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Website:
www.neurologyindia.com
DOI:
10.4103/0028-3886.333478

A Rare Cause of Globus Pallidus and Dentate Nucleus Hyperintensity in Childhood: MBOAT Mutation

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Abstract:

Mutations in mammalian membrane-bound *O*-acyltransferase domain-containing (*MBOAT*) 7 gene are a rare cause for intellectual disability, developmental delay, autistic findings, epilepsy, truncal hypotonia with appendicular hypertonia, and below-average head sizes. Pathogenic variants in *MBOAT7* gene show these nonspecific clinical features that are seen in many other neurometabolic diseases. Therefore, specific neuroimaging findings can be valuable key factors for differential diagnosis. Magnetic resonance imaging (MRI) findings of T2 hyperintensity in bilateral globus pallidi and dentate nuclei are seen in a few neurometabolic diseases with similar clinical features of developmental delay and hypotonia, as in our cases. While evaluating the patients with similar phenotypes and specific MRI findings, *MBOAT7* deficiency should be kept in mind. Here, we identified two brothers who had a novel homozygous variant in *MBOAT7* gene and aimed to raise awareness about this newly described disease.

Key Words:

Dentate nucleus, globus pallidus, *MBOAT7*

Key Message:

T2 hyperintensity in both bilateral globus pallidi and dentate nuclei are specific MRI findings that point to the diagnosis of rare neurometabolic diseases such as *MBOAT7* deficiency.

Mammalian membrane-bound *O*-acyltransferase (MBOAT) protein family consists of five acyltransferases. The *MBOAT7* gene is located on chromosome 19, encodes lysophosphatidylinositol acyltransferase-1 contributing to the regulation of free arachidonic acids in cells that take part in inflammation pathways.[1-3] *MBOAT7* is involved in the development of cerebral cortex in mammals.[1] Patients with *MBOAT7* mutations have common brain magnetic resonance imaging (MRI) findings of cerebellar atrophy, disorganized cerebellar folia, and prominent perivascular spaces.[3] Patients showed a wide spectrum of clinical features, including intellectual disability (ID), epilepsy, autistic spectrum disorder (ASD), truncal hypotonia, and appendicular hypertonia that demonstrates the importance of inflammatory pathways in brain function.[1,4,5] Here, we present the clinical and genetic findings of two siblings with a novel pathogenic variant of *MBOAT7* gene.

Case History

The two affected patients were brothers born to healthy consanguineous parents with no family history of neurologic diseases. The older brother was four years old who was referred to our clinic with global developmental delay in early milestones accompanied by truncal hypotonia, ID, and speech delay. He had no prenatal or postnatal insults and had normal birth weight and head circumference. Since birth he had shown a delay in neurodevelopmental milestones. He gained the ability to control his head at 8 months, sit independently at 1.5 years, walked independently at 2.5 years, and could speak only a few words. He had no seizures. Neurological examination showed truncal hypotonia and increased deep tendon reflexes. He had a below-average head size with 45.5 cm, which is 3–10 p. Routine laboratory tests and metabolic workup, including complete blood count, biochemistry, plasma amino acids, urinary

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How to cite this article: Ozpinar E, Kaytan I, Topcu Y, Kılıc B, Aydin K. A Rare Cause of Globus Pallidus and Dentate Nucleus Hyperintensity in Childhood: MBOAT Mutation. Neurol India 2021;69:1838-40.

Submitted: 22-Mar-2021 **Revised:** 22-Nov-2021
Accepted: 30-Nov-2021 **Published:** 23-Dec-2021

organic acids, and carnitine–acylcarnitine profile, were normal. Electroencepahlogram was normal. Brain MRI showed T2 hyperintensity of bilateral symmetric globus pallidi and dentate nuclei [Figures 1 and 2].

The younger brother was 16 months old. He was full-term but followed up in neonatal intensive care unit for 10 days due to transient tachypnea of neonate. He could not gain head control. Neurological examination showed truncal hypotonia and increased deep tendon reflexes. His head circumference was 48.5 cm (10–25 p). He experienced myoclonic seizures since 12 months old. Vigabatrine treatment was begun. Routine laboratory tests and metabolic workup, including complete blood count, biochemistry, plasma amino acids, urinary organic acids and carnitine–acylcarnitine profile, were normal. Aspartate transaminase was 37.7 and alanine transaminase 23.2 U/L. The findings of brain MRI were similar to his brother's, including bilateral symmetric globus pallidi and dentate nuclei signal changes. We performed whole exome sequencing (WES) because the two brothers have similar symptoms, normal metabolic tests, and consanguineous parents. WES identified a homozygous, likely pathogenic variant in *MBOAT7* gene (p. R271Pfs*25). Sanger sequencing method was used to confirm the mutation. Segregation analysis revealed that the unaffected parents were both heterozygous for the same variant.

Discussion

We describe two brothers with a novel, homozygous, likely pathogenic variant in the *MBOAT7* (p.R271Pfs*25), who had global developmental and speech delay with basal ganglia hyperintensities. The p.R271Pfs*25 variant is not present in Exome Aggregation Consortium, ClinVar, 1,000 Genomes Project, or Genome Aggregation Database.

