Rare Inherited Hypomagnesemias - An Endocrine Case Series

Hypomagnesemia is a common dyselectrolytemia with serious manifestations. The purpose of the current series is to highlight the importance of systematically working up inherited hypomagnesemias. We describe five patients from three families with genetically proven hypomagnesemias. First family had twin sisters with Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) and second (two siblings) and third family had Hypomagnesemia with secondary hypocalcemia (HSH) both of which are rare inherited hypomagnesemias. Diagnosis was made only during systematic workup of hypomagnesemia many years after initial presentation.

Patients 1and 2: These were 22 year old twins incidentally discovered to have mild elevation of serum creatinine with bilateral medullary nephrocalcinosis at the ages of 15 and 18 and were being managed conservatively by nephrologist. They were referred to endocrinology for evaluation of high parathyroid hormone levels (PTH) (711.5 pg/mL and 589 pg/mL). Both were physically well on examination with a normal blood pressure and sterile pyuria. Evaluation revealed vitamin D deficiency (5.56 ng/mL and <3 ng/mL) secondary hyperparathyroidism, hypercalciuria and hypomagnesemia (1.5 mg/dL in both). Fractional excretion of magnesium (FEMg) was elevated in both (10.2% and 14.9%) indicating renal magnesium (Mg) wasting. FHHNC was suspected in view of mild renal failure, hypomagnesemia and nephrocalcinosis. Genetic testing revealed a novel heterozygous pathogenic mutation c.313G>A (p.D105N) in CLDN16 exon 1 in both the sisters. They were started on oral magnesium supplements and cholecalciferol which normalised their Mg and PTH values.

Patients 3,4 and 5: Patient 3 was a six year male child with refractory seizures since one month of age treated with multiple antiepileptic drugs (AEDs). Neuroimaging was normal. Baby was referred to endocrinology at four years of age in view of hypocalcemia. The child's elder female sibling (patient 4) had intractable seizures since one month of age and died at six months of age from status epilepticus. Her reports showed hypocalcemia and hypomagnesemia but treatment details were unavailable. Endocrine workup of patient 3 also showed hypomagnesemia (1 mg/dL), hypocalcemia (5.4 mg/dL) and normal PTH levels. His urine calcium creatinine ratio was 0.02, FEMg was <2% with no nephrocalcinosis. Clinical diagnosis of HSH was suspected. Genetic analysis revealed a novel homozygous mutation of TRPM 6 in intron 18 (c.2392 -3 T>G) with parents heterozygous for the same mutation confirming the diagnosis of HSH. He was started on high dose magnesium supplements with which hypocalcemia resolved and child has remained seizure free off AEDs. Diagnosis of HSH was made retrospectively in patient 4. Patient 5 was a one year old female child with recurrent seizures from five months of age and mild developmental delay. Workup revealed hypocalcemia (5.93 mg/dL) and hypomagnesemia (0.8 mg/dl). Initial FEMg was low (1.03%) when the serum Mg was low. After intravenous Mg loading, FEMg increased clinically confirming the diagnosis of HSH. Child is seizure free on magnesium supplements. Genetic testing reports are awaited.

FHHNC, first described as Michelis-Castrillo syndrome occurs due to mutations in the CLDN16 (chromosome 3) and CLDN19 (chromosome 1) genes, encoding claudin-16 and 19, respectively [1]. Claudins are paracellular proteins in the thick ascending limb (TAL) of Loop of Henle involved in calcium and magnesium reabsorption. Claudin-19 mutations are associated with macular coloboma, pigmentary retinitis and nystagmus. Only 100 patients with *CLDN16* mutations and 70 patients with CLDN19 mutations have been described till date in literature [2]. FHHNC typically presents in infancy with recurrent urinary tract infections, polyuria, convulsions and failure to thrive. Sterile pyuria, hypercalciuria, hypo-magnesemia and nephrocalcinosis are classical, with occasional incomplete distal renal tubular acidosis and hypocitraturia. Amelogenesis imperfecta has also been reported [3]. Approximately 50 % of FHHNC patients develop progressive renal failure leading to end stage renal disease (ESRD) in the second decade.

The distinguishing features of FHHNC are its progression to ESRD and uncommon occurrence of acute hypomagnesemia. Current treatment options include magnesium supplemen-tation, hydrochlorthiazide and prostaglandin antagonist/(indomethacin). Renal transplantation is the definitive treat-ment [4]. Discovery of claudin-14 as an inhibitor of claudin-16/19 complex has made it an upcoming therapeutic target [5].

HSH or Primary intestinal hypomagnesemia due to TRPM6 mutations has been reported only in 50 cases so far. TRPM6 gene (chromosome 9q22) encodes a magnesium channel in the distal small intestine and renal distal convoluted tubule. This is the most severe form of inherited hypo-magnesemia, autosomal recessive modulated by x linked gene [6]. Hypocalcemia can be due to PTH resistance, impaired PTH release or impaired vitamin D synthesis, but the exact mechanism is unknown. Infants present with recurrent seizures and tetany. Adults present with hypertension, arrhythmias or osteomalacia and keratoconus in third decade. The diagnostic feature is a low FEMg at baseline which increases when serum Mg is normalized by intravenous Mg supplementation indicating impaired intestinal Mg absorption as well as renal Mg wasting. High doses of elemental magnesium (0.7-3.5 mmol/kg/day) ensures normalization of calcium even if Mg remains at low normal levels. Hence, whenever a child presents with refractory seizures and hypocalcemia, Mg should be checked and if low, HSH should be suspected. HSH responds poorly to high dose AEDs and calcium leading to poor neurodevelopmental outcome and even death as in patient 4 but completely recovers with magnesium supplementation as exemplified in patients 3 and 5. Till date, only one case each of genetically proven FHHNC and HSH have been reported from India. Inherited hypomagnesemias though rare should be suspected in appropriate clinical settings which will help us to prevent major morbidity and mortality. Workup of refractory seizures should always include measurement of serum calcium, magnesium and its fractional excretion.

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