Ocular bobbing is a descriptive term for abnormal vertical eye movements that are usually seen during coma, anoxia, status epilepticus, and metabolic encephalopathy, and it implies a poor prognosis.[10] So ocular bobbing never develops in normal infants like our patients. Epileptic attacks might be another possible cause. The downward gazing is so episodic that it can be confused with epileptic seizures. We could not rule out epilepsy in case 2 because an ictal EEG was not performed. However, his clinical episodes seemed to be a reflex, and even if they represented epilepsy, it could have been benign because the episodes ceased spontaneously.

The "setting sun" phenomenon associated with hydrocephalus probably results from pressure-induced dysfunction of the vertical gaze centers in the tectum. However, this is not a probable mechanism in normal healthy infants. During infancy, motor activity largely comprises a reflex and postural reaction. Although the mechanism underlying the downward gazing in normal neonates and infants is unknown, the "setting sun" phenomenon might be related to the presence of a normal oculocephalic response. I considered that it might represent a maturation delay in one of the reflex systems involved in eye movements, and benign "setting sun" phenomenon probably occurs more frequently than has been reported. In conclusion, this report suggested that the phenomenon occurs by 6 or 7 months of age even in normally developed infants.

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Infantile Sandhoff's Disease: Multivoxel Magnetic Resonance Spectroscopy Findings

ABSTRACT

Sandhoff's disease is a rare, genetic lysosomal storage disease leading to delayed myelination or demyelination. Although neuroimaging findings in this disease have been reported previously, magnetic resonance spectroscopy findings have not been reported. In this report, we present magnetic resonance imaging and magnetic resonance spectroscopy features of two cases with Sandhoff's disease. Magnetic resonance spectroscopy revealed findings indicating widespread demyelination in both cases and neuroaxonal loss and anaerobic metabolism in the second case. Magnetic resonance spectroscopy could provide useful information in the explanation of the clinical picture of cases with Sandhoff's disease. (*J Child Neurol* 2003;18:425–428).

Sandhoff's disease is an extremely rare, autosomal recessively transmitted lysosomal storage disease.[1–3] Lysosomal hydrolase β-hexosaminidase activity deficiency is the metabolic basis of Sandhoff's disease.[4] Although systemic findings are not specific, delayed myelination and myelin breakdown are the most important neurologic involvement features of this disease.[5] Central nervous system imaging reveals diffuse white matter, which is more prominent, and gray-matter involvement. But there is a lack of correlation between neuroimaging findings and clinical presentation.[1] Magnetic resonance spectroscopy could show the metabolic consequences of disease processes. To determine the possible metabolic changes owing to specific enzyme deficiency, we performed multivoxel proton magnetic resonance spectroscopy in two cases (a 30-month-old boy and a 28-month-old girl) with an enzymatically proven diagnosis of Sandhoff's disease. To our knowledge, this is the first report of the proton magnetic resonance spectroscopic features of Sandhoff's disease.

Case 1

A 30-month-old boy was admitted to hospital owing to generalized tonic-clonic seizures. He was born after a full-term, uncomplicated pregnancy. His parents were first-degree relatives. His first admission to hospital was at 9 months, at which time hypotonia, macrocephaly, development delay, and augmented startled response to noise were present. Fundoscopy at the first admission revealed cherry red spots at the maculae. Light reflexes were sluggish. At the present admission, his weight was 9800 g (< 3rd percentile), height was 82 cm (3rd–10th percentile), and head circumference was 52 cm (> 97th percentile). His consciousness was confused. Mild hypertonic spasticity and quadriparesia were noted. Deep tendon reflexes were hyperactive. An electroencephalogram (EEG) was normal. Hepatomegaly was present.

Case 2

A 28-month-old girl was admitted to hospital owing to frequent lung infection. She was born after a full-term, uncomplicated pregnancy. There was no consanguinity between her parents. Past medical history revealed macrocephaly, developmental delay, hypotonia, and augmented startle response to noise, which were diagnosed at 7 months. After 12 months, she developed spastic quadriplegia. Fundoscopy at the first admission revealed cherry red spots at the maculae. The opticokinetic response was absent. Her

