Imaging Findings in *TRPM6*-Related Hypomagnesemia with Secondary Hypocalcemia

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A 3-year-old girl, first born to third-degree consanguineous couple from Bangladesh was brought for the evaluation of mild delay in motor milestones since early infancy and recurrent generalized tonic-clonic seizures since 4 months of age. On general examination, depressed nasal bridge and epicanthic folds were observed. Examination of higher mental functions and cranial nerves were normal. Dysmetria was observed. Severe hypomagnesemia 0.8 mg/dL (normal range: 1.72-2.2 mg/dL) and hypocalcemia 4.2 mg/dL (normal range: 8.5-10.5 mg/dL) were documented at 4 months of age. Serum vitamin D and parathyroid hormone (PTH) levels were normal. She was treated elsewhere with levetiracetam, vitamin D, calcium, and magnesium supplementation. She was evaluated in our hospital and a repeat blood biochemistry revealed serum magnesium of 1.39 mg/dL (normal range: 1.8-2.4 mg/dL), calcium of 10.3 mg/dL (normal range: 8-.3-10.4 mg/dL), PTH of 9.5 pg/mL (normal range: 8-74 pg/mL), and vitamin D of 48.5 ng/mL (normal: 30-75 ng/mL). A homozygous pathogenic nonsense variant was identified in the transient receptor potential cation channel, subfamily M, member 6 (*TRPM6*) gene at exon 16, c.1926delT (p.Cys642Ter) and parents were heterozygous for the same variant. Magnetic resonance imaging (MRI) of brain showed bilateral symmetrical T2-hyperintensity in the cerebellar cortex with facilitated diffusion suggesting vasogenic edema, and persistent signal changes with mild atrophy at follow-up [Figure 1a-f]. She was seizure-free after a high dose of oral magnesium supplementation. The child had significant developmental gains and there were residual cerebellar signs on regular follow-up.

Hypomagnesemia with secondary hypocalcemia, a rare autosomal recessive disorder is caused by a defect in the intestinal absorption of magnesium with renal magnesium wasting resulting from mutations in the *TRPM6* gene, expressed in the gastrointestinal tract and the distal convoluted tubule.[1,2] Children with this disorder commonly manifest with generalized seizures and tetany from early infancy.[2] Other manifestations include mental retardation, hyperactivity, failure to thrive, muscular weakness, ataxia, and cardiac arrhythmia.[2,3] Biochemical markers in this disorder are very low serum magnesium level, low serum calcium level, and a low PTH level. Another case has been reported from India with refractory seizures since the neonatal period and evaluation revealed low serum calcium and magnesium, imaging findings of cortical atrophy and non-specific signal changes in basal ganglia and mutation in *TRPM6* gene.[4] Magnesium plays an essential role to regulate neurotransmission and stabilize the vascular endothelium.[3,5] Hypomagnesemia may mimic findings of posterior reversible encephalopathy syndrome (PRES) on imaging.[3,5] The imaging findings in our case were limited to the cerebellum and unlike PRES, did not involve the supratentorial cortex.[5] The reason for the selective involvement of the cerebellum in severe hypomagnesemia remains unclear and may have additional underlying mechanisms. This report expands the spectrum of differentials of cerebellar cortex hyperintensity associated with cerebellar atrophy in children. Other causes of cerebellar cortex hyperintensity associated with cerebellar atrophy are mitochondrial disorders, congenital disorders of glycosylation type 1A, coenzyme Q10 deficiency, late-onset Tay- Sachs disease, late infantile neuroceroid lipofuscinosis, infantile neuroaxonal dystrophy, Marinesco-Sjogren syndrome, spinocerebellar ataxia, pontocerebellar hypoplasia type 7 and Christianson syndrome.[6]

Patients with *TRPM6*-related hypomagnesemia with secondary hypocalcemia are managed with lifelong oral magnesium supplementation in high doses.[2] High oral doses of magnesium facilitates passive paracellular transport across the intestine.[3] Early diagnosis and appropriate treatment would determine the neurodevelopmental outcome.[2] Children presenting with unexplained infantile-onset seizures or tetany and cerebellar cortex hyperintensity must be evaluated with serum magnesium level to identify underlying hypomagnesemia, either inherited or acquired, as early diagnosis and treatment are essential to improve the clinical outcome in these patients.

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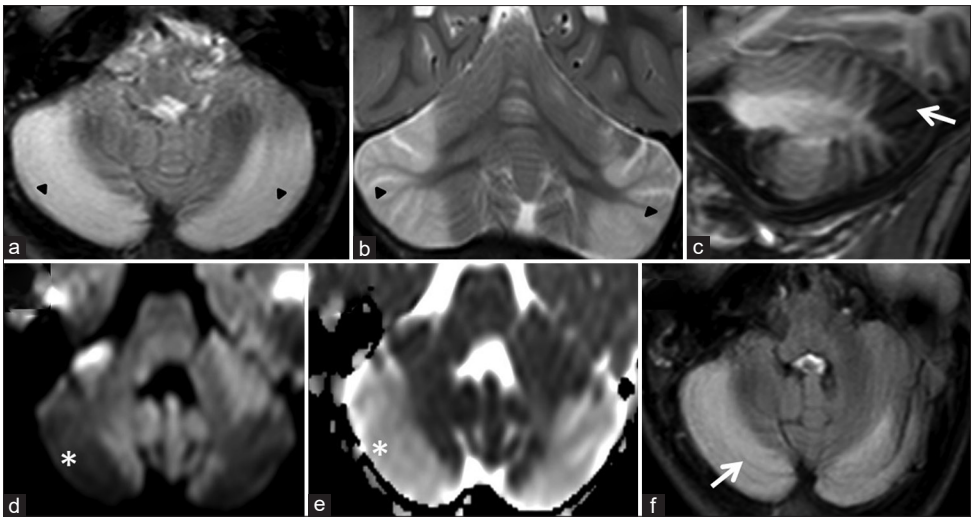

Figure 1: Axial, coronal T2-weighted images (a, b) show bilateral symmetrical hyperintensity involving the cerebellar cortex (black arrowheads). Posterior predominance noted on sagittal T1-weighted image (white arrow in c). Diffusion-weighted images (d) and apparent diffusion coefficient (e) show facilitated diffusion (asterisk in d, e). T2 FLAIR image (f) on follow-up shows persistent signal changes with mildly prominent foliae (white arrow in f) suggestive of cerebellar atrophy

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Conflicts of interest

There are no conflicts of interest.

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