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S Babour

Department of Pediatrics,
Military Hospital of
Instruction Mohamed V,
Rabat, Morocco

A Ourrai

Department of Pediatrics,
Military Hospital of
Instruction Mohamed V,
Rabat, Morocco

A Radi

Department of Pediatrics,
Military Hospital of
Instruction Mohamed V,
Rabat, Morocco

R Abilkassem

Department of Pediatrics,
Military Hospital of
Instruction Mohamed V,
Rabat, Morocco

A Hassani

Department of Pediatrics,
Military Hospital of
Instruction Mohamed V,
Rabat, Morocco

M Kmari

Department of Pediatrics,
Military Hospital of
Instruction Mohamed V,
Rabat, Morocco

A Agadr

Department of Pediatrics,
Military Hospital of
Instruction Mohamed V,
Rabat, Morocco

Corresponding Author:

S Babour

Department of Pediatrics,
Military Hospital of
Instruction Mohamed V,
Rabat, Morocco

Infantile onset form of Canavan disease: 2 case reports

S Babour, A Ourrai, A Radi, R Abilkassem, A Hassani, M Kmari and A Agadr

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Abstract

Canavan disease or N-acetyl-aspartic acid (NAA) is a rare and severe, autosomal-recessive metabolic leukodystrophy that causes spongy degeneration of the white matter by brain accumulation of NAA acid due to aspartoacylase (ASPA) deficiency. We report a 13 month-old boy case presented with macrocephaly, abnormal tonus, psychomotor delay and blindness. Brain magnetic resonance imaging and chromatography of urinary organic acids allowed to make the diagnosis. Furthermore, we also report the observation of a 12-year-old girl with healthy psychomotor development which revealed that she was experiencing facial myoclonus at a frequency of 5 seizures per day. The cerebral MRI findings indicated the presence of leukodystrophy, and MRI spectroscopy validated the diagnosis of Canavan disease by revealing an elevated N-acetyl aspartate peak. Our aim is to describe clinical, radiological, and biological presentations in the light recent literature.

Keywords: Canavan disease - macrocephaly - psychomotor delay - leukodystrophy

Introduction

Canavan disease or N-acetyl-aspartic aciduria (NAA) is a rare progressive hereditary metabolic leukodystrophy responsible for spongy degeneration of the white matter. It is inherited in an autosomal recessive manner and due to an enzyme deficiency in aspartoacylase (ASPA), which hydrolyzes NAA into aspartate and acetate.

The diagnosis is evoked by the clinical appearance of macrocrania associated with psychomotor regression, tonus disturbance and blindness, and the appearance of diffuse, symmetrical leukodystrophy on imaging. The diagnosis is confirmed by urinary organic acid chromatography. Our aim is to describe the clinical, radiological and biological aspects in the light of recent data in the literature.

Patients and Observations

Case Report 1

E.I. is a unique 14-month-old infant of first-degree consanguineous parents. The pregnancy was well monitored and carried to term. Delivery was by vaginal delivery for gravidic toxemia. There was no evidence of neonatal distress. Birth weight was 3200g, with a height of 52cm and a head circumference of 35cm. Breastfeeding was exclusively maternal, with diversification at 6 months. There were no similar cases or deaths in infancy in the family. The neonatal period was uneventful. Psychomotor development was normal until the age of 3 months, with a responsive smile and eye tracking at 2 months, and vigorous spontaneous limb motility.

On examination, E.I weighed 10 kg, measured 83 cm in height and had a macrocrania at 51.5 cm (+3DS). E.I did not speak or follow with his eyes. Neurological examination revealed axial hypotonia, limb spasticity and exaggerated osteotendinous reflexes. The rest of the physical examination was normal. Ophthalmological examination revealed optic atrophy. Cerebrospinal fluid examination was unremarkable. Magnetic resonance imaging showed a T₂ hypersignal and T₁ hyposignal of the supratentorial and subtentorial white matter. This included subcortical white matter, juxta-cortical white matter (U-shaped fibers), thalami and pallidums. Diffusion restriction was also observed, as evidenced by the hypersignal in the B1000 diffusion sequence (Figure 1). Subtentorially, these abnormalities involved the posterior parts of the brainstem, the dentate nuclei and the cerebellar white matter.

