NON-JEWISH CHILD WITH CANAVAN DISEASE

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KEY WORDS

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ABSTRACT

Canavan disease (CD) is a rare autosomal recessive inherited disorder caused by a deficiency of aspartoacylase, which leads to defective myelinisation and occurrence of leukodystrophy. Most frequently it occurs in the population of Ashkenazi Jews, while in the Central European non-Jewish population only about 5 % of outbreaks occur. The most common symptoms are progressive spasticity, serious developmental delay, macrocephaly, blindness, and seizures. The features crucial for diagnostics include clinical history, laboratory proof of N-acetyl-L-aspartate (NAA) accumulation in urine, magnetic resonance imaging (MRI) of the brain, and molecular analysis of the genetic mutation. Genetic therapy has already been known and used, while therapy with stem cells and glyceryl triacetate is still in the phase of research. We diagnosed a six-month non-Jewish girl with leukodystrophy suspect symptoms without EEG or clinically expressed epileptic activity. NAA elevation was proved in urine. Brain MRI showed diffused affection of the brain's white matter. The diagnosis was definitively confirmed by molecular analysis where the 914C>A mutation was found, which is most frequently expressed in the Central European non-Jewish population. The genetic confirmation explained the essence of this serious neurological disorder and allowed for a better determination of prognosis, which is unfavourable. In Central Europe, only symptomatic therapy of epileptic paroxysms has been used, along with rehabilitation. Negotiations leading to the establishment of gene therapy, which has already been used elsewhere, have not yet been initiated in this region, as it is extremely demanding and rare in Central Europe.

ABBREVIATIONS USED

ASPA – gene for enzyme aspartoacylase
BAEP – brainstem-evoked potentials
CD – Canavan disease

DNA – deoxyribonucleic acid
EEG – electroencephalography
EMG – electromyography
CSF – cerebrospinal fluid
MRI – magnetic resonance imaging
NAA – N-acetyl-L-aspartate
TORCH – intrauterine infections (toxoplasmosis, rubella, cytomegalovirus, herpetic viruses)
VEP – visual evoked potentials

Table 1
The severity of the disease is dependent on mutation and population

	Jewish population	Non-Jewish population
Mild disease	854 A>C (E285>A) 82.9 %	(G212>A)
Severe disease	693C>A (tyr231>ter) 14 %	914C>A (A305>E) 60 %

ASPA gene placed on the 17th chromosome has 6 exons and 5 introns. Dependence of the severity of the disease on location of the mutation and representation of the mutations in populations has been described. Up to date, there exist in the non-Jewish population over 14 mutations with different percentage substitution

INTRODUCTION

In Central Europe, CD is a very rare autosomal recessive inherited leukodystrophy with a known metabolic defect. It is caused by the mutation of the gene for N-acetylaspartate acid amidohydrolase (aspartoacylase), which catalyses the transformation of N-acetylaspartate acid to acetyl and aspartate, and actively participates in myelinisation. Due to the defective enzyme, the substrate accumulates in astrocytes with the result of leukodystrophy followed by spongiform degeneration of the brain's white matter [1, 4]. There are several types of mutation of the gene for aspartoacylase, occurring predominantly either in the population of Ashkenazi Jews (854A>C) or in the non-Jewish Central European population (914C>A) (Table 1) [3]. This means that the diagnosis of CD is, besides clinical symptoms, laboratory proof of NAA elevation in urine and MRI signs of leukodystrophy, based mostly on molecular analysis of the genetic mutation characteristic of a particular population. We have described a case of a six-month-old non-Jewish child suffering from CD, which is very rare in our country.