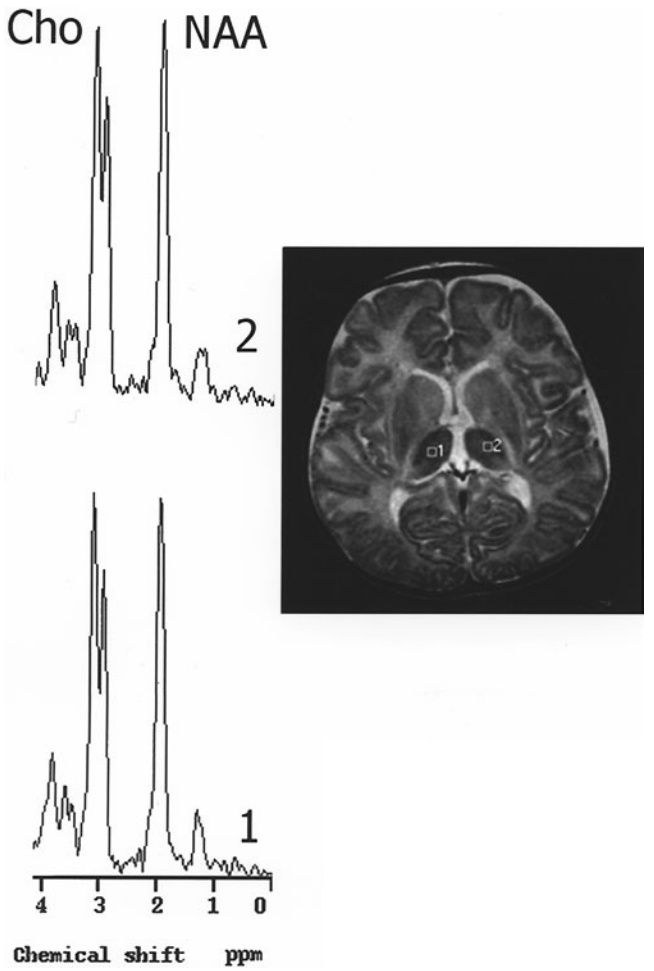

Figure 1. Magnetic resonance spectra (TR: 1500, TE: 136 ms) obtained from the thalami demonstrate increased choline (Cho) and normal *N*-acetylaspartate (NAA).

weight, height, and head circumference were 7700 g (< 3rd percentile), 80 cm (3rd percentile), and 51 cm (> 97th percentile), respectively.

Both Cases

In both cases, routine laboratory examination revealed that the consciousness was confused. Deep tendon reflexes were hyperactive. Slow-wave activity on the EEG was normal. Serum and leukocyte total hexosaminidase levels were found to be decreased. The patients were diagnosed as having Sandhoff's disease (gangliosidosis GM_2).

Magnetic resonance imaging (MRI) was performed on a 1.5 Tesla system (Philips, Gyroscan Intera Master, Best, The Netherlands). T_1-weighted images (TR: 560, TE: 15) were obtained in the axial and sagittal planes (with 5 mm thick slices). T_2-weighted images (TR: 4530, TE: 100) were obtained in the axial and coronal planes. They were sedated with chloral hydrate (dose, 50 mg/kg of body weight). MRI in both cases revealed involvement in cerebral white and cortical gray matter, cerebellar white matter, and bilateral internal and external capsules on T_2-weighted images. There was also diffuse thinning of the corpus callosum and cerebellar atrophy and cerebral cortical atrophy in both cases. Whereas the hypointensity was observed only in the bilateral thalamus in case 1, it was noted in both the bilateral thalamus and basal ganglia in case 2 on T_2-weighted images.

Multivoxel proton magnetic resonance spectroscopy data sets were acquired by using point-resolved spectroscopy with acquisition parameters of 1500/136/1 and a transverse field of view 230 mm with a 16 × 16 rectangular sampling array. After three orthogonal base images were obtained with automatic shimming of the magnetic field, a 30 mm thick volume of inter-

