

# Asparagine Synthetase Deficiency Causing Recurrent Microcephaly: A Rare Case Report

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## ABSTRACT

Asparagine synthetase deficiency is rare autosomal recessive inborn error of metabolism. It mainly presents as triad of congenital microcephaly, severe developmental delay and axial hypotonia followed by spastic quadriplegia. It can manifest as microcephaly, intractable seizures and progressive cerebral atrophy. This disorder can only be diagnosed by genetic testing. Recessive mutations in ASNS are responsible for severe neurological phenotype characterised by progressive microcephaly and developmental delay.

**Keywords:** ASNS Deficiency, Autosomal Recessive, Microcephaly

## Case Report

A 27 Year old female Gravida 5 Para 4 Iuid 4. No living child is presented for consultation and management. She had no complaints at the time of presentation.

Her menstrual cycles were regular. Obstetric history:-

Consanguineous marriage. Married since 9 years

G1- Female / 3kg / normal delivery / 2013 / expired after 25 days of birth in nicu.

G2- Female child / 2.7kg / died on day 5 in nicu / 2015./ normal delivery./baby had microcephaly

G3- Male child / 1.7kg / cesarian section for antepartum haemorrhage/ Microcephaly / 2017./ baby expired.

G4-Female / 3kg / microcephaly/ died of 5th day of life / 2020.

G5-PP.

As patient had previous history of recurrent microcephaly and dysmorphic features in previous babies clinical exom sequencing done and the report showed a homozygous missense mutation in Exon 14 of the ASNS gene. (chromosome 7.9.97481735T > C) depth 107 x, that resulted in amino acid substitution of aspartic acid for asparagine at codon 508 was detected. Results of microarray analysis showed normal microarray and increased total homozygosity - the clinical significance of which is unknown.

Patient presented to us in prenatal period for pregnancy management. As previous case reports showed normal antenatal course till 28 weeks & thereafter there is growth lag detected in

biparital diameter. In 2013 both parents karyotyping showed normal results. Only significant abnormality detected was the progressive microcephaly on USG in all the pregnancies. Magnetic resonance imaging of 2nd born female baby (2016) showed underdeveloped sulci in bilateral fronto-temporal lobes and widening of Sylvian fissure. With prominent CSF spaces in bilateral front temporal region and lack of myelination in posterior limb of internal capsule on either side MR spectroscopy reveals raised choline and reduced NAA peak in bilateral frontal lobes and basal ganglia. Patient was thoroughly investigated and started on folic acid supplementation Genetic counselling done in prenatal period. In the present pregnancy we followed patient. Nuchal translucency scan and dual marker reports were normal. Amniotic fluid trio clinical exom sequencing done which showed A heterozygous C1522 A> G (pass 508asp) variant in ASNS Gene.

Patient was followed up in antenatal period hematinics protein, multivitamin, Dydrogestron, amino acid, folic acid supplementation and Ecosprin started due to suspected factor deficiency. Elective cesarian section was done at 38 weeks delivering a male child weighing 3.2 kg with normal phenotype. At the time of writing this case baby is 3 month old having normal growth parameters.

## Discussion

The pathophysiology of ASNSD is not exactly known. Asparagine Synthetase gene catalyses the synthesis of asparagine and glutamate from aspartate and glutamine in an ATP dependent Amino-transferase reaction [1-3].

The congenital and progressive microcephaly and simplified gyration in children with ASNSD indicates that significant brain damage occurs during embryonic development suggesting that asparagine synthesise activity is critical for brain development, either due to accumulation of substrate or a deficiency in its products [4].

This ASNSD (asparagine synthesise deficiency) is an autosomal recessive disorder causing microcephaly, severely delayed psychomotor development, cortical atrophy, progressive encephalopathy seizures or hyperekplektic activity having its onset in utero or at birth or may also present with normal early development followed by infantile onset seizures and neurodevelopmental delays.\*

Due to enzyme deficiency there is accumulation of aspartate and glutamate in brain causing increased hyper-excitability, seizure activity and neuronal damage This disorder is diagnosed by genetic testing by identification of biallelic pathogenic variants in ASNS on molecular genetic testing. Most of affected babies develop apnea, excessive irritability and seizure soon after birth and many babies may not attend routine developmental milestones [5]. Spastic quadriplegias can cause severe limb contractures and neurogenic scoliosis.

Feeding difficulties due to gastro-oesophageal reflex, vomiting, swallowing dysfunction and Gastro-oesophageal incoordination are major problems. Many babies can develop cortical blindness. Other symptoms that babies may present with includes dehydration, developmental delays, brain disease that progressively gets worse (progressive encephalopathy) failure to thrive, lethargy, vomiting and seizures.

