Effect of topiramate on enlargement of head in Canavan disease: a new option for treatment of megalencephaly

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Canavan disease (CD) is a rare autosomal recessive genetic disorder characterized by early onset progressive spongy degeneration of the brain involving the axon's myelin sheath. Patients with CD have leukoencephalopathy and megalencephaly; clinically they show a variable course ranging from slow neurodegenerative course to no neurological development or rapid regression. Current treatment is symptomatic including management of seizures and spasticity. Topiramate (TPM) is a novel antiepileptic drug for treatment of a broad spectrum of seizure types in adults and children. We used TPM in two of our patients diagnosed with CD at six months of age. At seven months and 15 months' follow-up, respectively, each patient showed a decrease in head growth velocity. We suggest that TPM can be used in patients with CD and possibly in other childhood neurodegenerative diseases with leukoencephalopathy and megalencephaly. Further studies are required to reveal the underlying mechanisms that lead to decreased head growth velocity, and to conclude whether this ameliorates the clinical course of CD.

Key words: Canavan disease topiramate, megalencephaly, leukoencephalopathy.

Canavan disease (CD) is a rare autosomal recessive genetic disorder characterized by early onset progressive degeneration of the brain[1]. Mutations in aspartoacylase gene located on short arm of chromosome 17, resulting in loss of enzyme activity, lead to an excess of N-acetylaspartate (NAA)[2,3]. The diagnosis can be confirmed by elevated NAA in the urine, blood and spinal fluid, and in the brain by using magnetic resonance spectroscopy, in a child presenting with megalencephaly, developmental delay and neurodevelopmental deterioration[3,4]. Prenatal diagnosis and genetic counseling are possible by molecular analysis when the mutations are known, and by analysis of amniotic fluid for NAA using stable isotope dilution technique[5].

The management currently is symptomatic, such as treatment of seizures and spasticity. Gene therapy protocols are under development[4-6]. A number of drugs and other substances have been reported to be able to reversibly modify the NAA content of the vertebrate brain in vitro. Ethanol and alcohol dehydrogenase inhibitors have been shown to reduce NAA levels of brain in mice in vivo[7]; however, the role of these agents in the treatment of CD is not established.

Topiramate (TPM) is a new antiepileptic drug effective for treatment of a broad spectrum of seizure types in adults and children. In vivo and in vitro preclinical studies indicate that TPM has multiple mechanisms of action and suggest a broad spectrum of anticonvulsant activity[8]. Results of placebo-controlled trials using TPM as adjunctive therapy in children 16 years of age or younger indicate that the most commonly reported adverse events were somnolence, anorexia, fatigue, and nervousness. During the double-blind portion of the placebo-controlled studies involving children, the use of TPM did not result in any discontinuations due to an adverse event[8].

We used TPM for the treatment of seizures in two of our patients with Canavan disease, taking into consideration its broad antiepileptic

spectrum, safety profile in children, and neuroprotective effect, to see whether TPM would have an effect on enlargement of the head, control of seizures, and the clinical course of the disease.

Case Reports

Case 1

This 13-month-old girl was first evaluated in our clinic at the age of six months with the complaints of enlargement of the head, developmental delay, and decreased alertness. Parents were first cousins. The family had two healthy children, a 12-year-old boy and a 10-year-old girl. Two male sibs with similar complaints died at eight months and nine months of age. Parents refused further evaluation at that time. Physical examination of our patient at the age of six months revealed a head circumference of 48 cm (>95p). She was unresponsive to the environment, had no head control and was unable to follow objects. She had spasticity and brisk deep tendon reflexes; plantar responses were extensor bilaterally. Clinical diagnosis of CD was confirmed by laboratory evaluation including urinary organic acid profile with an excretion of NAA, 1680 mmol/mol creatinine (Normal: 0-15 mmol/mol creatinine), and cranial magnetic resonance imaging (MRI) demonstrating diffuse involvement of cerebral and cerebellar white matter with brainstem involvement. She started to experience subtle seizures around six months of age and was placed on TPM 2 mg/kg. Her head circumference was 48 cm (>95p) at the age of seven months and 48.7 cm (>95p) at the age of 13 months. Her head-growth curve is shown in Figure 1. After initiation of TPM, her head growth velocity decreased, and she had no clinical seizures. Follow-up visits revealed optic atrophy, and persistence of spasticity. Developmentally she showed no gains compared to initial evaluation. The amount of NAA excretion in urine remained high at 1840 mmol/mol creatinine.

