Diffusion-Weighted Magnetic Resonance Imaging and Proton Magnetic Resonance Spectroscopy of Sjögren-Larsson Syndrome: Case Report

Sjögren-Larsson Sendromunun Difüzyon Ağırlıklı Manyetik Rezonans Görüntüleme ve Proton Manyetik Rezonans Spektroskopi ile Değerlendirilmesi

Elif KARADELİ, MD,[a]
E. Meltem KAYAHAN ULU, MD,[a]
Mehmet TEKŞAM, MD[b]

[a]Department of Radiology,
Başkent University Faculty of Medicine,
[b]Department of Radiology,
Fatih University Faculty of Medicine,
Ankara

Geliş Tarihi/*Received:* 07.11.2009
Kabul Tarihi/*Accepted:* 13.04.2010

Yazışma Adresi/*Correspondence:*
Elif KARADELİ, MD
Başkent University Faculty of Medicine,
Radyoloji AD, Ankara,
TÜRKİYE/TURKEY
elifkaradeli@gmail.com

ABSTRACT Sjögren-Larsson syndrome (SLS) is a rare, autosomal recessive congenital disorder that affects mainly skin and central nervous system. It is characterized by spastic diplegia or tetraplegia, mental retardation and congenital ichthyosis. We report a 2-year-old patient with SLS in whom both mildly restricted diffusion of water in immediate periventricular white matter and mildly increased diffusion of water in the rest of periventricular white matter were observed on diffusion-weighted images. Brain magnetic resonance spectroscopy demonstrated typical high, sharp lipid peak at 1.3 ppm that was stable at long TEs.

Key Words: Sjögren-Larsson syndrome; diffusion magnetic resonance imaging

ÖZET Sjögren-Larsson sendromu (SLS) nadir görülen, ağırlıklı olarak santral sinir sistemi ve deriyi etkileyen otozomal resesif, konjenital bir hastalıktır. Spastik dipleji veya tetrapleji, mental retardasyon ve konjenital iktiyosis karakterizedir. Biz burada iki yaşındaki SLS'li bir olgunun periventriküler beyaz cevherdeki hafif kısıtlanmış difüzyonunu ve geri kalan periventriküler beyaz cevherdeki artmış difüzyonu difüzyon ağırlıklı görüntülerde gözlemledik. Beyin manyetik rezonans spektroskopide uzun TE değerlerinde 1.3 ppm'de tipik yüksek, keskin lipid pikini gösterdik.

Anahtar Kelimeler: Sjögren-Larsson sendromu; difüzyon manyetik rezonans görüntüleme

Turkiye Klinikleri J Med Sci 2011;31(6):1578-84

Sjögren-Larsson syndrome (SLS) is a rare, autosomal recessive congenital disorder that affects mainly skin and central nervous system. It is characterized by spastic diplegia or tetraplegia, mental retardation and congenital ichthyosis.[1]

The defect in fatty alcohol oxidation is caused by the deficiency of microsomal fatty aldehyde dehydrogenase (FALDH), a component of the fatty alcohol, nicotin adenin dinucleotid (NAD) oxidoreductase enzyme complex. In addition to this deficiency, genetic mutations on chromosome 17 also cause this syndrome.[2,3]

In the case presented here, we describe the nature of the cerebral involvement in SLS. We document conventional magnetic resonance (MR) imaging, diffusion-weighted imaging (DWI), and proton MR spectroscopy (H-MRS) findings.

