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Case Report

Rare cause of drug-resistant epilepsy due to GABA transaminase deficiency: A case report from India

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ABSTRACT

Gama aminobutyric acid (GABA) transaminase deficiency is an autosomal recessive disorder caused by mutations in the 4-aminobutyrate aminotransferase (ABAT) gene. The disorder is characterised by epileptic encephalopathy, hypersomnoloscnec, movement disorders, and tone changes. Here, we report a 4-year-6-month-old boy child born to non-consanguineous marriage with a normal birth history presented with global developmental delay, refractory seizures, and increased sleep. On examination showed normal anthropometry with mild dysmorphism. Neurological examination showed autistic features and spasticity with brisk deep tendon reflexes. On investigation, electroencephalography showed multifocal epileptiform discharges with secondary generalisation, and magnetic resonance imaging of the brain showed mild hyperintensity of the superior cerebellum. Exome sequencing identified compound heterozygous variants in the ABAT gene and segregates with the condition in the family. The child was treated with antiseizure medications and responded partially. For any child with excessive sleep on the background of epileptic encephalopathy with a movement disorder, a diagnosis of GABA transaminase deficiency has to be considered.

Keywords: Gama aminobutyric acid Transaminase deficiency, ABAT mutations, India

INTRODUCTION

Gama aminobutyric acid transaminase (GABA-T) is an enzyme involved in the metabolism of GABA and converts GABA into succinate semialdehyde. GABA-T deficiency results in an accumulation of GABA and other toxic metabolites and manifests as epileptic encephalopathy either in the infantile or neonatal period. In addition, patients usually have excessive sleepiness, movement disorder, and tone abnormalities. The GABA-T: Online Mendelian Inheritance in Man (OMIM) #613163 deficiency is an autosomal recessive disorder caused by mutations in the *ABAT* gene.[1-3] Here, we present an Indian child with GABA-T deficiency due to a compound heterozygous mutation in the *ABAT* gene.

CASE REPORT

Here, we report a 4-year-6-month-old boy child born to non-consanguineous marriage presented with global developmental delay, refractory seizures and increased sleep. The child was full-term born through normal vaginal delivery with a birth weight of 2.5 kg, cried immediately after birth and had no neonatal encephalopathy. Developmentally child attained neck holding- at 7 months, sitting with support by 10 months and walking at 2 years of age. The child started scribbling at 3 years of age. He attained social smile by 7 months, stranger anxiety by 12 months, play-by-self by 18 months,

cooing by 4 months and speaking one word with meaning at 14 months. The child developed fever-triggered seizures at 1 year of age followed by unprovoked multiple-type semiology of seizures requiring multiple antiseizure medications. The child was noted to have excessive daytime sleepiness.

On examination showed normal anthropometry with mild dysmorphism. Neurological examination showed autistic features and spasticity with brisk deep tendon reflexes with cerebellar signs. On investigation, complete hemogram, liver function, renal function, serum ammonia, serum lactate, arterial blood gas, tandem mass spectrometry and urinary organic acids were all normal. Electroencephalography (EEG) showed multifocal epileptiform discharges with secondary generalisation. Magnetic resonance imaging brain showed mild hyperintensity of the superior cerebellum. Exome sequencing identified 2 heterozygous variants in the *ABAT* gene: Variant-1: c.43C>T:pGln15Ter, variant-2 is c.1295C>T:p.Thr432Ile. Variant-1 is a nonsense variant that changes Glutamine to stop codon and leads to truncation. It is absent in population databases (gnomAD and 1000 genome) and disease databases (ClinVar). The variant is classified as likely pathogenic [American College of Medical Genetics and Genomics (ACMG) criteria: Pathogenic very strong (PVS1), pathogenic moderate (PM2)]. Variant-2 is a missense variant that leads to an amino acid change from Threonine to Isoleucine. The variant is absent in both population and disease databases. This variant is classified as a variant of unknown significance [ACMG criteria: PM2, Pathogenic supportive (PP3)]. Variant-1 is inherited from the father and variant-2 is inherited from the mother.

DISCUSSION

In summary, we present an Indian child who presented with a global developmental delay with hypersomnolence with epilepsy. The differential diagnosis considered wee epilepsy syndromes especially epileptic encephalopathies and inborn errors of metabolism. There is wide variability in the clinical presentation of the disorder with some cases reporting a death in early childhood.[1]

Hegde *et al.* reported two siblings who presented with a developmental delay, intractable seizures, behavioural abnormalities and movement disorder in their adolescence and adulthood.[4] The most consistent features reported are neurodevelopmental disorder, drug-resistant seizures, movement disorder and hypersomnolence.[5] Neuroimaging usually shows delayed myelination and restriction diffusion in the external and internal capsule with a white matter of the subcortical region.[6]

The possible hypothesis is increased inhibition of inhibitory interneurons and paradoxical depolarising effects of GABA as in immature neurons with reversed chloride gradients with downregulation of GABA receptors.[7] Our case had classical features of drug-resistant epilepsy, developmental delay, hypersomnolence and abnormal EEG.

CONCLUSION

The GABA transaminase deficiency should be considered in children with developmental delay, autistic features, drug-resistant epilepsy and hypersomnolence.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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