Case 2

This was a 21-month-old boy who presented to our clinic at the age of six months with the complaints of global developmental delays, no head control and megalencephaly. He had myoclonic jerks during sleep and episodes of cyanosis lasting for a few seconds. Pregnancy and delivery were uneventful. He was the first child, and his parents were relatives; family history was otherwise negative. Physical examination revealed a head circumference of

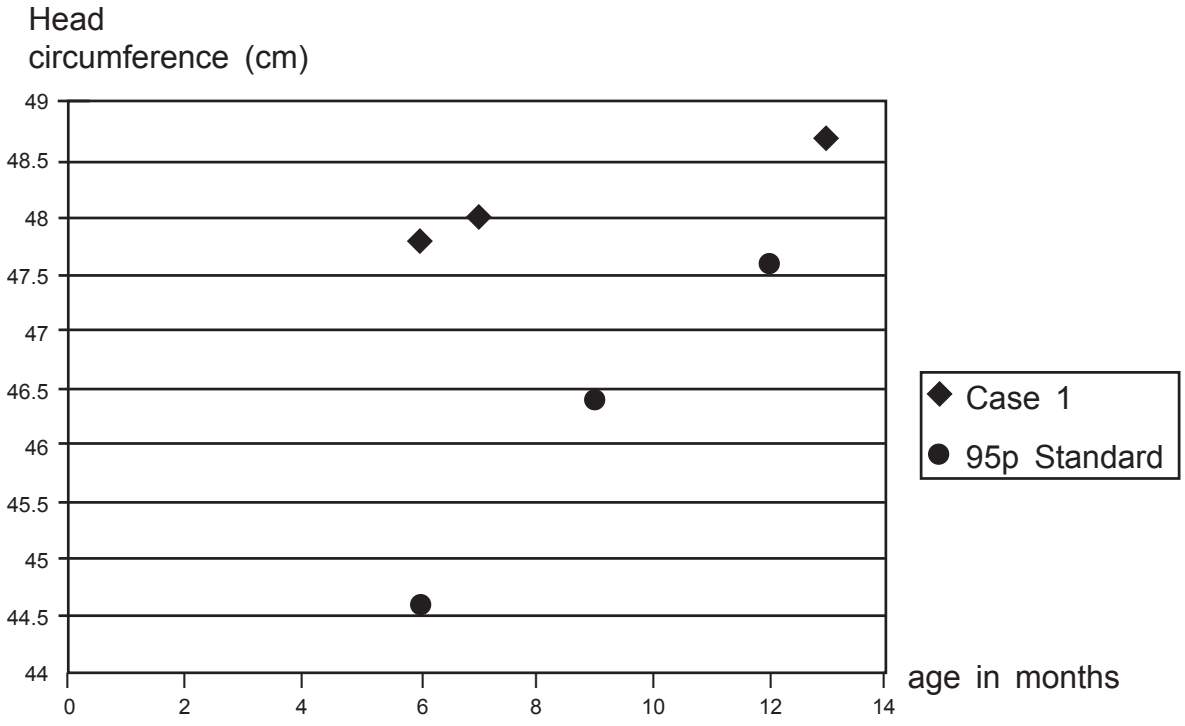

Fig. 1. Head circumference of case 1 compared to 95 p of standard.

