Severe Microcephaly and Metabolic Epilepsy due to Asparagine Synthetase Deficiency

Sir,

A 2.5-year-old girl presented with global developmental delay and drug-refractory epilepsy. The seizures started at three months of age as right-sided, focal-onset, and clonic seizures associated with fever. Subsequently, she developed unprovoked focal and generalized tonic seizures. An abnormal startle reaction was noted by the parents by one year of age. She was first born to non-consanguineously married parents. Perinatal period and family history were not contributory. On examination, she had severe microcephaly (head circumference of 36 cm; -7.27 Z-score), spastic quadriparesis, impaired visual tracking, hyperreflexia, and hyperekplexia. A clinical diagnosis of global developmental delay and early-infantile onset epilepsy due to a structural, metabolic, or genetic cause such as Dravet syndrome was considered. The early presence of hyperekplexia pointed to an excitotoxic or neurodegenerative process.

Serology for intrauterine infections of the TORCH group and cytomegalovirus polymerase chain reaction was negative. Brain stem evoked response audiometry was normal. Visual evoked potential revealed bilateral delayed latencies. Magnetic resonance imaging (MRI) of the brain showed diffuse atrophy and delayed myelination [Figure 1a-c]. Electroencephalogram showed bilateral, multifocal, interictal discharges with a burst-suppression pattern consistent with epileptic encephalopathy. Mass spectroscopy-based analysis of blood and urine for abnormal metabolites was normal. Biotinidase assay showed normal enzyme levels. The clinical exome analysis showed a homozygous missense variation in exon 11 of the *ASNS* gene, c. 1138G>T (p.Ala380Ser), suggestive of asparagine synthetase deficiency (ASNSD). Sanger sequencing of parents revealed that both were carriers for the c. 1138G>T (p.Ala380Ser) variant in exon 11 of the *ASNS* gene. Currently, she is under follow-up and managed by a multi-disciplinary team.

ASNSD (MIM#615574) is a rare, autosomal-recessive neurometabolic disorder of amino acid metabolism due to pathogenic variations in the *ASNS* gene (MIM*108370). It is characterized by severe congenital microcephaly, global developmental delay, progressive encephalopathy, cortical atrophy, intractable epilepsy, hyperekplexic activity, and progressive cerebral atrophy.[1,2] Depletion of asparagine in the brain, and accumulation of aspartate and glutamate

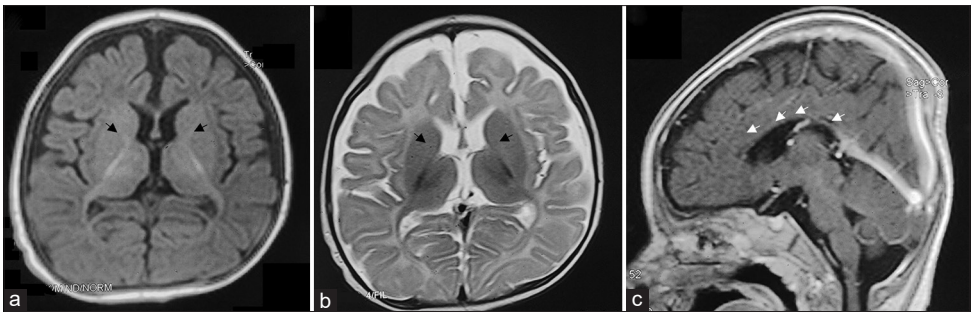

Figure 1: MRI brain at 6 m of age: Axial T1w (a) and T2w (b) images show lack of myelination in the anterior limb of internal capsule (black arrows). There is mild diffuse atrophy of the brain with white matter loss and prominent sulcal spaces. (c) Sagittal post-contrast T1w images show lack of myelination in corpus collosum with marked atrophy

cause impaired neurological development and seizures by excitotoxic damage. *ASNS* gene encodes the asparagine synthetase enzyme that catalyzes the conversion of aspartate and glutamine into asparagine and glutamate, through an ATP-dependent amidotransferase reaction.[3] Asparagine synthetase is expressed more in the brain. Hence, its deficiency leads to elevated levels of aspartate and glutamate, which in turn cause apoptosis of neurons and neuronal hyperexcitability. Asparagine is essential for cell growth and function. These biochemical alterations cause progressive and severe brain atrophy, hyperekplexia, and refractory seizures.[4] Usually, the levels of asparagine are low in blood and cerebrospinal fluid, but the absence of a low value does not rule out *ASNS* deficiency as in the index case. It is a pan-ethnic disorder, and cases have been reported from twenty-two unrelated families.[5] The clinical presentation overlaps with several other conditions with congenital microcephaly; hence, exome sequencing is warranted in such patients to establish a diagnosis. The cardinal features of global developmental delay, spastic quadriparesis, and severe microcephaly can also be seen in severe hypoxic ischemic insult, TORCH infections, and Aicardi-Goutières syndrome. Congenital and progressive microcephaly is characteristic, and the absence of sutural overriding differentiates it from secondary causes of microcephaly. The absence of calcification, chorioretinitis, or organomegaly differentiates it from typical TORCH infections.

In our patient, the homozygous missense mutation detected has been previously reported in an Indian family.[4] The *ASNS* gene has 11 exons and 561 amino acids. It has an N-terminal domain, that catalyzes the hydrolysis of glutamine to ammonia and a C-terminal domain, that catalyzes the condensation of ammonia and aspartate into asparagine. Replacement of Ala380 at the C-terminal domain by serine [c. 1138G>T (p.Ala380Ser)] disrupts the helix-turn-helix motif and causes loss of function of asparagine synthetase. There is no specific therapy, and the prognosis is poor due to progressive neurodegeneration. Worsening of seizures after supplementation with asparagine and partial resolution of seizures by valproic acid as compared to other antiepileptic drugs have been reported.[6]

Disorders such as asparaginase synthetase deficiency and adenylosuccinate lyase deficiency are inherited neurometabolic disorders where neurodegeneration and cerebral atrophy are dominant.[5,7,8] These are a difficult group of disorders as they may not have an easily detectable biochemical or radiological marker and are only diagnosed based on genetic testing. However, for the astute clinician, severe microcephaly, cerebral atrophy, and a progressive clinical course should be important alerts to such an underlying disorder. Additionally, asparaginase synthetase deficiency should be added to the list of metabolic epilepsies presenting in early infancy.[9]

In conclusion, ASNSD is a rare inborn error of metabolism resulting in a progressive neurodegenerative phenotype. As these children present with microcephaly, global developmental delay, spasticity, and epilepsy, they may be mistaken for non-progressive disorders such as cerebral palsy. Severe microcephaly is an important clinical clue toward these neurometabolic disorders. As there is no clear-cut biochemical biomarker, genetic testing can only confirm the diagnosis and may help in prevention.

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Conflicts of interest

There are no conflicts of interest.

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