Case Report
Canavan Disease: A Rare Neurodegenerative Disorder

Archana Singh*, Kumar Arpit**, Vivek Prakash**, Alka Singh**

Junior Resident*, Senior Resident**,Professor***, Dept of Pediatrics, NMCH Patna ,Bihar .
Corresponding Author: Dr Alka Singh, Professor***, Dept of Pediatrics, NMCH Patna, Bihar.
Mobile: 9835217017 Email:dralka24@ yahoo.in
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Abstract:
Canavan disease is rare genetic neurological disorder characterized by the spongy degeneration of the white matter in the brain. It belongs to a group of disorders known as the leukodystrophies. Incidence in Indian population is not known. It affects all ethnic groups, but occurs with greater frequency in individuals of Ashkenazi Jewish descent. We are reporting a case of this rare disorder which got admitted in Dept of Pediatrics NMCH, Patna. Aspartoacylase deficiency, or Canavan disease, is autosomal recessive disorder characterized by macrocephaly, developmental delay appearing between 3 to 6 mo of age and severe hypotonia eventually changing to spasticity in advanced stage of the disease[1]. Seizures occur in about 50 % of affected children. Leukodystrophy with involvement of sub-cortical white matter changes are characteristic features on MRI[2]. Elevated levels of N-acetyl aspartate either in urine/ plasma or on Proton Magnetic resonance spectrometry (MRS) of the brain are pathognomonic features[3].The gene coding for the Aspartoacylasenzyme (ASPA) has been mapped to chromosome 17p13-ter and comprises of six exons spread over 29 kilobases[4].

Case Report:
Anshu Kumari, a 5 year old girl from Vaishali district of Bihar, born to a nonconsanguineous couple, at term after uneventful pregnancy and delivery, got admitted to our emergency with complaints of progressive difficulty in walking, decreased oral acceptance and multiple episodes of seizure.

On further evaluation, it was noted that there was no gross delay in attainment of milestones upto 6 months of age. However, walking without support was attained at around 2 and half years of age. She developed first episode of seizure at 7 months, generalized tonic type. Next few episodes occurred at an interval of 4-5 months. Her general condition deteriorated over the next 18-20 mo, with increased frequency of seizure, inability to sit, stand or turning over in bed and progressively enlarging head size. At about 5 yrs of age, she became bed-ridden with no eye to eye contact, poor response to vocal stimuli and other surroundings. She had generalized spasticity with brisk deep tendon reflexes and bilateral ankle clonus. Her head size was 55 cm (>97th percentile), weight 16 kg (>25th percentile) and length 105 cm (25th centile). There was frontal bossing (fig 1). Anterior fontanelle and sutures were closed. Fundoscopic examination was unremarkable. Development of speech,language and higher mental functions were normal until the child became completely bed ridden. Facies was normal and no organomegaly was detected.

Fig 1
Clinical presentation suggested towards neurodegenerative disorder. To come to a diagnosis, MRI brain was done which reported megalencephaly with diffuse hyperintense signal in deep and subcortical white matter on both sides involving U fibres with moderate sized cystic gliotic changes in bilateral temporal and parietal region with mild dilatation of the ventricular system suggestive of leukodystrophy (fig. 2), most likely CANAVAN disease.

![Fig 2. MRI T2W images showing diffuse leukodystrophy. There is also a generalized cortical atrophy with ventricular dilatation. Hyperintense signal in deep and subcortical white matter involving U fibres.](image)

Lumbar puncture for CSF analysis was also performed with results within the normal limits.

The child was given supportive treatment and antiseizure medications. We counseled the parents regarding the genetic inheritance of the disease and referred the patient to higher centre for a molecular diagnosis and to go for antenatal screening for the disease during next pregnancy.