Case: The six-month-old girl, born to non-related non-Jewish parents, from uncomplicated gravidity and without perinatal risks, was brought to our department for the diagnostics of aetiology of severe developmental delay which was on the level of a pathological newborn infant with central hypotonic syndrome and beginning spasticity of the lower extremities. Epileptic seizures were not expressed yet in the infant. Brain ultrasound examination had led to the suspicion of an inherited developmental brain disorder. The objective neurological finding also noticed suspect amaurosis and macrocephaly. EEG, EMG from the legs and BAEP were normal, VEP examination confirmed lesion in the visual tract without the possibility of a closer topisation. The basic metabolic sampling was complemented by special tests for inherited metabolic disorders with the discovery of NAA elevation in the urine. After structural brain examinations, MRI was carried out, upon which diffused affection of the white matter was described along with a myelinisation disorder and reduction of the cortex, which are all signs of leukodystrophy (Figures 1, 2). Now we could express our suspicion of CD. To prove it we sent the patient's and her parents' DNA for genetic analysis. Heterozygote mutation 914C>A was proved in both parents, and upon the test of the ASPA gene (6th exon) of the patient, 914C>A (A305E) mutation was found in homozygote condition, which is characteristic of the Central European non-Jewish population (Table 1). In our conditions the only therapy available is symptomatic treatment of epileptic seizures and rehabilitation. The girl's prognosis is therefore catastrophic due to the very substance of the disorder, as well as to the therapeutic possibilities in our country. The parents were instructed about the 25% risk of the same disorder occurring in any of their children, boys or girls, and in the case of the mother's next gravidity amniocentesis would be carried out as part of the perinatal diagnostics and monitoring of this family.

Discussion: The main symptom of our little patient was a serious developmental delay and a central hypotonic syndrome with spasticity on the lower extremities. The same symptoms are present in children with infantile poliomyelitis, which includes positive perinatal risks in the

