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Case Report

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Canavan Disease: First Normocephalic Case from North Cyprus

Mehmet Alp Dirik[2], Burcin Şanlıdağ[1], Nail Bulakbası[2], Nedime Sekakıncı[3], Eray Dirik[1]

[1]Department of Pediatric Neurology, Near East University School of Medicine, Nicosia, Cyprus
[2]Department of Radiology, University of Kyrenia School of Medicine, Kyrenia, Cyprus
[3]Department of Medical Genetics, Near East University School of Medicine, Nicosia, Cyprus

ORCID ID of the author: M.A.D.: 000-0003-1011-475X ; B.Ş.: 0000-0003-1011-475X; N.B.: 0000-0001-7528-8107, N.S.: 0000-0002-1884-0839; E.D.: 0000-0002-4429-6478.

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Canavan disease is an autosomal recessively inherited leukodystrophy characterized by white matter degeneration. The defective gene is the aspartoacylase gene that encodes the enzyme aspartoacylase. Head lag, macrocephaly, and hypotonia are the primary characteristic physical examination findings. A 6 month-old patient presented with developmental delay and normocephaly. Brain magnetic resonance imaging showed delayed myelinization at the corpus callosum, genu of the internal capsule, and posterior limb and hyperintensity of the globus pallidus, thalamus, dorsal aspect of the brain stem, corticospinal tract, and cerebellum. Magnetic resonance spectroscopy demonstrated a prominent N-acetyl aspartate peak, which is a typical pathological finding. Genetic testing revealed the presence of a homozygous c.79, G>A (p.G27R) mutation, which confirmed the diagnosis of Canavan disease. During follow-ups, the child was normocephalic, even at the 1 year visit.

Keywords: Canavan disease, normocephaly, magnetic resonance spectroscopy, genetic testing

INTRODUCTION

Canavan disease (CD) is a leukodystrophy characterized by the degeneration of white matter that is replaced by fluid, thereby causing vacuolating myelinopathy (1, 2). It is an autosomal recessively inherited disorder. The defective gene is the aspartoacylase (ASPA) gene that encodes the enzyme aspartoacylase. Aspartoacylase hydrolyses N-acetyl aspartate (NAA), providing the acetyl group to dendrocytes for myelin synthesis. Defective enzyme activity results in decreased myelin synthesis and dysmyelination. Although CD has a higher incidence in the Ashkenazi Jewish population, it can also be seen in other populations. Its incidence various between 1:200,000 and 1:400,000 in the non-Jewish population (3). The classical triad in infantile CD is hypotonia, macrocephaly, and head lag (4). In the current report, the first case of a patient with CD from North Cyprus and having normal head circumference has been presented.

CASE PRESENTATION

A 6-month-old female presented with global developmental delay and a history of generalized tonic seizures for 4 months. Her perinatal history and delivery were unremarkable. She was the first child of second-degree consanguineous parents. She was born at term without any complication. No family history of neurologic or metabolic disorder was reported. At 2 months of age, her family recognized that she was irritable, did not visually tract objects, did not laugh, and was not interested in her surrounding environment. Her physical examination indicated that she had a body weight of 6.190 g (10th percentile), body length of 63 cm (10th percentile), and head circumference of 42 cm (50th percentile). She had severe hypotonia, head lag, and hypertonicity in the extremities and would not interact socially. Brain magnetic resonance imaging (MRI) showed delayed myelinization at the corpus callosum, genu of the internal capsule, and posterior limb. MRI also showed hyperintensity of the globus pallidus, thalamus, dorsal aspect of the brain stem, corticospinal tract, and cerebellum. Subsequently, proton magnetic resonance spectrometry (MRS) revealed a prominent NAA peak on the posterior deep white matter lobe, which is considered a typical pathological finding. The findings were consistent with those observed in CD (Figure 1). The diagnosis was confirmed by genetic testing, in which a homozygous c.79, G>A (p.G27R) mutation was identified in the ASPA gene. Head circumference was within normal limits according to age at 1 year age control. No improvement was observed in developmental steps, despite lithium citrate treatment. Informed consent was taken from the parents.