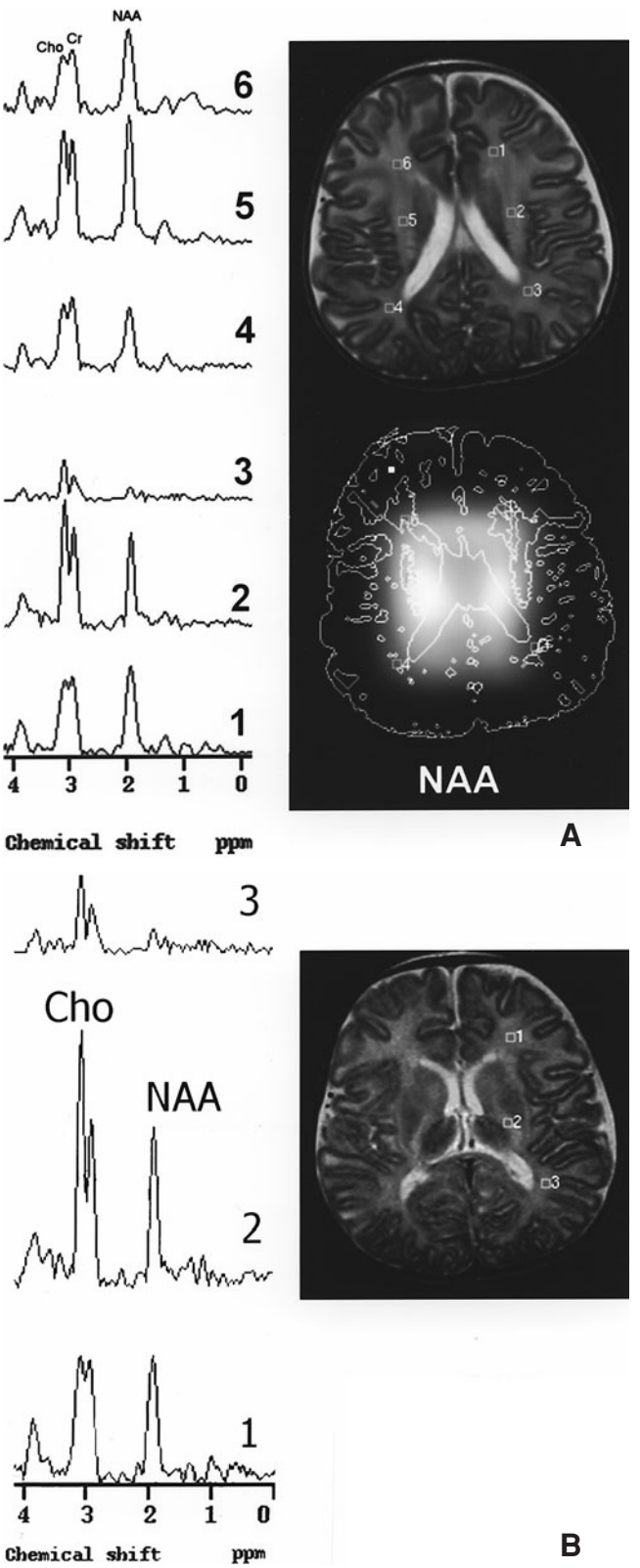

Figure 2. *A,* Magnetic resonance spectra (TR: 1500, TE: 136 ms) obtained from the periventricular white matter show increased choline (Cho) (2, 3, 5). Also, the *N*-acetylaspartate (NAA) decrease in the left parietal white matter is noted. *B,* Magnetic resonance spectra obtained from the left occipital white matter (3) and the left posterior limb of the internal capsule (2) demonstrate increased choline and decreased *N*-acetylaspartate. Frontal white matter (1) shows increased choline and normal *N*-acetylaspartate. Cr = creatine.

