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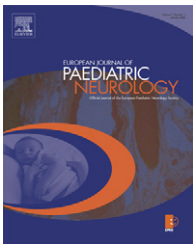

Case study

Proton MRS of a child with Sandhoff disease reveals elevated brain hexosamine

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ABSTRACT

Sandhoff disease (gangliosidosis type 0) is a lysosomal storage disorder with a deficiency of hexosaminidases A and B. After an initially normal development the clinical course of affected children is severe and rapidly progressive leading to spastic tetraparesis, epileptic seizures and early death. In a 10-month-old girl with enzymatically established diagnosis of Sandhoff disease MRI of the brain showed signal changes in the periventricular white matter, pyramidal tract, basal ganglia, and cerebellar hemispheres. Proton MR spectroscopy (MRS) at the age of 13 months revealed a reduction of total *N*-acetylaspartate (neuroaxonal marker) as well as strongly elevated inositol (glial marker) in white matter, gray matter, and basal ganglia. A new resonance at 2.07 ppm was detected in all regions and ascribed to *N*-acetylhexosamine with highest concentrations in white matter and thalamus. While conventional MRS findings are in line with neuroaxaonal damage and pronounced astrocytosis, the observation of *N*-acetylhexosamine appears as a specific marker of Sandhoff disease indicating accumulation of hexosamine-containing oligosaccharides. This interpretation is supported by a recent in vitro MRS study of a Sandhoff mouse model. In conclusion, proton MRS of cerebral metabolites offers specific insights into the pathopysiologic processes of children with Sandhoff disease and may prove to represent another disease specific MRS pattern of the brain.

1. Introduction

Gangliosidoses are inherited lysosomal diseases with a defect in the enzyme hexosaminidase which is responsible for removal of *N*-acetylgalactose from the complex ganglioside molecules. Types B, O, and AB refer to three distinct biochemical defects according to the respective enzyme deficiency. Sandhoff disease corresponds to type O and represents 7% of patients with GM2 gangliosidosis.[1] It is based on a deficiency of both A and B components of hexosaminidase and clinically indistinguishable from a classic Tay-Sachs type gangliosidosis. Clinical onset of Sandhoff disease is between 3 and 9 months of age. After an initially normal development children loose acquired milestones and

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the muscle tone becomes hypotonic. The course of the disease is rapidly progressive with early muscular hypotonia replaced by spastic tetraparesis and epileptic seizures. A cherry red spot is found in macular areas. Very rapidly the children are helpless.[2] Up to now no treatment is available.

GM2 gangliosidosis is primarily a neuronal disease diagnosed by the absence of hexosaminidase A or both A and B. Sandhoff disease is characterized by storage of glycosphingolipid and accumulation of oligosaccharides derived from glycoproteins.[3] MRI typically reveals hyperintensities in T2-weighted images of gray and white matter with involvement of thalamus and basal ganglia.[4] Kroll and co-workers reported white matter MRI changes in GM2-affected animals[5] which were very similar to those found in GM1 gangliosidosis.[6] An unusual presentation of Sandhoff disease was reported by Nassogne et al. with diffuse signal changes exclusively in the brainstem of a 3-year-old girl.[7] Recently, Lowe and co-workers found an additional 2.07 ppm resonance in proton MR spectra of the brain of Sandhoff mice which could be identified as originating from *N*-acetylhexosamine.[8] Here we report similar proton MRS findings in a child with enzymatically proven Sandhoff disease.

2. Case report

The girl, the first child of unrelated parents of German origin, was examined by proton MRS at the age of 13 months with the diagnosis Sandhoff disease already established. The family history was normal and the pregnancy was uneventful. Delivery was performed at term by caesarian section because of an inguinal hernia of the mother. Birth weight was 3400 g, length 50 cm, head circumference 32 cm.The neonatal period was normal.

At 8 weeks of age missing eye contact and at 3 months increased startle response was noticed. Muscle tone was reduced. An ophthalmologic investigation at the age of 9 months found a macula cherry red spot. Biochemical investigations revealed a complete absence of hexosaminidase A and B in blood cells (Prof. Harzer, Tübingen) and in fibroblasts (Prof. Sandhoff, Bonn). First seizures occurred at 12 months during a febrile illness.

At the age of 13 months the girl was of normal size, head circumference was 48 cm (90th percentile). Spontaneous movements were slow, the child was able to turn over, but

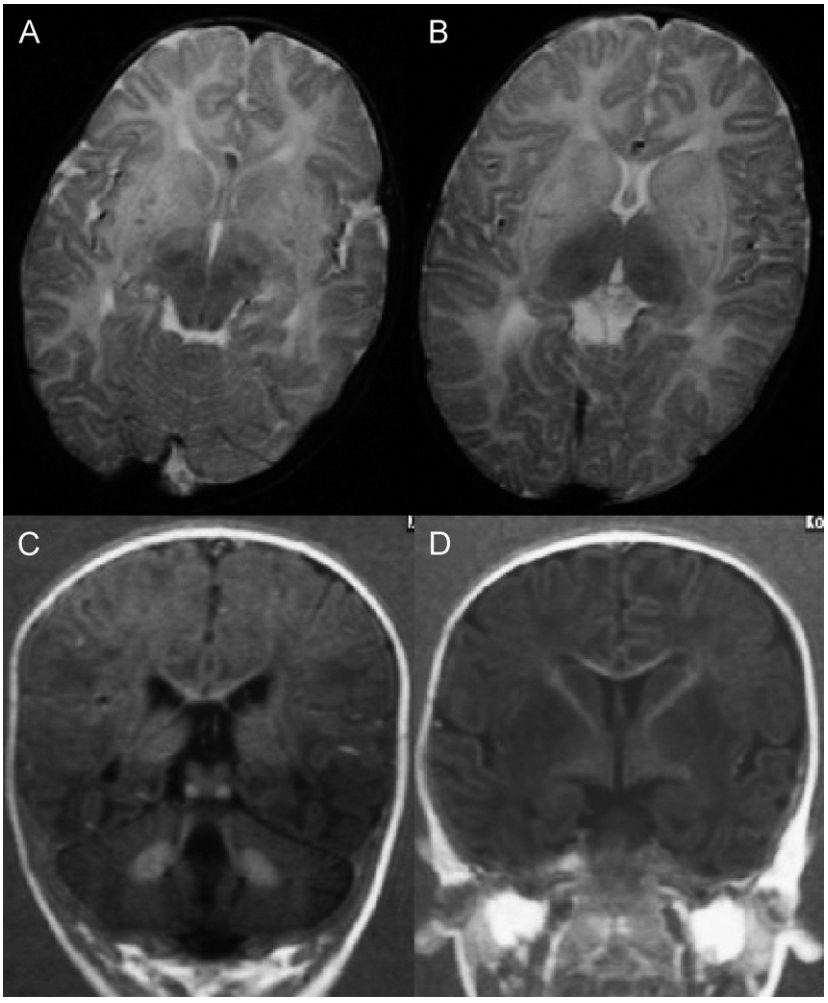

Fig. 1 – MRI of a child with Sandhoff disease with hyperintensities in (A,B) axial T2-weighted images of periventricular, frontal, and occipital white matter as well as in (C,D) coronal T1-weighted images of white matter and cerebellum (dentate nuclei).