All these anomalies were bilateral and symmetrical. The cortical and ventricular sulci were also enlarged, reflecting cortico-subcortical atrophy (Figure 2). MRI spectroscopy was not performed. Blood and urine amino acid chromatography was normal. Chromatography of organic acids in urine revealed a significant NAA peak, indicating a diagnosis of Canavan disease. Our patient is currently 4 years old. He presents with partially controlled generalized convulsive seizures. He is bedridden and visually impaired.

Case Report 2

We report the observation of a 12-year-old girl, with good psychomotor development, who had presented for 5 months with facial myoclonus at a rate of 5 seizures per day without secondary generalisation. The general clinical and neurological examination was unremarkable, with no signs of dystonia or hypotonia, and no other associated signs.

Cerebral MRI suggested leukodystrophy, MRI spectroscopy (figure 3) confirmed the diagnosis of Canavan disease with a peak in N-acetyl aspartate, and urinary organic acid chromatography showed an accumulation of N-acetyl aspartic acid. The patient was put on Levetiracetam with a reduction in the frequency of attacks, with close monitoring.

Discussion

Canavan disease or N-acetyl-aspartic aciduria is a rare neurodegenerative disorder described in 1931 by Myrtle Canavan. It is a progressive and severe leukodystrophy with autosomal recessive inheritance, characterized by spongiform degeneration of the brain's white matter. It is secondary to a deficiency in asparto-acylase (ASPA), which hydrolyzes N-acetyl-aspartate (NAA) into aspartate and acetate [6,4]. ASPA deficiency leads to NAA accumulation in oligodendrocytes, the precursor cells of myelin. Excess NAA, through its osmoregulatory property, causes water to migrate into the peri axonal space. The resulting intramyelin edema is responsible for progressive spongy degeneration of the white matter and megalencephaly. In addition, aspartate deficiency induces a defect in the synthesis of various classes of lipids associated with myelin [2]. The condition mainly affects Ashkenazi Jews (between 1/6,400 and 1/13,500 births), with the frequency of heterozygotes estimated at around 1/40 [1]. However, other ethnic groups may also be affected, notably in Saudi Arabia, where there is a significant outbreak [2]. The gene involved in this disease, or ASPA gene, is located on chromosome 17 at p13.2. Around 80 mutations have been described responsible for the disease in different populations. But in the Ashkenazi Jewish population, three mutations are responsible for over 97% of observed cases. These are the p.Tyr231 Stop, p.Glu285 Ala and p.Ala305 Glu mutations, with a heterozygote frequency of 1/80 [9]. The last mutation is also widespread in non-Jews (Around 40% of cases) [10]. Clinically, Canavan disease presents in 3 forms: congenital, infantile and juvenile. The infantile form, which is the most frequent and concerns our patient, begins between 3 and 6 months of age with progressive macro crania, followed by generalized hypotonia with difficulty holding the head and paucity of distal movements, apathy, weak crying and sucking, then progressive spasticity of the limbs with dystonia.

Blindness due to optic atrophy occurs between 6 and 18 months of age. Convulsions occur in 50% of patients. Pseudobulbar syndrome and decerebration come last [3]. The congenital form is very severe, with an early onset and rapid death. In the rare juvenile form, onset is later, at around 4 to 5 years of age, and deterioration is slower [11].

Radiologically, cerebral CT shows white matter hypodensity. Cerebral MRI shows diffuse, symmetrical white matter involvement and progressive cerebral atrophy with passive ventricular dilatation. These abnormalities are expressed as T₁ hyposignal and T₂ hypersignal. They begin in the semi-oval centers and extend to the subcortical regions, with damage to U-shaped subcortical fibers and obliteration of cortical sulci. Over the course of the disease, the corpus callosum, internal capsules, pallidums and thalami are affected, with relative preservation of the putamen and caudate nuclei. Cerebral atrophy occurs late [13]. The cerebellum and brainstem are constantly affected. On diffusion, the apparent diffusion coefficient (ADC) is increased in edematous areas, but may be decreased in gelatinous areas [12]. MRI spectroscopy shows an abnormal increase in the NAA peak compared with choline and creatine peaks, as well as lactate and inositol peaks, especially in frontal white matter [14].