Corresponding Author: Burcin Şanlıdağ
E-mail: burcinsanlidag@yahoo.com

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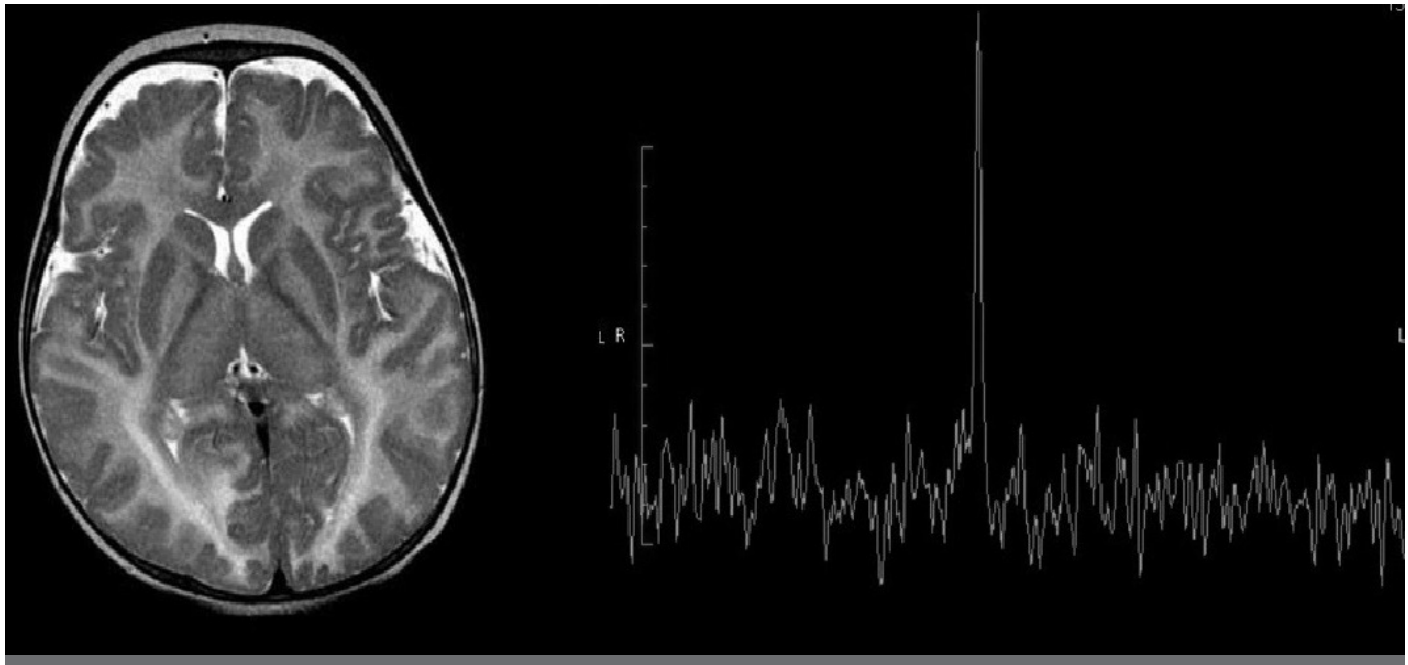

FIGURE I. MRI findings and prominent NAA peak of the presented case.

DISCUSSION

The classical triad in infantile CD in early childhood is hypotonia, macrocephaly, and head lag (4). Macrocephaly becomes evident within the first year of life, even if normocephaly is seen during the first months of life. Although macrocephaly is part of the classical triad, the presented case was normocephalic, even at the I-year follow-up visit. There are few cases of normocephaly reported in the literature (5, 6); there was a recent case of microcephaly reported in the literature (7). The presented case was normocephalic at the time of making the diagnosis and also in the subsequent follow-up visits. Macrocephaly can also be seen in other neurodegenerative disorders such as Alexander Disease and glutaric acidemia Type I that takes place in the differential diagnosis (8). Diagnosis is based on neurological findings, laboratory test results, the presence of cultured skin fibroblasts, and neuroimaging and genetic testing results.

Serum and urine NAA levels are approximately 200 times higher than those in normal age-matched individuals. Serum and urine NAA levels may normal in infants (9, I0). In the presented case, as MRI, MRS, and genetic testing confirmed the diagnosis, serum and urine NAA levels were not studied.

Brain MRI demonstrates diffuse loss of white matter including subcortical U-fibers (2, II). Bilateral globus pallidus involvement and thalamus involvement are usually observed. The putamen and caudate nucleus are not affected, which is very typical in CD. The cerebellum and brain stem tracts are also affected (I2). MRS revealed a prominent NAA peak, which is characteristic in CD. A low choline (Cho)/creatine (Cr) ratio, high myoinositol/Cr ratio, and high lactate level may be observed in some patients with CD (I2).

In the presented case, typical MRI findings and a prominent NAA peak were seen along with the normal Cho/Cr ratio (Figure I).

More than 70 mutations have been demonstrated to date in CD. Two mutations account for approximately 98% of the alleles of Ashkenazi Jewish patients, among whom the disease is highly prevalent: E285A and Y23IX. In non-Jewish patients of European origin, the A305E mutation accounts for 50% of alleles (I3). The homozygous c.79, G>A (p.G27R) mutation in the ASPA gene was detected in our patient.

Defective enzyme activity can be demonstrated via cultured skin fibroblasts. Results are highly dependent on culture conditions, but the demonstration of a lack of enzyme activity is diagnostic. As the mutation is known, the demonstration of enzyme activity was not performed via cultured skin fibroblasts. Cultured skin fibroblasts may be reserved for cases with novel mutations or for those in which mutations cannot be demonstrated.

There is a mild/juvenile form of the disease. This form usually presents in older age with mild developmental delay. It has also been demonstrated that usually, a heterozygous mutation with one mild variant and one severe variant causes residual ASPA activity (I4) that is responsible for the clinical course.

Genetic mutations may be effective on the clinical course of the disease, which is similar in the mild/juvenile form; therefore, studies evaluating genetic mutations with the clinical course of the disease are required.

There is no specific treatment for patients with CD. Human trials using lithium citrate, glyceryl triacetate, and topiramate have been documented. Lithium citrate treatment was given to our patient without obvious progress (4).

Gene therapy is one of the most promising treatment options; currently, it is being experimentally used (4). Therefore, prenatal diagnosis becomes more important. In conclusion, MRI and MRS findings are highly characteristic of CD. MRS should also be performed together with brain MRI in patients with suspect-

ed leukodystrophies even if macrocephaly is not seen. Genetic testing is important for confirming the diagnosis and for prenatal testing. In patients with a novel mutation, urinary NAA levels and skin fibroblast cultures become more important for making a definite diagnosis.

Informed Consent: Informed consent was obtained from patient's parents.

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