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# Proton MR Spectroscopy of Sjögren-Larsson's Syndrome

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**Summary:** We performed single-voxel proton MR spectroscopy ( $^1\text{H-MRS}$ ) in two children with Sjögren-Larsson's syndrome (SLS). Both patients showed two abnormal spectral peaks at 1.3 ppm and 0.9 ppm that were obtained with short echo times. These two abnormal spectral peaks were seen in high-intensity areas on T2-weighted images and also in basal ganglia of normal intensities.  $^1\text{H-MRS}$  may be useful for establishing the diagnosis and investigating the natural history of SLS, and for evaluating the efficacy of therapeutic approaches to SLS.

Sjögren-Larsson's syndrome (SLS) (McKusick 270200) is a metabolic disorder inherited as an autosomal recessive trait and is characterized by congenital ichthyosis, mental retardation, and spastic diplegia or tetraplegia. SLS patients have impaired fatty alcohol oxidation caused by deficient activity of fatty aldehyde dehydrogenase (FALDH), whose gene was recently mapped to chromosome 17p11.2 (1). Accumulation of long-chain fatty alcohol (ie, hexadecanol; octadecanol or phytol or both), which is detectable by chemical-shift analysis, is thought to be responsible for the cutaneous and neurologic symptoms of SLS (2, 3).

## Case Reports

### Patient 1

A 6-year-old Japanese girl was born at 35 weeks' gestation after a normal pregnancy and delivery. Birth weight was 2530 g. Ichthyosis initially was seen at birth and gradually worsened. Her mental and motor development was delayed. She was able to control her head and roll over at the age of 8 months and sat with support at 1 year. Spastic diplegia was noticed at this time, and physical therapy was started. She never gained the ability to walk or stand. Head CT and EEG revealed no abnormalities when she reached 1 year of age, but repeat CT at 2 years of age showed diffuse low-density areas in the white matter, and repeat EEG showed high-voltage slow waves predominantly in bilateral occipital areas. Brain MR im-

aging at the age of 2 years 6 months revealed abnormal high-signal lesions on T2-weighted images in the cerebral white matter. Her fibroblast enzyme activities were compatible with SLS (Table). Family history showed consanguinity, but there were no other relatives with SLS. MR imaging and  $^1\text{H-MRS}$  were performed when the patient reached 5 years of age (Fig 1). T2-weighted images revealed white matter disease involving the frontal and parietal lobes. MR spectra were collected from the frontal white matter, the basal ganglia, the parietal area containing the gray matter, and the cerebellar white matter (Fig 1). All spectra, obtained with 18-millisecond echo times, showed two abnormal spectral peaks with chemical shifts of 0.9 ppm and 1.3 ppm in the region expected for lipids (Fig 1B). The 1.3-ppm peak was high and sharp and did not disappear even when an echo time of 270 milliseconds was used. In contrast, the 0.9 ppm peak was lower and slightly broader than that of the 1.3-ppm peak, and it disappeared when an echo time of 140 milliseconds was applied. These two abnormal spectral peaks were seen not only in the high-intensity area of cerebral white matter on T2-weighted images, but also in the basal ganglia, which showed no abnormal intensity on MR images, and in the cerebellum. CSF fatty alcohol levels were analyzed by the method introduced by Rizzo et al (3). Fatty alcohols, however, could not be detected.

### Patient 2

A 5-year-old Japanese boy was born after an uneventful pregnancy and delivery at 35 weeks' gestation. There was no consanguinity. Birth weight was 2598 g. He showed congenital ichthyosis. Mental and motor retardation was noticed first at 8 months of age, and spastic diplegia was observed at 1 year. Between 9 months and 16 months of age, he experienced three episodes of convulsions associated with fever, which prompted therapy with anticonvulsant drugs. An EEG was normal. Brain MR imaging at 17 months of age showed abnormal high-intensity areas on T2-weighted images in the cerebral white matter. He had profoundly deficient FALDH enzyme activity in his skin fibroblasts (Table), and enzyme activity in cells from his parents showed heterozygote compatibility with SLS (data not shown). Mutation analysis of the FALDH gene in this child showed that he carried two deletions leading to premature termination of translation (1).  $^1\text{H-MRS}$  and MR imaging were performed at 4 years of age (Fig 2). MR spectra were obtained in the same manner as for Patient 1. The pattern of peaks and changes with different echo times was almost the same for both patients. The ratio of *N*-acetyl aspartate (NAA)/creatine (Cr) of Patient 2 was smaller than that of Patient 1. CSF fatty alcohols were not detected in this patient either.

$^1\text{H-MRS}$  measurements were performed on a 1.5-T whole-body scanner using a standard head coil. Water-suppressed  $^1\text{H}$  spectra were obtained using a chemical shift selective (CHESS) excitation (4). Volume-selective  $^1\text{H-MRS}$  was performed with a stimulated echo acquisition mode (STEAM) and point-resolved spectroscopy (PRESS). Acquisition parameters were 2000/18 (TR/TE), 2000/140, and 2000/270. The spectra were obtained on 256 averages. The volumes of interest were defined in several regions between 1 and 8 mL. Data processing was performed with SAGE software.