Diagnosis of the disease is confirmed by chromatography of organic acids in urine (CAOu), which shows a very sharp increase in NAA (up to 50-fold), or by a drop in ASPA activity in cultured fibroblasts [15]. CAOu can also be used to rule out other leukodystrophies with megalencephaly, such as glutaric aciduria type 1, L2-hydroxy glutaric acid deficiency, Alexander disease and GM2 gangliosidosis (Tay-Sachs and Sandhoff disease).

Screening for heterozygous forms in at-risk populations (Ashkenazi Jewish population) by certain learned societies (ACOG: College of American Obstetricians and Gynecologists 2004, SOGC: Society of Obstetricians and Gynecologists of Canada 2006) should lead to the disappearance of neonatal forms of the disease [5].

After the birth of a child with Canavan disease, genetic counseling for future pregnancies will be based on the type of mutation found. When the mutation is unknown, as in our patient's case, NAA is measured in the amniotic fluid using the stable isotope dilution technique during the subsequent pregnancy [16]. Once the mutation is known, germ cell DNA analysis can be performed [17].

Several therapeutics have been tried without any real success. These include lipoic acid, for its antioxidant action [18], and lithium citrate, which reduces NAA levels in the brain, but without any clinical improvement [19]. Gene therapy with a viral vector, on the other hand, has reduced the frequency of epileptic seizures and stabilized cerebral atrophy. It would therefore be of interest if carried out early in the course of the disease [20]. Death occurs during the first or second decade.

In the absence of gene therapy available to us, we can only advise our patient's young parents to carry out a genetic study. This will identify the type of mutation and enable early prenatal diagnosis. The decision to terminate the pregnancy will be taken with the parents' consent, within the legal framework provided for this purpose.

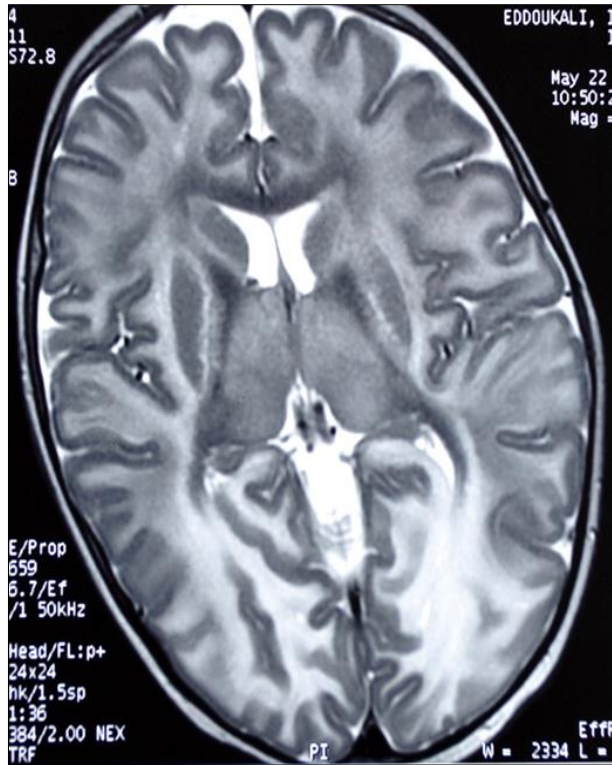


Fig 1: Magnetic resonance imaging in T₂ axial section reveals a hypersignal predominantly in posterior regions of the supratentorial white matter. It involves subcortical and juxtacortical white matter (U-shaped fibers), thalami and pallidum

