A Case of Asparagine Synthetase Deficiency Successfully Treated with Ketogenic Diet

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OBJECTIVES

Asparagine Synthetase Deficiency (ASNSD), one of the amino acid synthesis deficiencies, was first described in 2013 by Ruzzo et al.[1], as a extremly rare autosomal recessive neurometabolic disorder caused by homozygous or compound heterozygous mutations in the ASNS gene and clinically characterized by congenital progressive microcephaly, severe global developmental delay, early-onset refractory seizures and axial hypotonia followed by spastic quadriplegia.[1-4] Other associated clinical manifestations include jitteriness, hyperekplexia, apnea, feeding difficulties, and cortical blindness.[4] In addition, dysmorphic findings such as micrognathia, receding forehead and large ears can be seen.[5] Most common findings on brain imaging are progressive cerebral atrophy, congenital microcephaly, simplified gyral pattern and ponto-cerebellar hypoplasia.[6]

The seizures in ASNSD are considered as non-specific; and myoclonic, tonic, spasm and generalized tonic-clonic seizures, which are refractory and require multiple antiepileptic drugs, are reported.[7] Currently, there is no specific treatment for ASNSD, and drug-resistant seizures remain as a major problem for patients.

To date, there are no data on the use of ketogenic diet for controlling the seizures in ASNSD. We aim to report a case diagnosed with refractory epilepsy due to ASNSD and successfully treated with ketogenic diet.

CASE PRESENTATION

A 7-year-old male patient, who was noticed to have borderline microcephaly at birth, was first admitted to our clinic at the age of 8 months due to the afebrile seizures that had been around since he was 6 months old. His developmental milestones were normal up to the age of six months, and physical examination at the admission was normal. However, in the patient's follow-up, it was observed that he fell behind in the developmental stages, developed axial hypotonia and facial dysmorphism and his microcephaly was progressed. Biochemical and metabolic tests were within the normal range except for a borderline-low serum asparagine level (24 µmol/L, normal range: 26-100 µmol/L). His EEG showed multifocal epileptic discharges and cranial MRI revealed mild cerebral atrophy in bilateral frontotemporal regions.

The resistant and recurrent seizures of the patient were tried to be controlled with various combinations of AEDs. However, these attempts were failed and his seizures continued. The patient was started on a ketogenic diet approximately one year ago. In the first month of the ketogenic diet; it was observed that the frequency of seizures significantly decreased and the duration of seizures was shortened.

On whole exome sequencing (WES) analysis, a novel compound heterozygous mutation [c.83G>A (p.R28Q) and c.1082A>T (p.E361V)] in the ASNS gene was found and our patient was diagnosed with ASNSD. The patient is still followed up under the ketogenic diet and multiple antiepileptic treatments; valproate 30mg/kg/d, clobazam 1mg/kg/d, levetiracetam 30mg/kg/d and topiramate 6mg/kg/d.

DISCUSSION

ASNSD is a recently identified neurometabolic disorder.[1] The pathophysiology of the disease can be explained by increased neuronal apoptosis and excitability.[2]

Various combinations of AEDs are used in seizure control in ASNSD cases. Although there are cases in the literature that respond well to antiepileptic treatment[2,7-9], resistant seizures continue to be an important problem in this patient group.

The ketogenic diet is used as a non-pharmacological therapeutic approach in drug-resistant epilepsy patients.[10] There is currently no study in the literature on the use of a ketogenic diet in the control of drug-resistant seizures in ASNSD cases. We suggest that it may be a potential alternative treatment for epilepsy associated with ASNSD.

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