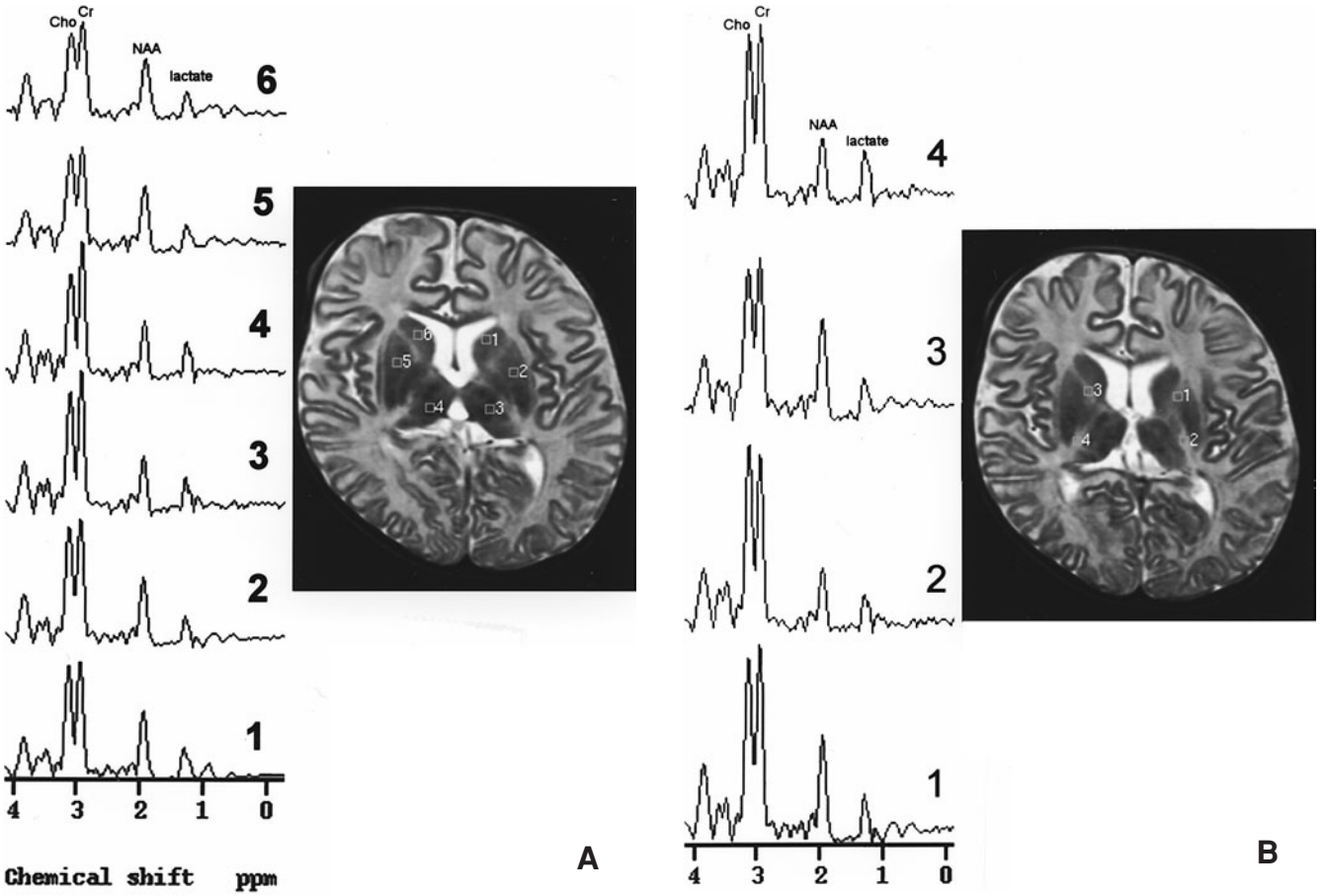

Figure 3. *A,* Magnetic resonance spectra (TR: 1500, TE: 136 ms) obtained from the thalami and basal ganglia show decreased *N*-acetylaspartate and moderately increased choline (Cho) and lactate. More prominent neuronal loss is observed in the thalami. *B,* Magnetic resonance spectra show a more prominent increase in choline and a decrease in *N*-acetylaspartate in the posterior limb of the left internal capsule (2). Cr = creatine.

est was identified. The volume of interest was placed to cover the basal ganglia, thalamus, and periventricular white matter. Multivoxel proton magnetic resonance spectroscopy data were accumulated after the optimal water signal was suppressed by the chemical shift-selective technique. The whole examination, including MRI and multivoxel proton magnetic resonance spectroscopy, was completed within approximately 30 minutes.

Multivoxel protein magnetic resonance spectroscopy in case 1 showed a moderate choline increase in the periventricular white matter, internal and external capsules, basal ganglia, and thalami (Figure 1). Choline increase was prominent in the internal capsule. Chemical shift imaging demonstrated a prominent *N*-acetylaspartate decrease in the posterior white matter. Also, *N*-acetylaspartate was found to be decreased in the posterior limb of the left internal capsule and left parieto-occipital white matter (Figure 2).

In case 2, multivoxel proton magnetic resonance spectroscopy revealed an increase in choline and lactate and a decrease in *N*-acetylaspartate in the basal ganglia, thalami, cerebral white matter, and internal capsule. Chemical shift imaging showed an increase in choline in the periventricular white matter. An increase in choline and a decrease in *N*-acetylaspartate were more prominent in the left posterior limb of the internal capsule and left thalamus (Figure 3).