**Discussion:**

Canavan disease is classified among the group of leukodystrophies that are inherited disorders of myelin formation and/or maintenance secondary to molecular abnormalities in the glial cells. N-acetylaspartic acid, a derivative of aspartic acid, is synthesized in a high concentration in the brain. It serves as a reservoir for acetate, which is needed for myelin synthesis. The enzyme aspartoacylase cleaves the N-acetyl group from N-acetylaspartic acid and provide the substrate required for myelin synthesis. Deficiency of the enzyme leads to improper myelination and subsequently deposition of N-acetylaspartic acid in the brain causing vacuolization and spongy degeneration of the white matter.

The severity of Canavan disease however covers a wide spectrum. The severity and symptoms vary, and so all children will not have all the symptoms. It is usually associated with hypotonia (particularly occurs in the neck muscles) hyperextension of the legs, flexion of the arms, blindness, megalencephaly, feeding difficulties, nasal regurgitation, swallowing difficulties, reflux with vomiting, seizures and mental retardation. The case being reported here presented with most of the above findings which helped us to clinch the diagnosis. The clinical features and neuroimaging are very helpful and specific for Canavan disease. CT scan often reveals diffuse hypo density of the white matter of the cerebral hemispheres, as well as of the cerebellum, usually with involvement of globus pallidus and sparing of caudate nucleus and putamen. The leukodystrophy evident on cranial MRI has a centripetal progression with involvement of subcortical U fibres of white matter followed by central areas. Typically, the globus pallidus and thalamus are involved while there is sparing of putamen and caudate nucleus. In later stages, there is a diffuse widespread involvement of white matter with dilatation of lateral ventricles. Conventionally the diagnosis of Canavan disease is established using an enzyme assay (Aspartoacylase enzyme) on cultured skin fibroblasts, but elevation of metabolite, N-acetylaspartate (NAA) in body fluids is now considered pathognomonic. The NAA levels are very high in urine (as detected via Gas Chromatography-Mass Spectrometry). With the advent of Proton MR Spectroscopy (MRS), the diagnosis has become easier and is now increasingly being utilised. The MRS reveals a very high resonance of NAA relative to choline (which is decreased on account of hypo-myelination) and is diagnostic. However, The most accurate and
A definitive test for the diagnosis of Canavan disease is via molecular studies and identification of two causal mutations in the ASPA gene.

The prevalence of Canavan disease in the Indian subcontinent is unknown. The disease is most common in the Ashkenazi Jewish population where the carrier frequency is 1/40-57. In India, the most common cause of leukodystrophy is Megalencephalic leukodystrophy with subcortical cysts (MLC1). The clinical course and neuroimaging findings in MLC1 are however very different from those seen in Canavan disease and thus can be distinguished easily. Still, it is not much diagnosed owing to rarity and cumbersome investigations required to reach to a definitive diagnosis.

Awareness about the clinical and radiological presentation of the disease would help us to come to diagnosis in resource limited settings. Definitive diagnosis can then be established by molecular testing and genetic study.

Diagnosis of Canavan disease is important because of its devastating course, recessive nature with 25% risk of recurrence in the family. Once suspected, the diagnosis is relatively easy. Genetic studies are essential for confirming the diagnosis and for reliable and accurate prenatal diagnosis.

Conclusion:

Canavan disease is a rare autosomal recessive neurodegenerative disorder. It is most common in the Ashkenazi Jewish population, though can occur in any ethnic group. The prevalence of Canavan disease in the Indian subcontinent is unknown and is not much suspected. It is important to recognize this disease to prevent recurrence in a family, given its devastating course and non-availability of treatment.

Since, it is an autosomal recessive disorder, the chance of having an affected child is 25%. Genetic counseling and genetic testing are recommended for parents to prevent the inheritance in subsequent pregnancies.

Declarations :

**Contribution of authors:** Archana Singh - concept, strategy; Kumar Arpit – supervision and revision of manuscript, Alka Singh – guidance, Vivek Prakash, data collection.

**Conflict of interest:** Nil

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