Farnè *et al*.[3] described 44 published cases of neurological disorder related to *MBOAT7* mutations in 2020. Forty-two cases are born from consanguineous parents. All cases had ID. The other common symptoms are delayed motor milestones (41/44) with speech (41/44) and motor delay (37/40), seizures (32/40; myoclonic: 8/37), and truncal hypotonia (35/37).[3] Delayed early milestones and hypotonia were two presenting symptoms in our patients. ID and severe speech delay were other findings. Epilepsy was present in the younger brother with myoclonic seizures. Unlike the patients reported by Johansen *et al*.,[6] our patients had no hypertonia. Hypotonia was noted in our patients along with delayed early motor milestones. Microcephalic, macrocephalic, and normocephalic patients are notified in reviews. Our patients had head circumferences within the normal range.

Brain MRI findings, such as cortical atrophy, polymicrogyria, leukoencephalopathy, and cerebellar dysgenesis (22/40) had been described by Farnè *et al*.[3]. Johansen *et al*.[6] reported normal MRI findings except in two subjects who had cortical atrophy and mild polymicrogyria. Heidaria *et al*.[1] also described three patients with the presence of globus pallidus signal changes in MRI. Our patients had T2 hyperintensity in both dentate nuclei and globus pallidi in MRI, which could support the diagnosis of the disease. Other diseases that cause the same MRI findings include methylmalonic acidemia, succinic semialdehyde dehydrogenase deficiency, pyruvate dehydrogenase deficiency, l-2-hydroxyglutaric aciduria, and glutaric aciduria type 1. Because most of the patients with these diseases present with developmental delay and hypotonia, as in our cases, differential diagnosis is often difficult to make. Long examination and investigation processes are mostly required for a definite diagnosis. Clinical information and different presentations of these rare diseases should be well-known to reach a definite diagnosis in a short period.

MBOAT7 protein has a role in liver homeostasis, and some genetic variants increase the risk of fatty and alcoholic liver cirrhosis with elevated phosphatidylinositol turnover. A common variation, MBOAT7 rs641738, was also shown to be associated with cancer and fatty and alcoholic liver disease. Mice with specific downregulation of the *MBOAT7* in the liver showed normal cognitive function and higher fat in the liver. Therefore, chronic liver changes can be a clue for this disease. Chronic liver diseases also involve in differential diagnosis of signal changes of globus pallidi and dentate nuclei. Nevertheless, we did not trace any sign of fatty liver diseases in our patients by checking liver enzymes, but the presence of

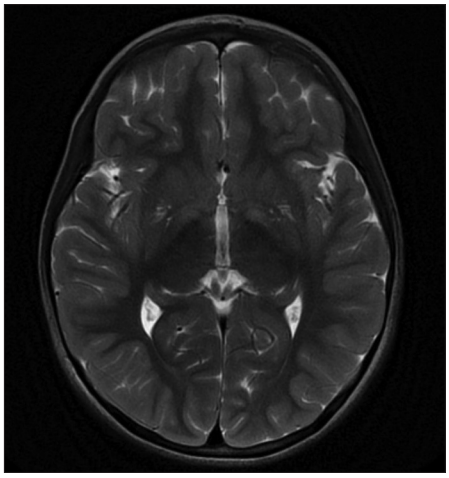

Figure 1: Bilateral globus pallidi hyperintensity

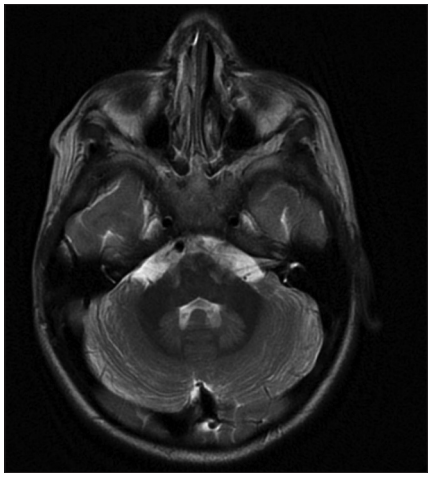

Figure 2: Bilateral dentate nuclei hyperintensity in T2

globus pallidus signal changes in MRI might be indicative of metabolic changes as a result of loss of *MBOAT7* expression in hepatic cells. It should be kept in mind that liver functions may not be affected in the early period; some patients had high liver enzyme levels after diagnosis. Due to the young age of our patients, the liver disease might manifest later, so should be screened periodically.[7,8]

In conclusion, we report a novel genetic variant in *MBOAT7* gene causing ID and hypotonia in the two brothers. Although the same mutation was detected, one patient had epilepsy and the other patient did not. We suggest that the *MBOAT7* gene defects in the differential diagnosis of neurometabolic diseases might cause hyperintensity in globus pallidi and dentate nuclei with ID, seizure, developmental delay, especially with no sudden exaggeration in existing symptoms or progressive course. Because this disease was described in recent years, *MBOAT7* deficiency should be kept in mind. WES is important in the identification of rare and novel neurometabolic diseases, defining different phenotypes and MRI findings providing recognition of diseases with the same genetics. We want to notify differential diagnosis of specific MRI findings with *MBOAT7* disease that are not defined in detail.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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