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Canavan Disease: A Case Report

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ABSTRACT

Canavan disease is an autosomal recessive leukodystrophy associated with hypotonia, megalencephaly, mental retardation, blindness and spasticity. The biochemical deficiency of aspartoacylase (ASPA) causes CD. Deficiency in ASPA, which hydrolyzes N-acetylaspartate, results in NAA building up to high millimolar amounts in the brain. The hallmarks of the disease are loss of oligodendrocytes and spongy myelin degradation in the CNS. However, it is unclear whether the disease's pathophysiology is caused by the accumulation of NAA, the absence of NAA-derived acetate, or the absence of any unknown roles of the ASPA enzyme. In this Review, we present an important and timely update on the current and emerging aspects of this neurological disease. Following a brief overview of canavan disease, we discuss current knowledge of neurological findings, pathophysiology, diagnostic approaches, current canavan disease treatment, and gene therapy's future prospects.

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Introduction

Canavan disease was first identified as a spongy degeneration of central nervous system myelin in infancy in the early twentieth century. In 1987, N-acetylaspartic aciduria owing to aspartoacylase deficiency was discovered in a leukodystrophy. It wasn't until 1988 that researchers realized this leukodystrophy was indeed Canavan disease.

Canavan disease is caused by a mutation in the ASPA gene on chromosome 17pter-p13, which encodes the enzyme aspartoacylase, resulting in aberrant N-acetylaspartic acid (NAA) metabolism. It causes N-acetylaspartic acid (NAA) accumulation in the brain, as well as oligodendrocyte dysfunction, spongiform alterations, myelin loss, and increased NAA excretion in the urine up to 200 times normal, as measured by gas chromatography/mass spectrometry. Aspartoacylase deficiency is a spongiform leukodystrophy that affects a large percentage of Ashkenazi Jews, with carrier frequencies ranging from 1:37 to 1:57 and prevalence rates ranging from 1:6000 to 1:14,000.

Lethargy and listlessness, a weak cry and suck, poor head control, hypotonia, and a lack of extremity movement are among the earliest signs, which appear at the age of three months. Poor feeding, irritability, and visual inattention have all been described in neonates. Macrocephaly and hypotonia may proceed to spasticity, hyperreflexia, extensor plantar reflexes, tonic extensor spasms, and extensor spasms in response to noise by three to six months. Blindness due to optic atrophy can occur between the ages of 6 and 18 months. Approximately one-third of patients have seizures in their first year of life, which is frequently generalized tonic-clonic; the prevalence of seizures increases with age. The terminal stage is characterized by pseudobulbar symptoms and decerebrate posture. With substantial swallowing difficulties and acid reflux, feeding is a major problem. Although survival into the teen years is typical, death can occur in childhood as a result of improved medical therapy, particularly alternate feeding regimens.

The diagnosis is suspected by high levels of urine N-acetylaspartic acid (NAA) in MR spectroscopy and/or biallelic pathogenic mutations in ASPA discovered by molecular genetic testing in symptomatic newborns with comparable clinical characteristics and neuroimaging findings.

There is no effective treatment for aspartoacylase deficiency. Management is supportive and aimed at maintaining nutrition and hydration, protecting the airway, preventing seizures, minimizing contractures, and treating infections. Potential treatments include gene transfer, enzyme replacement therapy, acetate supplementation, anaplerotic therapy, reduction in NAA production, and lithium.

Case Report

A 12 year old girl presented with the stiffness of bilateral limbs and was first diagnosed with a seizure disorder. The child later developed progressive psychomotor retardation, cerebellar signs,

pyramidal signs, and relative megalencephaly despite optimal treatment. By the age of 2 years and three months, she had triad symptoms of head lag, macrocephaly, and hypotonia of bilateral lower and upper limbs. On examination, there was absent sucking and swallowing reflex, no eye contact, absent vocalization, unable to sit, stand or walk with overall delayed developmental milestones.

Her computed tomography scan (CT) showed findings of leukodystrophy and diffusely reduced myelination of the white matter in both supratentorial and infratentorial compartments. A definite diagnosis of leukodystrophy was not made. Magnetic Resonance Imaging (MRI) revealed diffuse white matter changes, hypointense on T1 and hyperintense on T2, and non-enhancing on contrast. In addition, there were hyperintense signal changes in bilateral globus pallidus and anterolateral part of thalami with involvement of corpus callosum. Dilation of ventricles was noted, and MRS showed characteristic N-Acetyl-Aspartate (NAA) peaks suggestive of Canavan disease.