Discussion

Sandhoff's disease is the severe form of gangliosidosis GM_2, which is an inherited disorder of sphingolipid metabolism. It is characterized by an autosomal recessive pattern of inheritance. The deficiency of both hexosaminidase A and B is the main cause of this disease.[1] Intracellular accumulation of lysosomal enzyme substrates, ganglioside GM_2, and other glycolipids are present in Sandhoff's disease and cannot be eliminated from the cells in which they are produced.[1] Additionally, lysosomal swelling and cellular destruction lead to neurologic dysfunction and usually death.[1,3] Progressive psychomotor retardation, macular red cherry spot, blindness, startle reaction, and hypotonia are the main clinical features. Sandhoff's disease is classified clinically into acute, subacute, and chronic forms. The acute, infantile-onset form is a rapidly progressive neurodegenerative process and leads to death by 4 years of age.[4] Early onset of symptoms, usually in the first 6 to 18 months of life, is a characteristic feature of the infantile form of Sandhoff's disease.[2]

There is no definitive treatment for Sandhoff's disease other than supportive therapy. Also, there is no correlation between the severity of the central nervous system imaging findings and the clinical presentation.[1] Although this is the case, the determination of neuroimaging features of Sandhoff's disease is important from the point of diagnosis and follow-up.

In the histopathologic studies, it was reported that decreased cross-sectional width of white matter was especially apparent in

the internal capsule and subcortical white matter, regions known to myelinate later in development. These findings support a developmental delay in maturation of white matter. MRI could reveal changes in the myelination of white-matter tracts that might be secondary to neuronal damage.[3] Also, the cerebral white matter shows homogeneous or patchy high signal intensity, suggesting a combination of delayed myelination and demyelination. Mild cortical atrophy, corpus callosum thinning, and abnormal signal intensities in the cerebral white matter, caudate nucleus, globus pallidum, putamen, cerebellum, and brain stem are among the reported neuroimaging features of Sandhoff's disease in the literature.[1,3,6] MRI findings in our case were consistent with the reported features of Sandhoff's disease. Additionally, we have noted cortical gray-matter involvement on T_2-weighted images.

Thalamic involvement, hypointensity on T_2-weighted images, had frequently been stressed in the literature and regarded as an early, specific finding of gangliosidosis GM_2.[1,3] An accumulation of calcium, associated with the intracellular storage of GM_2 ganglioside, loss of axon and myelin in the central cortical neurons, and gliosis were suggested to be the causes of hypointense thalami.[5,7] In addition to bilateral thalamic involvement, there was hypointensity, probably owing to calcium accumulation, in the bilateral basal ganglia in case 2.

Information on neuronal/axonal viability, cellular energetics, and cellular membrane status could be obtained by magnetic resonance spectroscopy.[8] Because most of the pathologic conditions demonstrate a combination of processes, such as demyelination, neuronal dysfunction, and anaerobic glycolysis, magnetic resonance spectroscopy could help in recognizing these processes. Changes in *N*-acetylaspartate to creatine and choline to creatine ratios in children with developmental delay could reflect underlying abnormalities of myelination or hypomyelination.[9] Choline elevations could indicate myelin abnormalities, and normal *N*-acetylaspartate levels could be attributable to absence of neuroaxonal loss. The increase in the choline to creatine ratio might point to an inability to properly incorporate choline-containing molecules into myelin. Also, loss or disruption of normal myelin increases the availability of choline-containing compounds.[9] The effects of a decreased *N*-acetylaspartate to creatine ratio owing to damaged myelin, loss of normal myelin, or decreased numbers of normal neurons were not apparent on MRI but were detectable with magnetic resonance spectroscopy. The increased lactate peaks could indicate anaerobic metabolism.

Magnetic resonance spectroscopy in case 1 revealed choline elevation and normal *N*-acetylaspartate in the frontal and cerebellar white matter, thalami, and basal ganglia. These findings could indicate demyelination and absence of neuroaxonal loss. Additionally, a decrease in *N*-acetylaspartate in the left posterior limb of the internal capsule and parieto-occipital white matter might support demyelination and neuronal loss. Magnetic resonance spectroscopy in case 2 demonstrated findings (a decrease in *N*-acetylaspartate and an increase in lactate and choline in the basal ganglia, thalamus, cerebral white matter, and internal capsule) that could be interpreted as neuroaxonal loss and anaerobic metabolism in addition to demyelination. These findings were more prominent in the posterior limb of the left internal capsule and left thalamus. Although MRI findings in both cases were almost similar to each other, these findings did not correlate well with the clinical picture. On the other hand, we have demonstrated different metabolite changes in the involvement areas. Whereas there was only demyelination in the basal ganglia and thalami in case 1, there were anaerobic glycolysis and neuroaxonal loss in addition to demyelination in these regions in case 2.

Our magnetic resonance spectroscopy findings were consistent with the clinical picture of Sandhoff's disease. For that reason, we believe that magnetic resonance spectroscopy could play an important role in the determination and follow-up of metabolic changes in the brains of infants with the diagnosis of gangliosidosis GM_2.

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