47.5 cm (>95p), spasticity with increased deep tendon reflexes, and no head control. His urinary organic acid profile was consistent with CD. He was started on TPM 2 mg/kg at six months of age. Follow-up at 12 months and 21 months showed head circumference to be 50 cm (>95p), and 50.5 cm (>95p), respectively. His head-growth curve is shown in Figure 2. He began to recognize his mother at the age of 16 months; however, showed no further developmental gains. The amount of NAA excretion in urine was 2170 mmol/mol creatinine (N: 0-15). MRI of the head at the time of the diagnosis is shown in Figure 3.

Discussion

The pathogenesis of CD is characterized by degeneration of the axons' medullary sheaths, while the axons themselves remain intact. Further, there is elevated cerebrospinal fluid pressure, intramyelinic edema and a spongioform degeneration associated with swelling of astrocytes. These indicate a profound fluid inbalance in the brain. Deficiency of aspartoacylase, a lysosomal enzyme, results in accumulation of NAA, leading to NAA acidemia and NAA aciduria[9]. Currently there is no known function for NAA, and the treatment for CD is symptomatic including

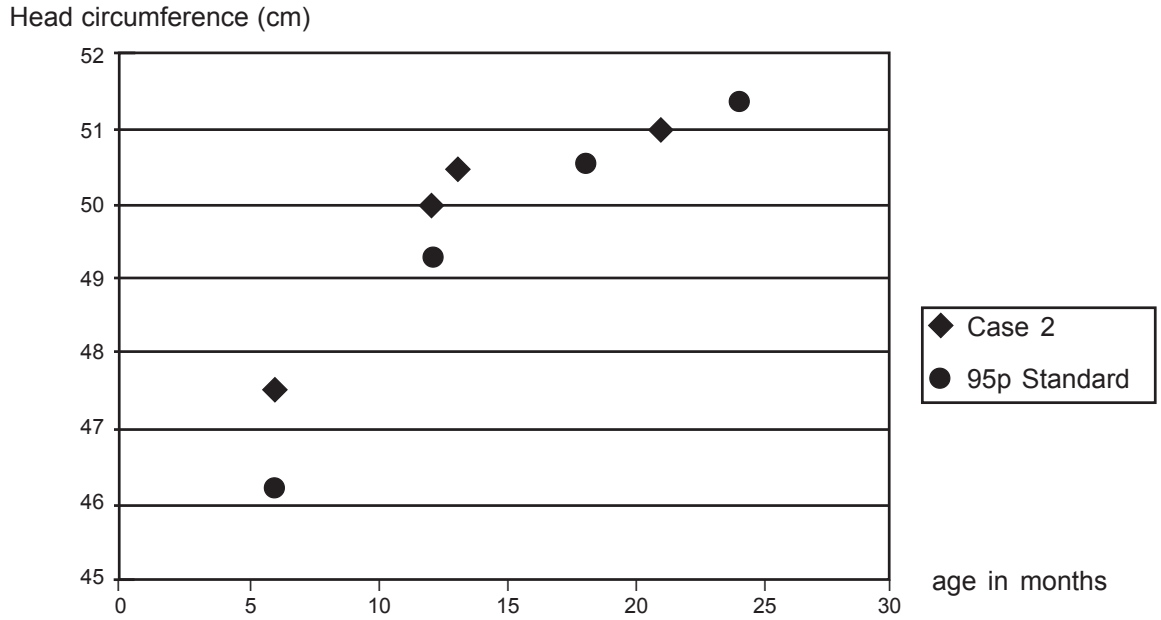

Fig. 2. Head circumference of case 2 compared to 95 p of standard.

