EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 12 (2008) 56–60

Official Journal of the European Paediatric Neurology Society

Case study

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

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ARTICLE INFO

Article history:
Received 12 February 2007
Received in revised form
15 May 2007
Accepted 19 May 2007

Keywords:
MRS
Gangliosidosis
Lysosomal storage disorder
N-acetylhexosamine

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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doi:10.1016/j.ejpn.2007.05.008

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

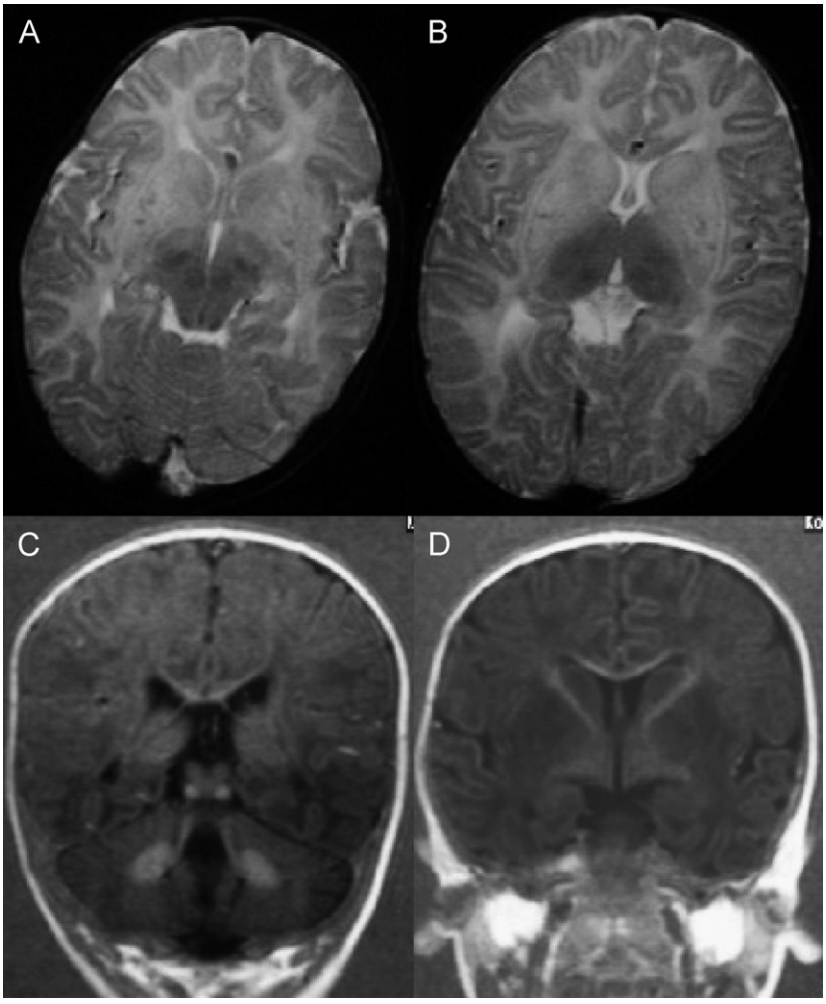

Fig. 1 – MRI of a child with Sandhoff disease with hyperintensities in (A,B) axial T2-weighted images of periventricular, frontal, and occipital white matter as well as in (C,D) coronal T1-weighted images of white matter and cerebellum (dentate nuclei).

preferred a supine position. There was marked truncal muscular hypotonia and an increased extensor tone in both legs. Reflexes were brisk, no Babinski sign was present. Visual attention was decreased and an intermittent rotating nystagmus was noticed in both eyes, whereas acustic reaction was prompt. Fundoscopy confirmed the macular cherry red spot.

There was no organomegaly or any other relevant abnormality on physical examination. Epileptic seizures were fairly well controlled by carbamazepine. Over the following years a slow regression of all mental and motor functions was observed. She died at the age of 3 1/2 years from pneumonia due to gastroesophageal refluxes and aspiration. Postmortem examination was not performed.

MRI at 1.5 T (Gyroscan, Philips, The Netherlands) was performed at the age of 10 months and included axial T2-weighted spin echo images as well as coronal T1-weighted inversion recovery images. Proton MRS at the age of 13 months was performed at 2.0 T (Magnetom Vision, Siemens, Germany) using the standard head coil. Fully relaxed short-echo time proton MR spectra (TR/TE = 6000/20 ms, 64 accumulations) were acquired using a single voxel stimulated echo acquisition mode (STEAM) localization sequence.[9] Volumes-of-interest (VOI) were located in the parietal–occipital white matter, thalamus, and basal ganglia (4.1 ml each) as well as in paramedian parietal gray matter (12 ml). Absolute quantification of metabolite concentrations was performed with use of LCModel.[10] Technical and biochemical details[9,11] as well as regional metabolite concentrations of age-matched controls[12] have been described elsewhere.