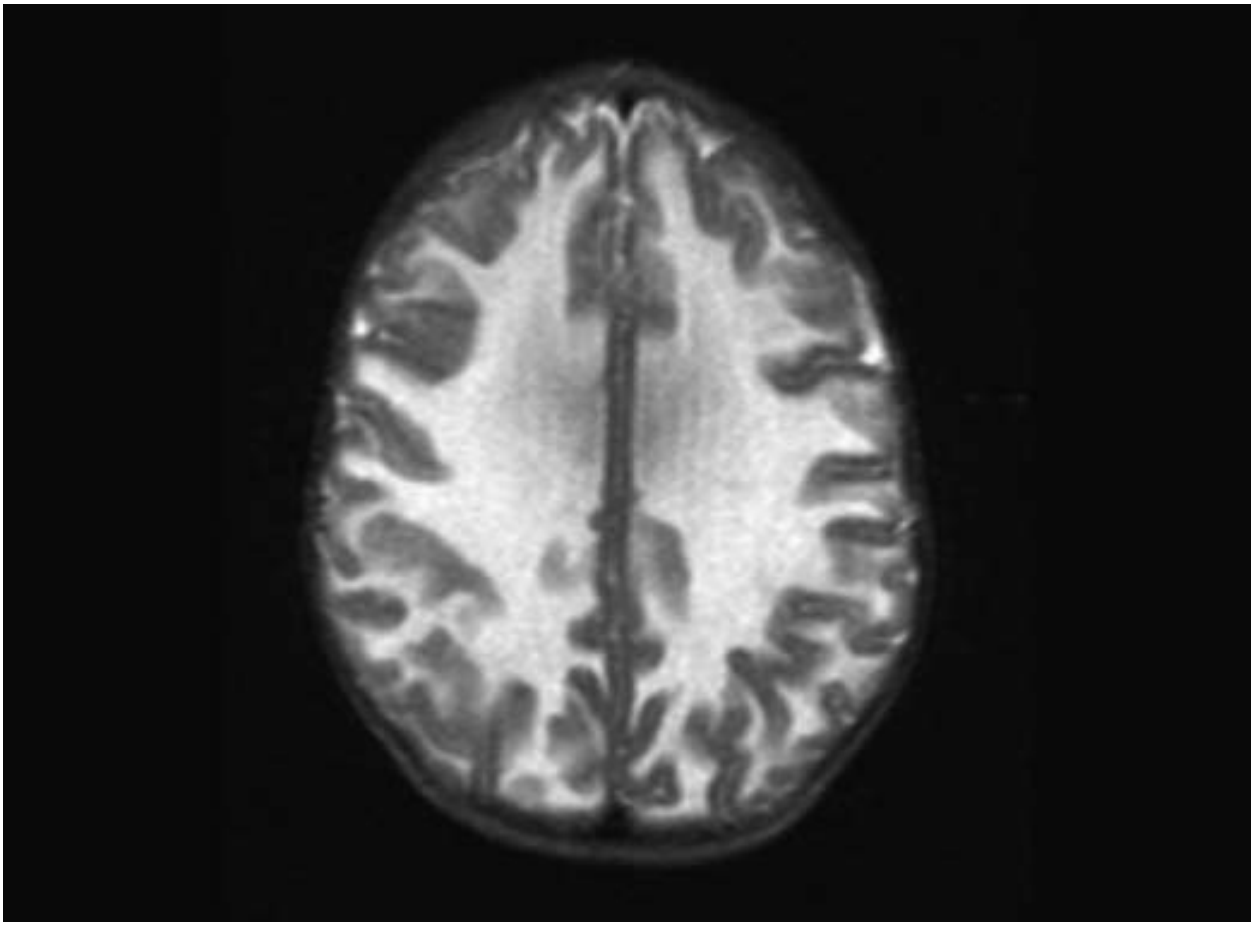

Figure 1
MRI T2W imaging – hyperintensity of white matter mainly localised subcortically, signs of grey matter reduction

patient's history that are negative in our case. Macrocephaly and developmental delay are also mentioned with the Pelizaeus-Merzbacher leukodystrophy, including a similar expression of the defective myelinisation in the T2-weighted brain MRI images, but in detailed biochemical examination and molecular analysis no concrete metabolic defect is found [1, 4]. In our case we found NAA elevation in the urine and, if lumbar puncture had been carried out, the increased NAA concentration would be present in the CSF as well [2]. Macrocephaly and developmental delay can also be diagnosed in hydrocephalus occurring after intrauterine infection. Laboratory proof of TORCH was negative in our patient. Clinical epileptic seizures have not yet occurred in our case, as these develop with the reduction of the brain's grey matter; EEG showed a mature curve of basic activity without any abnormities.

Unlike patients described in the literature, who suffer defective development of the cochlear apparatus and deafness, there was no proof of any hearing defect or lesion in the auditory pathway of our little patient [5].

For the purpose of the molecular analysis of the ASPA gene mutation, the non-Jewish origin of both parents was considered and the analysis was carried out directly for the A305E mutation, which was confirmed [3]. This mutation is present in approximately 60 % of the Central European non-Jewish population, and currently about 14 new mutations are available, whose detection would surely extend the time of the early diagnostics (Table 1). However, the prolongation of diagnostics unfortunately has no influence on the patient's prognosis. In Central Europe, no therapy other than symptomatic has been used at the moment. In 1996 gene therapy was launched in New Zealand followed by the USA; it is based on the introduction of the normal ASPA gene in the affected areas of the brain