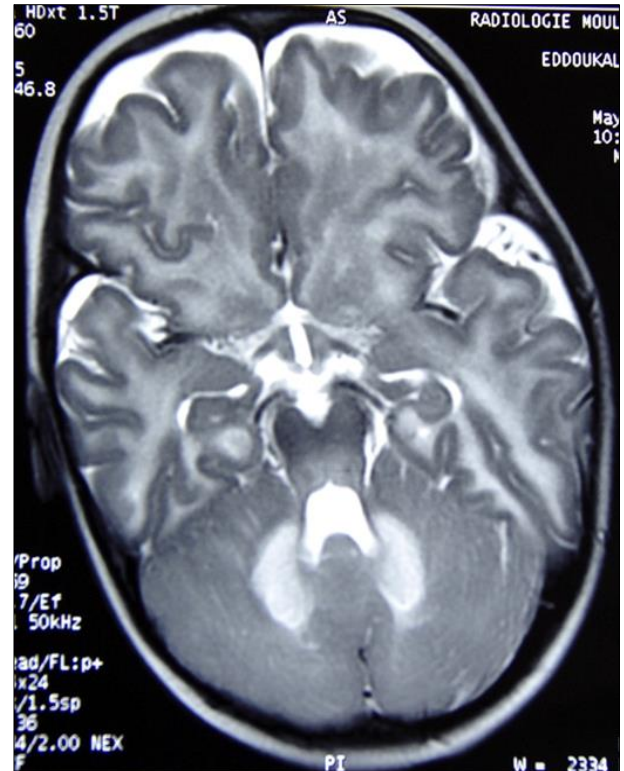


Fig 2: Magnetic resonance imaging in axial section through the posterior fossa showing T₂ hypersignal of the dentate nuclei (arrow)

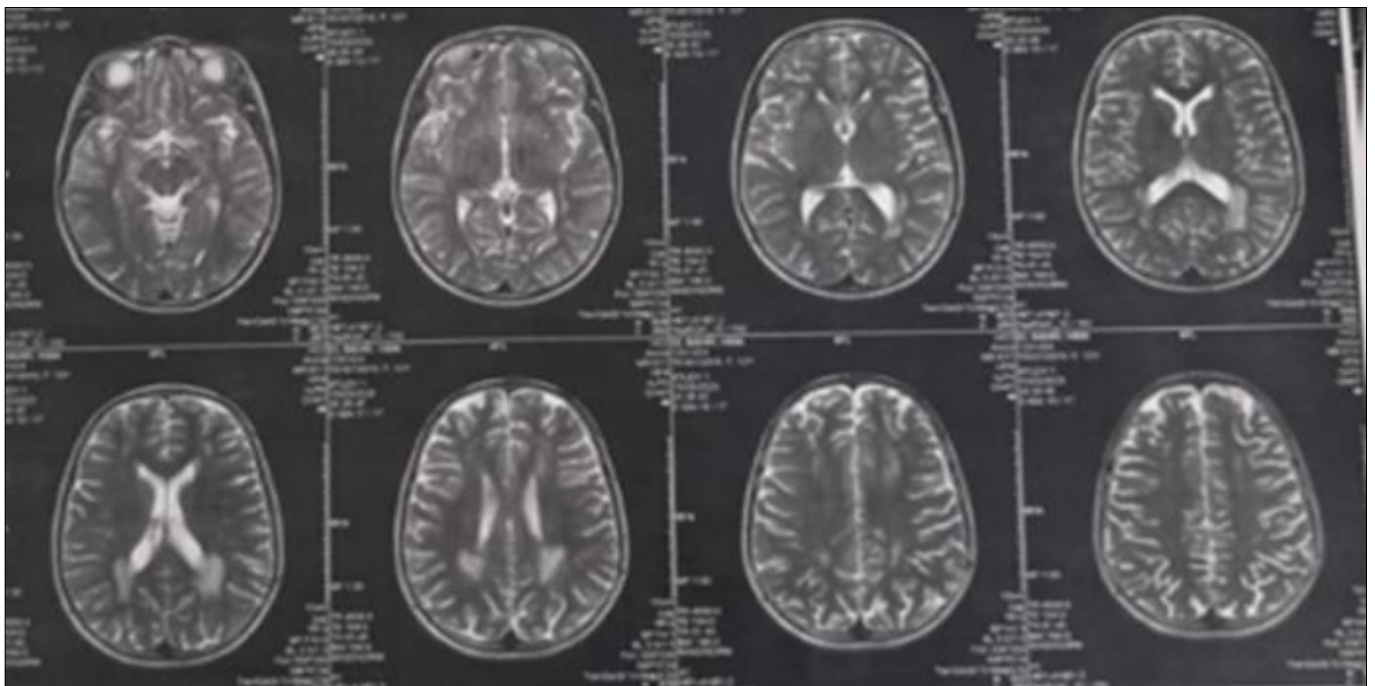


Fig 3: MRI spectroscopy showing accumulation of N-acetyl-aspartate

Conclusion

Canavan disease is a rare, incurable genetic progressive metabolic leukodystrophy. Its management is based on genetic exploration of the patient and his or her parents, in order to achieve an early prenatal diagnosis and prevent the birth of a new family case.

Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

All authors have read and approved the final version of the manuscript.

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