3. Results

As shown in Fig. 1 MRI showed extended T2 hyperintensities in periventricular, frontal, and occipital white matter. Further abnormalities were observed in basal ganglia including thalamus and the pyramidal tract as well as in the cerebellum especially in the dentate nuclei. Fig. 2 depicts proton MR spectra of the patient and a gray matter spectrum of an age-matched control. Almost all regions were characterized by reduced resonances of *N*-acetylaspartate and *N*-acetylaspartylglutamate (tNAA) and prominently elevated resonances of *myo*-inositol (Ins). In addition, a new spectral contribution next to the *N*-acetyl resonance of tNAA was discovered and provisionally labeled NAHex. While this resonance appeared as a shoulder in gray matter, it became even more evident in white matter and in thalamus but not in basal ganglia (Fig. 2). As demonstrated in Fig. 2, slightly resolution-enhanced white matter spectra of the patient yielded a resonance frequency of about 2.07 ppm.

Table 1 summarizes absolute metabolite concentrations of the child with Sandhoff disease in comparison to data from age-matched controls.[12] In agreement with the qualitative spectral findings, the quantitative analysis revealed reduced concentrations of tNAA in all investigated regions except the thalamus. The concentration of choline-containing compounds (Cho) was within normal ranges in all regions, while creatine and phosphocreatine (tCr) levels were elevated in white matter and reduced in basal ganglia. Ins was strongly elevated in white matter, gray matter, and thalamus, where *scyllo*-inositol (Sc) was enhanced well above detectability as well. The new resonance NAHex was present in all regions and, based on the assumption of an *N*-acetyl group, had a concentration of about 1–3 mM.

4. Discussion

In agreement with recent findings by Lowe et al. in a Sandhoff mouse model[8] we identified an identical proton MRS resonance in white matter, gray matter, basal ganglia, and thalamus of a child with enzymatically proven Sandhoff disease. Based on high-resolution proton NMR spectroscopy of perchloric acid (PCA) extracts of the brains of Sandhoff mice, the new resonance has been assigned to the *N*-acetyl

Table 1 – Absolute metabolite concentrations (mean ± SD in mmol/l VOI) of a child with Sandhoff disease in comparison to age-matched controls (0.5–1.5 years; for thalamus 0.3–2.9 years)

	tNAA	tCr	Cho	Ins	Sc	NAHex
White matter						
Right	4.2*	6.3*	1.7	8.5*	0.7**	2.7**
Left	4.6*	6.2*	1.6	6.3*	n.d.	2.2**
Control ($n = 12$)	6.4 ± 0.6	5.1 ± 0.5	2.0 ± 0.2	3.6 ± 0.5	n.d.	n.d.
Gray matter						
PMP	3.9*	6.6	1.6	8.0*	0.5**	1.3**
Control ($n = 8$)	6.8 ± 0.8	5.7 ± 0.7	1.3 ± 0.2	4.3 ± 0.4	n.d.	n.d.
Basal ganglia						
Left	3.9*	5.9*	1.7	4.3	n.d.	1.7**
Control ($n = 6$)	7.1 ± 0.8	7.4 ± 0.4	1.9 ± 0.2	3.7 ± 0.5	n.d.	n.d.
Thalamus						
Right	5.4	7.1	2.3	10.1*	1.1**	2.3**
Control ($n = 7$)	6.3 ± 1.3	6.9 ± 1.1	1.9 ± 0.3	4.1 ± 1.3	n.d.	n.d.

*>2 SD from controls.
**Elevated in comparison to controls where concentrations were not detectable (n.d.).
PMP: paramedian parietal.

