic diarrhea, steatorrhea, malabsorption or inflammatory bowel, or recovery after acute tubular injury. Once the diagnosis of FHSH is made, the condition is treated by parenteral magnesium followed by long-term therapy of oral magnesium salt, which by default corrects the hypocalcemia.[7,8] Our case had normal levels of serum phosphate, contrary to other reports, where elevated phosphate levels are seen due to decreased secretion and resistance to PTH action caused by hypomagnesemia.[7] This can be confused with hypoparathyroidism if serum magnesium levels are not done.

Genetic testing for mutation analysis for the TRPM6 gene can be done to confirm the diagnosis of FHSH, but the patient was not affordable, so it was not possible in our case. Whenever a baby presents with seizures, metabolic workup including calcium is done, and hypocalcemia as a cause is ruled out, but the etiology of hypocalcemia is not investigated. Even if hypomagnesemia is found, it is not adequately managed due to a lack of oral magnesium supplements. Therefore, it is essential to sensitize the practitioner regarding FHSH to rule out hypocalcemia secondary to hypomagnesemia and treat accordingly in case of refractory seizures.

Early diagnosis and treatment are essential to prevent irreversible neurological damage. Restoring serum magnesium concentrations to normal values by high-dose magnesium supplementation can overcome the apparent defect in magnesium absorption and serum calcium concentrations. Life-long supplementation with magnesium is required to overcome the defect in these individuals and avoid long-term complications.[9]

Familial hypomagnesemia should be kept in mind in a case presenting with refractory seizure and non-responsive to anti-epileptics. Being an autosomal recessive condition, there is the scope of genetic counseling and educating the parents about the disease. It helps in preventing the child from exposure to unnecessary anti-epileptics and sometimes, multiple anti-epileptics and their side effects.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Amit Kumar Pandey, Prashant Nigwekar

Department of Pediatrics, Rural Medical College and Pravara Rural Hospital, PIMS, Loni, Maharashtra, India

Address for correspondence: Dr. Amit Kumar Pandey, Department of Pediatrics, Rural Medical College and Pravara Rural Hospital, PIMS, Loni, Maharashtra, India.
E-mail: amit952.pandey@gmail.com

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