MRI findings are nonspecific but many includes cortical atrophy, delayed myelination, small pons, the corpus callous, enlarged ventricular system, left transverse sinus thrombosis, cerebral dysgenesis, bilateral caudate atrophy and simplified gyro pattern.

Clinically this may present as triad of congenital microcephaly, severe developmental delay and axial hypotonia followed by spastic quadriplegia.

Low CSF level of asparagine helps to differentiate this disorder from other inborn errors of metabolism.

One study having 22 babies summarised the clinical manifestation of these babies follows [1,6].

#### Neonatal onset (95%)

Severe global developmental delay (100%) Congenital & progressive microcephaly (100%) Hyper-reflexia(100%) Axial hypotonia f/b spastic quadriplegia (95%) Seizures (73%) Jitteriness (87%) Cortical blindness (60%) hyperekplexia(32%)

Nonspecific dysmorphic facial features reported in approximately 50% of individuals includes brachycephaly, pear like head, sloping forehead, widely spaced eyes, big fleshy ears, prominent nasal tip and Micrognathia.

Gastrointestinal manifestations are also common and includes hypotonia, and Gastrooesophasial reflux disease [7,9].

Cortical blindness is found in approximately in 65% go babies. Seizures usually starts in neonatal period.they are usually not specific type and may be generalised tonic clonic(64%), myoclonic (50%), tonic (50%) partial complex seizures (21%) ans spasms reported in about 21% of babies.EEG studies are also not specific and reports shows multiple spike foci (65%) burst suppression, hyperarrhythmia and discontinuous EEG pattern.

Major common MRI findings noted in the babies are [8]. Delayed myelination(68%) Small pons Thin corpus callosum (55%) Enlarged ventricular system (50%) Bakers cyst and arachnoid cysts.

Left transverse sinus thrombosis. Cerebral dysgenesis. Increased lactate peak on MR spectroscopy Bilateral caudate atrophy.

The transmission pattern of ASNSD is consistent with autosomal recessive inheritance. Whole Exam sequencing in most cases is homozygous or compound heterozygous missense mutation in ASNS gene. Recessive mutation in ASNS gene causes neurometabolic syndrome with neurodegenerative disease course. Till date 26 disease causing variants have been identified in ASNS with most of them due to recessive missense mutation in C- terminal domain.

ASNS catalyses the synthesis of asparagine and glutamate from aspartate and glutamine in an ATP dependent aminotransferase reaction. Traditionally asparagine is considered as a nonessential amino acid because even in the absence of dietary intake sufficient amount can be generated from substrate glutamine and aspartate via ASNS.

As ASNS metabolically connects four amino acids aspartate, glutamine, glutamate and asparagine. The lack of asparagine and dysregulation of balance of excitatory neurotransmitter might contribute to neuronal damage and increased excitability in affected patients.

#### Mode of Inheritance

Asparagine synthesise deficiency is inherited in an autosomal recessive manner. The parents of affected child are obligate heterozygotes that is carriers of one ASNS pathogenic variants. carriers are asymptomatic and are not at risk of developing the disorder. At conception each sibling of an affected individual has 25% chance of being affected, 50% chance of being an asymptomatic carrier and 25% chance of being unaffected and not a carrier. Consanguinity is reported in about 50% of couples.

#### Management

To establish the exact of disease in an individual affected with ASNS deficiency following investigations are carried out.

Brain MRI,EEG studies [10]. Ophthalmoloc evaluation, Auditory evaluation & Growth parameter assessment.

Management requires multidisciplinary team approach and the treatment is primarily supportive.Seizures manages with anti epileptic drugs.

1. Spastic quadriplegia managed with anti spastic drugs eg. baclofen, botox injections
2. Hyperekplexia managed with clonazipine which appears to be most effective management option.

3. Hearing loss requires hearing AID.
4. Apnea-mechanical ventilation may be required in some babies.
5. Inadequate nutrition and feeding difficulties can be managed by nasogastric tube or gastrostomy.
6. GERD requires routine pharmacological treatment.
7. Kyphoscoliosis requires orthopaedic management.

Physiotherapy is recommended to maximise the mobility and to reduce the risk of contractures later on. Genetic counselling is most important part in the management. It is a process of providing individual and families with information on the nature, mode of inheritance, and implication of genetic disorder to help them make informed medical and personal decisions [11].

### Conclusion

Asparagine synthesise deficiency is an autosomal recessive neurometabolic disorder presenting as progressive microcephaly, seizures and progressive cerebral atrophy. From limited experience of this case it can be suggested that if any newborn baby is born with anomalies or patient is having bad obstetric history it is better not to wait for going beyond karyotyping and to opt for whole genome sequencing or newer molecular genetic testing along with genetic counselling so that we can have an idea about the likelihood of disease in unborn child so that appropriate steps can be taken.

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