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TABLE: Enzyme activities in cultured skin fibroblasts of the SLS patients

| Enzyme                             | Patient 1 | Patient 2 | SLS       | (pmol/min/mg protein)<br>Normal<br>Controls |
|------------------------------------|-----------|-----------|-----------|---------------------------------------------|
| Fatty alcohol: NAD+ oxidoreductase | 2.4       | 5.0       | 5.8 ± 2.5 | 75.1 ± 13.4                                 |
| Fatty aldehyde dehydrogenase       | 221.0     | 634.0     | 692 ± 402 | 8540 ± 1158                                 |

Discussion

SLS patients have deficient activity of fatty aldehyde dehydrogenase, a component of the fatty alcohol NAD+ oxidoreductase complex that is necessary for oxidation of fatty alcohol to fatty acid (5). Accumulation of long-chain fatty alcohol is thought to be responsible for neurologic disease in SLS, but pathogenetic mechanisms leading to the development of spasticity and mental retardation

are still unclear (6). Neuropathologic studies of SLS have shown ballooning of myelin sheaths, widespread loss of myelin, accumulation of sudanophilic fat droplets throughout the gray mater, and periodic acid Schiff–positive staining of the neurons and macrophages around vessels (7, 8). Nevertheless, the lipid composition of the brain in SLS has not been reported.

Miyanomae et al (6) first described the results of <sup>1</sup>H-MRS in a 20-year-old bedridden patient with SLS. <sup>1</sup>H-MRS (2000/135 [TR/TE]) revealed a high-lipid spectral peak of 1.3 ppm. In our two child patients with SLS, <sup>1</sup>H-MRS (2000/18 [TR/TE]) revealed two spectral peaks at 1.3 ppm and 0.9 ppm. Although the prominent sharp peak at 1.3 ppm is the same one that Miyanomae and colleagues observed, the low and slightly broad spectral peak at 0.9 ppm has not been recognized previously. When a longer echo time was applied, the height of the spectral peak at 1.3 ppm decreased but did not disappear even when an echo time of 270 milliseconds was used. In contrast, the lower

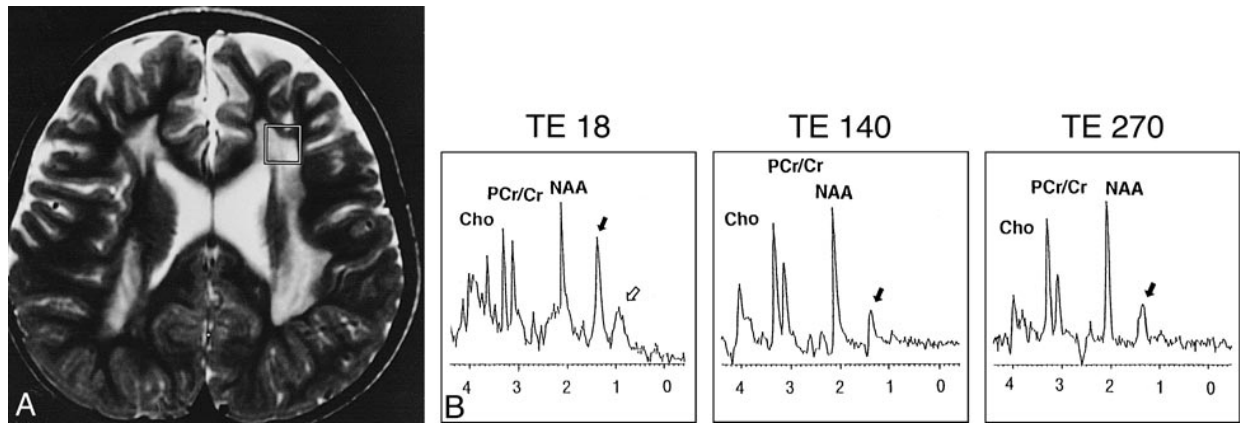


FIG 1. T2-weighted MR imaging (A) (4000/90 [TR/TE]) and <sup>1</sup>H-MRS (B) in the deep white matter of the frontal lobe in Patient 1. The volumes of interest are indicated by square boxes. The spectra using longer echo times (140 and 270 ms) also showed the extra peaks at 1.3 ppm (black arrow) and at 0.9 ppm (white arrow). Note.—Abbreviations: NAA, *N*-acetyl aspartate; PC, phosphocreatine; Cr, creatine; Cho, choline.