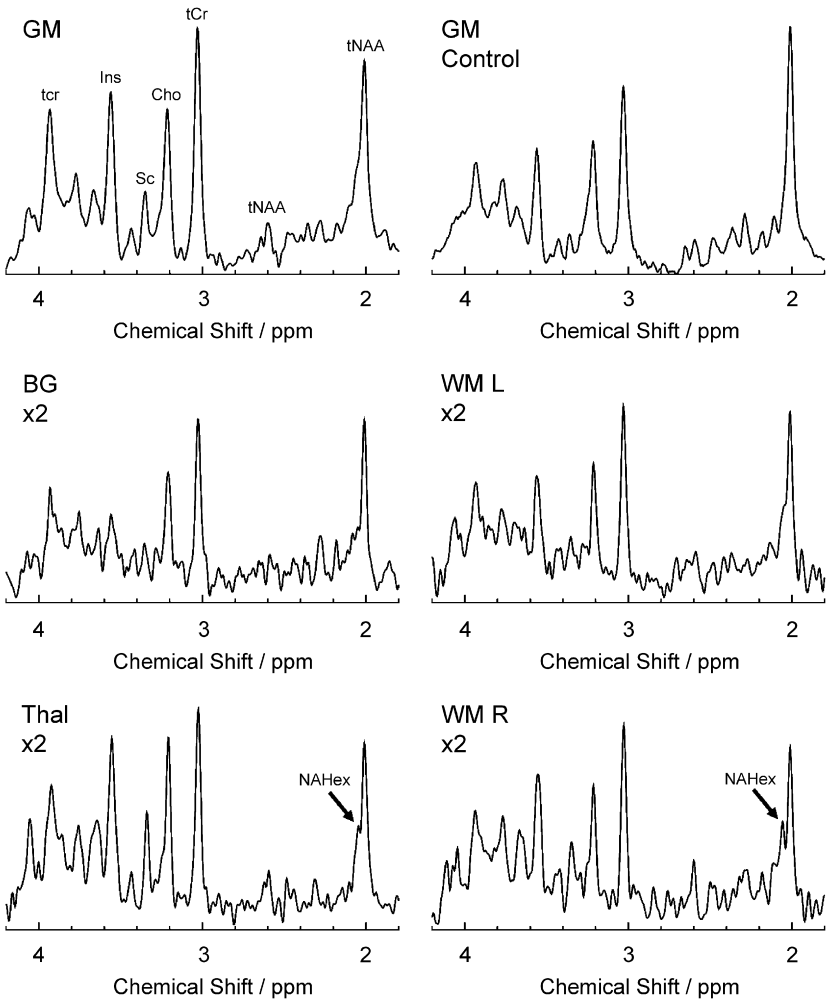

Fig. 2 – Proton MR spectra of a child with Sandhoff disease in paramedian parietal gray matter (GM), basal ganglia (BG), thalamus (Thal), and white matter (WM) in the left (L) and right (R) hemisphere together with a GM spectrum of a control showing resonances from *N*-acetylaspartate and *N*-acetylaspartylglutamate (tNAA), creatine and phosphocreatine (tCr), choline-containing compounds (Cho), *scyllo*-inositol (Sc), and *myo*-inositol (Ins). NAHex (arrows) refers to the newly detected resonance from *N*-acetylhexosamine.

moiety of *N*-acetylhexosamine (NAHex) which is a constituent of brain oligosaccharides. The proton MRS observation of NAHex in a patient with Sandhoff disease demonstrated here therefore directly relates to the pathophysiology of this rare inborn error of metabolism which is known to accumulate substances in the lysosomes of affected CNS cells. In fact, the present findings directly suggest the accumulation of oligosaccharides containing NAHex in cortical and subcortical gray matter as well as in white matter. The complementary metabolite pattern of reduced tNAA, a marker for intact neuroaxonal tissue,[13] and elevated Ins, a glial marker predominantly found in astrocytes,[14,15] is in line with neuroaxonal damage and gliosis as generalized signs of tissue degeneration similar to what has been described in other (demyelinating) brain disorders, for example in adrenoleukodystrophy.[16]

In the Sandhoff mouse model no correlation was found between the level of oligosaccharides and disease severity.[8] However, the described NAHex resonance became more pronounced in clinically terminal stages and, in a different study, the amount of stored glycosphingolipid has been reported to increase dramatically with disease progression.[17] In addition, it should be emphasized that the NAHex resonance in the in vitro MRS study of the Sandhoff mouse was already seen in presymptomatic animals. Thus, knowledge about the NAHex resonance may be of direct clinical relevance as MRS is increasingly used in children and adults for diagnostic reasons but also for supervising treatment stategies. At present, however, the detectability of NAHex in presymptomatic Sandhoff patients remains to be evaluated, before it can be considered as a specific finding.

Acknowledgments

We thank Prof. Harzer (Tübingen) and Prof. Sandhoff (Bonn) for permission to report their results and Dr. Waltz (Cologne)

for providing follow-up data. P. Dechent was supported by the VolkswagenStiftung.

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