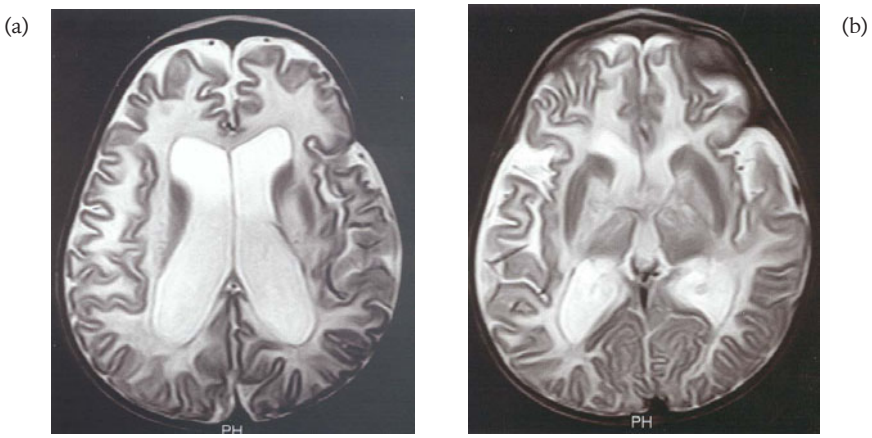

Fig. 3a-b. T2 weighted transverse images show enlargement of ventricles, involvement of cerebral white matter including u-fibers and globus pallidi. The thalami are also involved bilaterally.

management of seizures and spasticity. Baslow[10] attempted to explain the underlying pathophysiological mechanisms in CD and emphasized molecular water pumps. Baslow[10] proposed that in normal individuals the NAA-water that is liberated from the axon via an NAA-water co-transporter into the periaxonal water space between the axolemma and the surrounding oligodendrocyte or at the nodes is rapidly hydrolyzed by aspartoacylase on the myelin-containing membrane of the oligodendrocyte. After hydrolysis the aspartate and acetate can be actively taken up by astroglial processes that are present at the axon internodes and synapses, which may via additional astroglial processes also be connected to the blood system or the ventricular walls. In CD the observed absence of myelin-associated aspartoacylase on the juxtaposed glial-myelin membrane would result in the build-up of NAA-water in the space between the axon and the oligodendrocyte and increased hydrostatic pressure in that space. As NAA is not actively taken up by brain cells, the only pathway for NAA-water out of the axon-glial water space in CD is extracellular, between the axon-wrapped layers of the glial-myelin repeating lamellar membranes. It is proposed that in CD the continuous production and liberation of NAA-water from the axon would result in the intramyelinic edema that has been observed in this disease, the subsequent demyelination and loss of glial cells in the characteristic spaces, and in the spongy appearance of the white matter of the brain that is associated with advanced stages of CD.

In CD, macrocephaly is evident by six months, and at one year the head circumference is in the 90th percentile or above[11]. We observed that under treatment with TPM our patients showed a relative decline in head growth velocity, which we think could be due to decreased accumulation of water in the brain. Since our patients had persistent NAA acidemia while the head growth velocity decreased, we believe enlargement of the head ameliorated through a route that was not affected by the accumulation of NAA in the brain.

Preclinical studies indicate that TPM has at least four mechanisms of action that may contribute to its anticonvulsant activity[8]. These include the following: blockade of voltage-dependent NA+ channels, GABA potentiation through a novel or nonbenzodiazepine modulatory site, antagonism of a kainate subtype of the glutamate receptor, and inhibition of carbonic anhydrase. We believe the arrest of head growth velocity in our patients could have been due to TPM's effect on water transport in the brain. A trial with acetazolamide to reduce white matter concentration and NAA was tried for a period of five months. Acetazolamide was helpful in reducing the intracranial pressure, but did not reduce water concentration or NAA levels[12]. Therefore we think that the effect of TPM on water accumulation and head growth velocity may not be solely due to inhibition of carbonic anhydrase. We plan to obtain cerebral MRI and MR spectroscopy under treatment with TPM, to see if there are visible changes.

Long-term follow-up of patients is necessary to conclude whether arrested head growth will ameloriate the clinical course of the disease. NAA itself was shown to be neurotoxic[13], therefore one might conclude that preventing or decreasing water accumulation in the brain per se may not ameloriate all consequences of the disease. We suggest that studies on histological specimens and animal models of CD on the effect of TPM may be helpful not only for new treatment options for CD but also for other types of degenerative neurological disorders with leukoencephalopathy and megalencephaly.

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