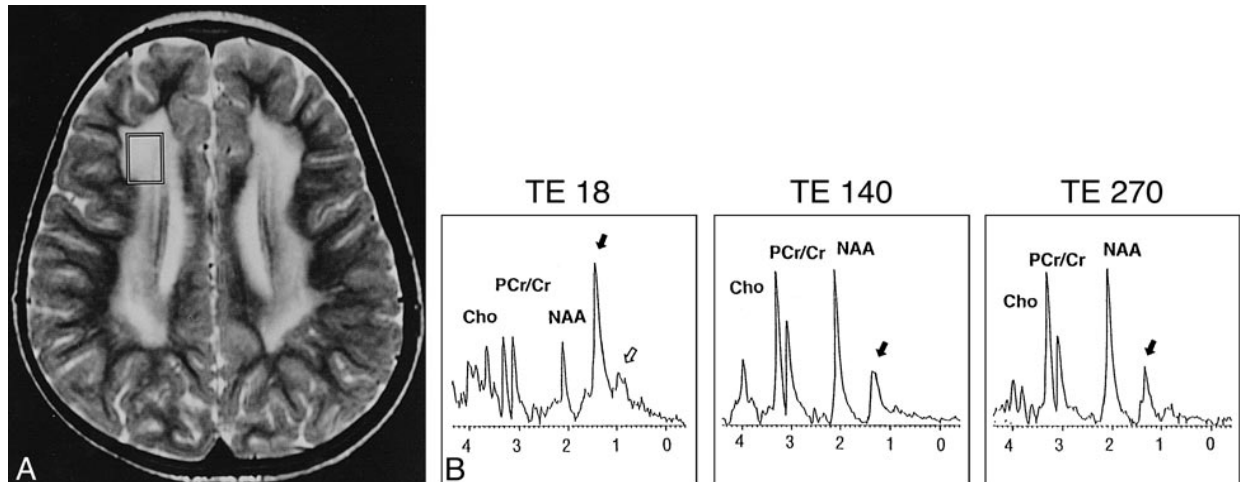


FIG 2. T2-weighted MR imaging (A) (4000/90) and <sup>1</sup>H-MRS (B) in the deep white matter of the frontal lobe in Patient 2. <sup>1</sup>H-MR spectra were similar to those shown in Figure 1B.

spectral peak at 0.9 ppm disappeared with an echo time of 140 milliseconds. From these data, the spectral peak at 1.3 ppm in SLS patients seemed to be more specific for the disease than was a 0.9 ppm spectral peak.

The spectra of 1.3 ppm and 0.9 ppm of  $^1\text{H}$ -MRS are thought to be assigned to the methylene and methyl groups of lipid, respectively. Although abnormal lipid spectra on  $^1\text{H}$ -MRS have been seen in several diseases, the spectral peaks were usually broad and disappeared on long TE sequences. To our knowledge, high peaks at 1.3 ppm and 0.9 ppm have been observed in multiple sclerosis (9) and Zellweger's syndrome (10). Both peaks were observed only on short TE sequences and appeared relatively broad. Davie et al (9) speculated that they represented breakdown of products of myelin secondary to demyelination. The spectral peak at 1.3 ppm found in our SLS patients is probably not the same as that observed by Davie et al because of its stability on long echo times. Miyanomae and colleagues (6) also reported the same phenomenon with respect to echo time that we observed. The fact that our SLS patients exhibited a strong 1.3 ppm peak in the basal ganglia, which was not associated with a high T2 signal intensity on MR imaging, strongly suggests that this spectral peak does not simply arise from demyelination or dysmyelination. Because the spectral peak at 1.3 ppm in SLS patients is as high and sharp as that of NAA, it may reflect the accumulation of a single lipid or substance.

It is tempting to speculate that the  $^1\text{H}$ -MR spectra of SLS patients arise from fatty alcohol or related metabolites.  $^1\text{H}$ -MR showed that the main peaks of hexadecanol, octadecanol, and phytol had chemical shifts at 1.3 ppm, 1.3 ppm, and 0.9 ppm, respectively (data not shown). Although these shifts are not proof of accumulation of these fatty alcohols in the brain of SLS patients, the results of  $^1\text{H}$ -MR, together with characteristic  $^1\text{H}$ -MR spectra in SLS patients and previous findings of increased plasma concentrations of octadecanol and hexadecanol (3), support this assumption. We, however, could not detect fatty alcohol in the CSF of our patients and, in the absence of brain tissue lipid measurements, we cannot rule out the possibility that the  $^1\text{H}$ -MR spectra originated from other lipids.

Our inability to detect fatty alcohol accumulation in the CSF of our patients does not rule out the storage of these hydrophobic lipids in the brain tissue itself. CSF is usually an unreliable source for

detecting lipids that accumulate in other lipid storage diseases. Long-chain alcohols are poorly soluble in aqueous solution and have very high partition coefficients for lipid membranes (11). Moreover, binding or transport proteins for fatty alcohols are not known to exist. Even in plasma, concentrations of total octadecanol in SLS patients are increased only about two- to threefold above normal, and hexadecanol levels tend to be about twice that of normal concentration (3). Plasma phytol concentrations tend to be normal in SLS, despite a profound defect in the ability of SLS skin fibroblasts to oxidize dihydrophytol, a closely related branched-chain fatty alcohol. Thus, measurements of fatty alcohols in plasma or CSF may not accurately reflect tissue levels.

Regardless of the origin of the abnormal MR spectra,  $^1\text{H}$ -MRS should prove useful for the clinical diagnosis of SLS and the investigation of the natural history of this neurologic disease, although no effective treatment for this disorder has been established (12). This noninvasive imaging technique may be an ideal way to monitor therapeutic approaches to SLS.

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