Discussion

Canavan disease (CD) is a severe, deadly leukodystrophy caused by aspartoacylase deficiency leading to the accumulation of its substrate, N-acetylaspartate (NAA), and spongy myelin degeneration [1]. The disease is prevalent among Ashkenazi Jews with three variants; infantile, congenital, and late-onset with few reports on enzyme defects [2]. NAA plays a crucial part in the normal functioning of the central nervous system. The ASPA enzyme catabolizes NAA, exclusively found in the brain, to acetate, which is then used by oligodendrocytes to make the lipid component of the myelin sheath [3]. Greater myelination correlates with increased ASPA activity throughout neuronal growth, according to research [4]. Furthermore in neurons, NAA appears to act as a molecular water pump [5]. These functions of NAA may be linked to the histology of Canavan disease, which includes astroglial swelling and intramyelinic edema, as well as MRI findings of anisotropy and diffusion coefficient changes [6].

Infants with Canavan disease have hypotonia during the first month of life, which progresses to spasticity and failure to achieve independent sitting, deambulation, or speech. From 3 to 5 months, macrocephaly, lack of head control, and developmental delay will appear [7]. The case we are presenting had a similar development of the disease, beginning with bilateral limb stiffness and progressing to spasticity and inability to vocalize. The purpose of follow-up is to ensure proper nutrition and hydration in order to prevent infectious diseases. The child is now 12 years old and is being treated symptomatically with hydration, nutrition, nebulization, and speech therapy. Despite receiving optimal supportive care, the child is developing other comorbidities such as bed sores, nutrition calorie deficit, frequent respiratory tract infection due to feeding and swallowing difficulties, and weight loss. Death usually occurs during the adolescent years. Death usually occurs during adolescence, which may be the circumstance in our case as well due to the fatality and complexity of the disease, as well as the lack of a new current treatment, which is out of reach for developing countries like the Maldives [7].

The disorder must be distinguished from other genetic syndromes with similar phenotypic presentations. For example Alexander disease, Tay-Sachs disease, and other neurodegenerative conditions have all been linked to macrocephaly. Additionally, macrocephaly and white matter involvement are caused by hydroxymethylglutaric aciduria. Viral encephalitis, mitochondrial dysfunction, and other metabolic illnesses can all cause the brain to degenerate in a spongy manner [8]. Similarly, RASopathies such as NS (Noonan Syndrome) and CIM (Chiari I malaformation) have overlapping features of macrocephaly, developmental delay, and neurological sequelae [9]. In our case due to finding like dilation of ventricles was noted, and MRS showed characteristic N-Acetyl-Aspartate (NAA) peaks suggestive of Canavan disease canavan disease was diagnosed. There is currently insufficient data to determine whether there is a possible link between Rasopathies and Canavan disease. As a result, we recommend that a thorough neurologic evaluation be performed on a regular basis, and that if any suggestive neurologic symptoms or signs develop, early brain imaging be obtained prior to the development of significant neurologic deficits or hydrocephalus. Establishing a link between RASopathies like NS and CIM may aid clinicians in the early recognition and diagnostic workup of associated genetic syndromes. Similarly, such a link may encourage treating physicians to incorporate surveillance neuroimaging into their standard of care in order to differentiate between various neurodegenerative diseases.

Although there is currently no cure, the situation has appeared to become better after recent experiments using early gene therapy [10]. A study conducted by Leone et al demonstrated that gene therapy with an adeno-associated viral vector carrying the ASPA gene (AAV2-ASPA) resulted in a decrease in elevated NAA in the brain and slowed progression of brain atrophy, with some improvement in seizure frequency and stabilization of overall clinical status. The prospect of novel treatments has sparked interest in learning more about Canavan disease's pathophysiology and early detection [11]. In humans, ASPA gene therapy has been demonstrated to be safe and efficacious in the Canavan mouse model [12]. Pharmacologic strategies for lowering osmotic pressure appear to be promising in Canavan [13]. If treatment is provided sooner rather than later, it can considerably delay the progression of the disease and preserve the newborn from further harm. This goal necessitates early detection through screening. However, screening is done only on high-risk populations [14]. Improved gene sequencing and advances in liquid chromatography-tandem mass spectrometry, on the other hand, could lead to the establishment of early neonatal screening [15].

Conclusions

In Canavan disease, cytotoxic edema with diffusion limitation on brain MRI is common, according to our case and literature analysis. These findings, combined with evidence that NAA levels are linked to myelin degeneration and the possibility of potential treatments to lower NAA levels, suggest that there is a possibility for therapeutic intervention and the need for early detection of Canavan disease patients.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Publish

Written informed consent was taken from the patient and her family for publication of this report.

Availability of Data and Materials

Secondary data were collected from the patient's hospital records.

Competing Interests

The authors have no competing interest for the publication of this case report.

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Authors' contributions
NS carried out the conception and design of the study. NS and AT acquired the data, analyzed and interpreted the data. SR and WT critically revised the manuscript and gave the final approval. All authors read and approved the final manuscript.

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