A case of Canavan disease with normocephaly - A rare entity

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ABSTRACT

Canavan disease (CD) is an autosomal recessive disorder with spongy degeneration of white matter of the brain. It typically presents with developmental delay, visual problems, and macrocephaly. Our patient presented with these features along with normocephaly. Brain magnetic resonance spectroscopy showed typical findings for CD (peaks of N-acetylaspartic acid). This case illustrates the fact that the presence of normocephaly should not be used in isolation to rule out the possibility of CD.

Key words: Canavan’s disease, Macrocephaly, Magnetic resonance spectrometry, N-acetyl-l-aspartic acid, Normocephaly

Canavan disease (CD; MIM#271900), identified in 1931 by Canavan, is an inherited autosomal recessive progressive leukodystrophy with onset in early childhood or infancy. CD is more prevalent among individuals of Ashkenazi Jewish background, with an incidence of 1/6400 to 1/13,500 of the population, making 1 in every 40-58 Ashkenazi Jews a carrier [1]. However, the exact prevalence of the disease in the Indian population is not known. CD (spongy degeneration of the brain) is caused by a deficiency of aspartoacylase or N-acetylaspartate amino hydrolase. This enzyme catalyzes the hydrolysis of N-acetyl-l-aspartic acid (NAA) into aspartic acid and acetic acid. It presents with global developmental delay, poor head control, poor eye contact, hypotonia, seizures, and macrocephaly [2]. Most patients die within first few years of life. We report a case of CD who presented with the unusual features of normocephaly.

CASE REPORT

A 16-month-old male child born to a healthy couple presented with a history of increased head size since 6 months of age and delayed developmental milestones. On examination, the child had a weight of 5.5 kg (<−3 Z score), length 74 cm (between −2 and −3 Z score), and head circumference 48 cm (50–85th percentile as per the WHO charts). The baby’s birth weight was 2.2 kg and head circumference 34.5 cm (50th percentile as per the WHO charts). The child had no perception of light but could respond to sounds. The child was lying flaccid on the couch (hypotonia) with decreased muscle power and bulk. The deep tendon reflexes were within normal with positive Babinski sign. Rest of the systemic examination, as well as fundus examination, was normal.

The baby was a product of non-consanguineous marriage, as term normal vaginal delivery without any antenatal and perinatal complications. The elder sibling is developmentally normal, and there is no significant family history. The child developmentally did not achieve milestones as per age. Neck holding as well as bidextruous grasp were absent. The child could make cooing sounds only. Initially, we kept the possibility of leukodystrophy or storage disorders, and we planned blood and radiological investigations. The blood investigations revealed normal hemogram, liver function tests, and renal function tests. Metabolic workup including blood glucose, arterial blood gas, and urine for reducing substances, ketones, serum lactate, ammonia, and tandem mass spectrometry were noncontributory. The infant was further evaluated with a magnetic resonance imaging (MRI) brain performed on a 1.5 T MR scanner (Philips Medical Systems). MRI brain revealed diffuse bilateral white matter T2/fluid-attenuated inversion recovery hyperintensities and T1 hypointensity involving bilateral subcortical U fibers, centrum semiovale, corona radiate, globus pallidus, and periventricular white matter with no contrast enhancement. Proton magnetic resonance spectroscopy (H-MRS) at echo time -23 ms, repetition time - 2000 ms showed high NAA and mI peak with NAA:Creatinine ratio of 7.27:1 (normal: 2.09±0.45) suggestive of CD. It was confirmed by a urinary organic acid profile by gas chromatography–mass spectrometry, which showed elevated urinary NAA levels to be 520 µmol/mmol creatinine (normal: <10 µmol/mmol creatinine).

DISCUSSION

CD is a globally occurring but rare early-onset human spongiform leukodystrophy associated with inborn genetic errors affecting the activity of aspartoacylase (ASPA), the enzyme highly expressed in oligodendrocytes that hydrolyzes NAA to acetate and aspartate. While the role of NAA in neuronal development is still unclear, its accumulation in the brain in CD is postulated to cause...
myelin damage and progressive spongiform degeneration [3]. In Ashkenazi Jews, the risk for affected children is 1:6400 to 1:13,500 [1]. However, the exact prevalence of the disease in the Indian population is not known. Patients usually present within the first 6 months of life with hypotonia, poor head control, loss of visual fixation, macrocephaly, and head lag. CD generally follows a rapidly progressive clinical course and results in death by the 3rd year of life [4].

One of the hypotheses suggested for the pathophysiology of CD is that excessive NAA accumulated in the brain due to the ASPA gene mutation acts as a water pump and produces astrocytic edema, intramyelinic vacuole formation, and spongy degeneration of the brain parenchyma which manifests as brain swelling. Macrocephaly results from a combination of brain swelling and abnormal skull growth in CD [5]. Our patient also presented at 6 months of age with hypotonia, loss of visual fixation and head lag and normocephaly. Most cases of CD reported in literature presented with macrocephaly. There are few reported cases of CD with normocephaly. These cases of normocephalic CD had a milder clinical course, and their cerebral and urinary NAA levels were less than those found in classic cases [6,7]. This could probably be due to a variable expression of the ASPA gene that led to a severe clinical course followed by a rapid neuronal loss.

Advanced stage of CD is associated with the loss of white matter and neurons [8]. This probably caused decreased NAA production and coupled with reduced ASPA enzyme activity, resulted in a moderate increase in NAA levels that was reflected on MRS. The relative decrease in NAA levels and neuronal loss could have prevented swelling of the brain. This in turn probably prevented excessive skull growth and resulted in normocephaly at the time of presentation. In the present case, the clinical course was similar to that of the classic CD. However, The cerebral NAA levels as demonstrated by MRS showed a moderate elevation of NAA, and the urinary NAA levels showed the levels to be 520 µmol/mmol creatinine, which is much less compared to the levels seen in classic cases of CD. These findings are consistent with the reports of Velinov et al., who ascribed the normocephaly, to the particular mutation seen in their cases [7]. In our patients, we could not do genetic analysis due to financial constraints. These findings are also consistent with the findings of Janson et al. [6]. Both triheptanoin as well as gene therapy are promising treatment approaches for CD, but they are still in their infancy to establish an approved therapy for patients with CD.

CONCLUSION

CD is a rare neurological disorder with an overall small number of patients. This case illustrates the fact that the presence of normocephaly should not be used in isolation to rule out the possibility of CD.

REFERENCES


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