A rare cause of refractory epilepsy and microcephaly: Asparagine Synthetase Deficiency

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Introduction

Asparagine synthetase deficiency (ASNSD, OMIM 615574), a rare autosomal recessive neurometabolic disorder, is characterized by a triad of congenital progressive microcephaly, profound developmental delay, and axial hypotonia followed by spastic quadriplegia. ASNS gene plays a unique role in brain development and its mutations may result in fetal death or stillbirth. The affected individuals typically do not acquire any developmental milestones. To date, mutations in the ASNS gene have been reported in children or newborns from a variety of ethnic origins but not in fetuses. ASNSD has been reported in newborns or children with either homozygous or compound heterozygous mutations in the ASNS gene on chromosome 7q21. The gene encodes asparagine synthetase enzyme which is involved in the synthesis of asparagine. The ASNS protein (561 aa) is expressed in the brain, pancreas, thyroid and testes and liver. The adult brain expresses particularly high levels asparagine synthetase. However, only some patients had lower Asn levels in plasma and cerebral spinal fluid, which prevented diagnosis on biochemical bases. Here we present a male newborn, who had frequently and drug-resistant seizures.

Case Presentation

A newborn male, who had frequently and drug-resistant seizures. There were startles from sound or touch. In addition to his microcephaly, he had feeding difficulties and hypotonia. No specific findings were detected in the patient's metabolic tests and lumbar puncture examination. Brain MRI revealed diffuse cerebral atrophy. Discontinuous EEG pattern was observed. In the patient's WES analysis, c.1193A>G (p.Tyr398Cys) homozygous mutation was detected in the ASNS gene (NM001673.5). Since oral nutrition was inadequate, a gastrostomy catheter was applied to the patient. The patient's frequently recurring seizures and intermittent hospitalization continue. During clinical follow-up, hypotonia followed by spastic quadriplegia, seizures, jitteriness, cortical blindness and hyperekplexia.

Discussion

So far, over 50 mutations in the ASNS gene have been reported to be associated with ASNSD and 101 ASNSD cases have been reported in Chinese and English literatures, most of which are due to recessive missense mutations . Among affected children, 71.9% (41/57) died before the age of one. Most surviving children exhibit symptoms such as intractable epilepsy and severe developmental delay.

ASNS catalyzes aspartate to asparagine via ATP, producing glutamate and ammonia from its N-terminal. ASNS loss results in reduced cellular asparagine levels critical for early neurological development. Common clinical manifestations of ASNSD include microcephaly, severe psychomotor developmental delay, cortical blindness, hyperreflexia, encephalatrophy, increased limb muscle tone, decreased trunk muscle tone, feeding difficulties, and seizures. Almost all the cases in newborns or children had microcephaly. In the current investigation, fetal ultrasound and MRI showed that the fetal biparietal diameter was stunted and small for 2 weeks. As these phenotypes are difficult to detect in prenatal fetus, the symptoms of intellectual disability, epilepsy and progressive cerebellar atrophy cannot be observed prenatally. Therefore, it is difficult to diagnose ASNSD in the third trimester of pregnancy. Herein, we diagnosed an ASNSD infant with the assistance of WES.

Hitherto, no case of prenatal diagnosis of ASNSD has been reported previously. There may be several reasons for this. Firstly, the diagnosis of ASNSD mainly depends on the clinical manifestations and the US or MRI after birth, half of the patients reported so far in the literature died during their first years and the others had poor neurological outcomes. Due to the limited clinical manifestations of the fetus in utero, the symptoms of intellectual disability, epilepsy and progressive cerebellar atrophy cannot be detected prenatally. Secondly, there is currently no specific biochemical examination method for the diagnosis of ASNSD, early detection and prenatal diagnosis of ASNSD may be valid tools to prevent the birth of affected. Previous reports have suggested that ASNSD should be considered in children with congenital microcephaly.

Conclusions

For fetuses with progressive small biparietal diameter or abnormal brain development, the disease should be considered, and genetic testing should be performed promptly. ASD is an important metabolic disorder that should be kept in mind in patients with microcephaly and diffuse cerebral developmental delay who have refractory seizures in the neonatal period.

References

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