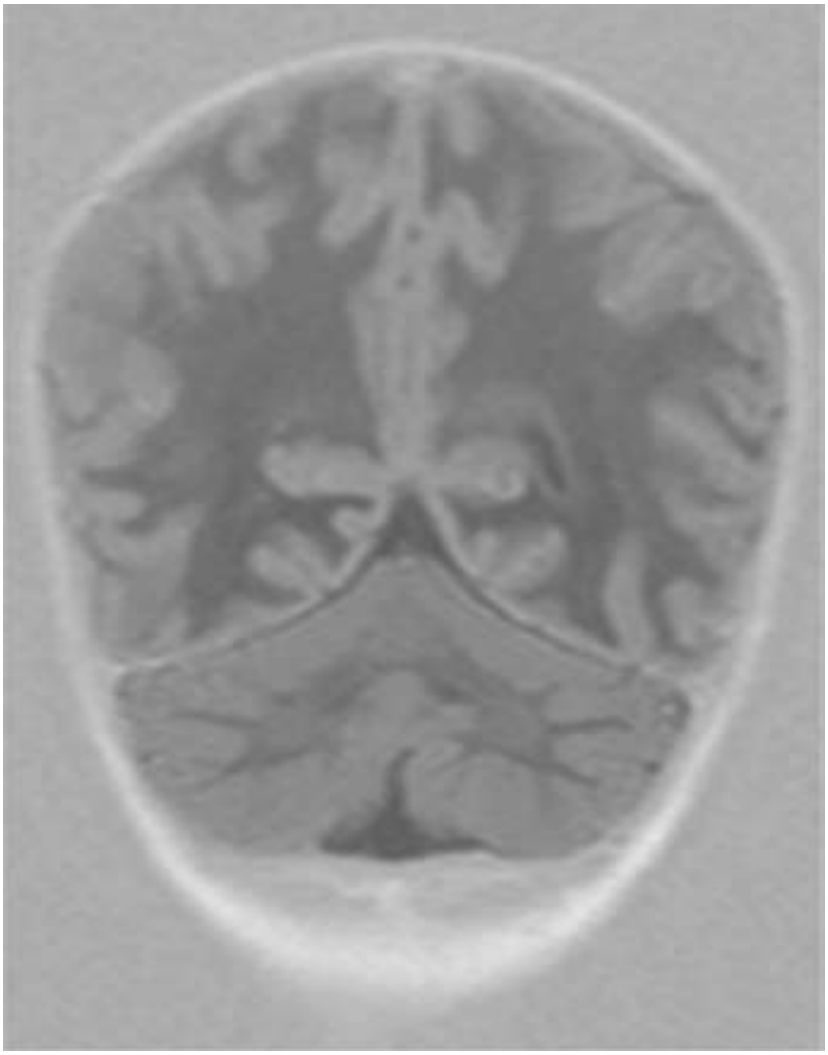

Figure 2
True inversion recovery – juxtacortical changes, reduction of grey matter

via recombinant virus particles [6]. The prognosis of patients treated in this way is much more positive, the quality of life improves, and they survive longer. The method of replacing the missing acetate to nerve cells for normal myelinisation is still in the research phase, with the chemical being glycerol triacetate [7]. Lithium citrate, on the other hand, drains the accumulating NAA from the glial cells – currently this is carried out in vitro only [8]. Studies with stem cells should be opened in the near future, which should offer even better prognoses to patients. The establishment of special treatment methods depends on the complications of the therapy, as well as on the incidence of the cases in individual states. With the increasing achievements of the research, specialised therapy should also be implemented in areas with low incidence of the disorder, thus improving the future prospects of patients and their families.

REFERENCES

1. Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov. /Omim/ Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD: MIM #*271900 CANAVAN DISEASE.
2. Matalon R, Michals K, Sebesta D, et al. Aspartoacylase deficiency and N-acetylaspartic aciduria in patients with Canavan disease. Am J Med Genet 1999; 87: 273–275.
3. Kaul R, Gao GP, Alova M, et al. Canavan disease: mutations among Jewish and non-Jewish patients. Am J Hum Genet 1994; 55: 34–41.
4. Toft PB, Geis-Holtorff R, Rolland MO, et al. Magnetic resonance imaging in juvenile Canavan disease. Eur J Pediatr 1993; 152: 750–753.
5. Ishiyama G, Lopez I, Baloh RW, Ishiyama A. Canavan's leukodystrophy is associated with defects in cochlear neurodevelopment and deafness. Neurology 2003; 60: 1702–1704.
6. Janson C, McPhee S, Bilaniuk L, et al. Gene therapy of Canavan disease: AAV–2 vector for neurosurgical delivery of aspartoacylase gene to the human brain. Hum Gene Ther 2002; 13: 1391–1412.
7. Mathew R, Arun P, Madhavarao CN, Moffett JR, Namboodiri MA. Progress toward acetate supplementation therapy for Canavan disease: glycerol triacetate administration increases acetate, but not N-acetylaspartate, levels in brain. J Pharmacol Exp Ther 2005; 315: 297–303. REpub 2005 Jul 7.
8. Baslow MH, Kitada K, Suckow RF, Hungund BL, Serikawa T. The effects of lithium chloride and other substances on levels of brain N-acetyl-L-aspartic acid in Canavan disease-like rats. Neurochem Res 2002; 27: 403–406.

Intensive care unit - nurse staff control centre

Evoked potentials laboratory