doi:10.5336/medsci.2009-16061

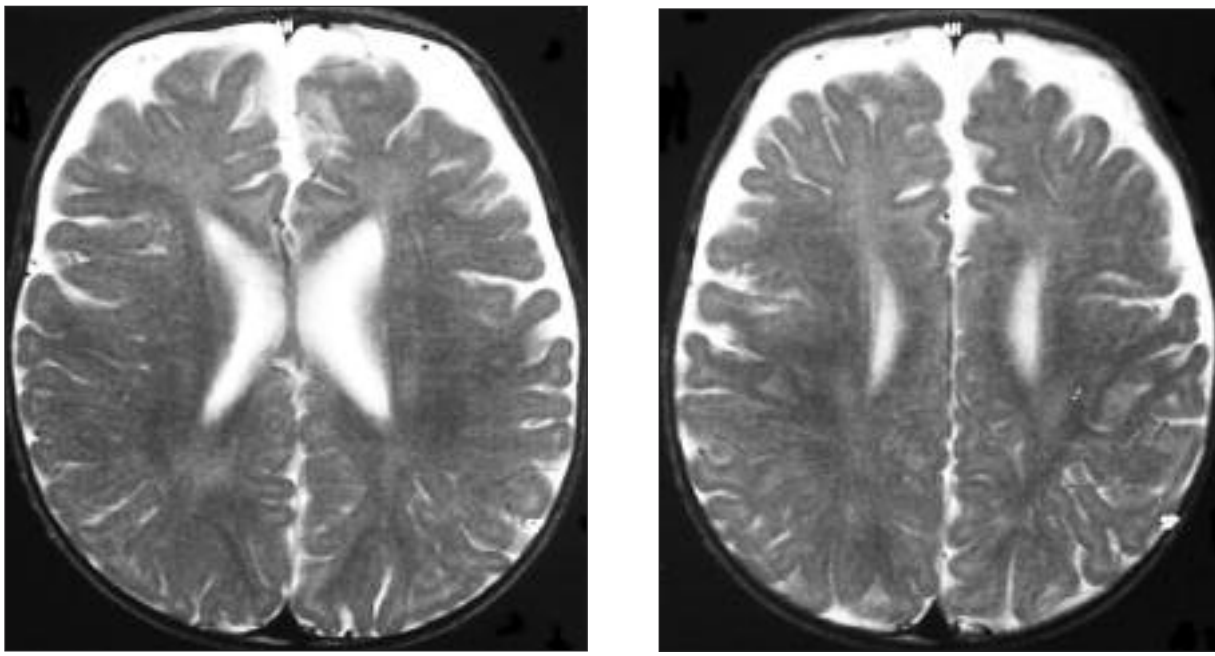
CASE REPORT

A 2-year-old boy was brought for evaluation of complaints of inability to walk, inability to speak, and dry, scaly lesions on the trunk. He was born after a full-term normal pregnancy and delivery without antenatal or perinatal complications. On physical examination, general dryness and scaling were noted all over his body that suggested SLS. Ichthyosis initially was seen at birth and gradually worsened. His mental and motor development was delayed. Blood pyruvate and lactate levels and urine amino acid levels were within normal ranges. Diffuse minimal abnormality was noted in electroencephalography (EEG). Brain magnetic resonance imaging (MRI) revealed a very subtle T2 abnormality in the periventricular white matter when he was 8-months of age (Figure 1).

However, brain MRI was repeated at two years of age and it was significantly abnormal. Brain MRI, diffusion MRI and H-MRS were performed on a Philips Gyroscan Intera (1.5 T) MR system by using a standard head coil**.**

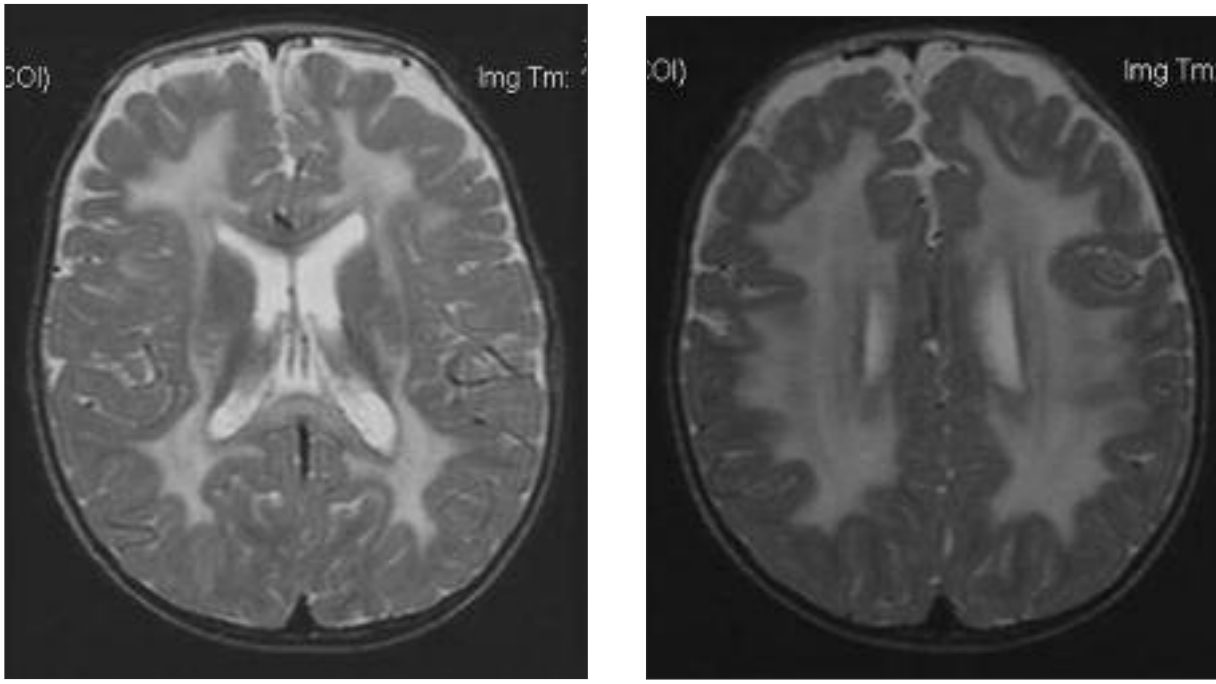
T2- weighted (TR: 4000, TE: 111, slice thickness 5 mm, FOV 160) and FLAIR (TR: 8200, TE: 109, slice thickness 5 mm, FOV 160) images revealed diffuse, severe white matter disease involving frontal and parietal lobes bilaterally (Figure 2). In addition, abnormal high-signal intensities were also noted in the splenium and genu of the corpus callosum on T2-weighted sequences. There was no abnormal contrast enhancement. The basal ganglia and cerebellum were free of abnormal T2 signal. Subcortical U fibers were spared.

DWI was obtained with single-shot echo planar imaging technique. The diffusion sensitivity parameters were altered by varying the gradient amplitude while keeping the gradient duration and separation time constant. Three diffusion-weighted images were acquired with *b* values of 0, 500, and 1000 s/mm^2 and slice thickness 5 mm. Apparend diffusion coefficient (ADC) values were calculated in the regions of abnormal T2 signals in cerebral white matter, bilaterally. ADC values where hyperintensities were observed in the immediate periventricular white matter on DWI ranged between 0.65-0.78 x10^{-3} mm^2/s indicating slightly restricted diffusion of water. ADC values



(A) **(B)**

FIGURE 1: (A) & (B) Axial T2-weighted images which were taken when the patient was 8 months year old, demonstrate very subtle T2 abnormality in the periventricular white matter of cerebral hemispheres bilaterally.



(A) **(B)**

FIGURE 2: (A) & (B) Axial T2-weighted images which were taken when the patient was 8 months year old, demonstrate very subtle T2 abnormality in the periventricular white matter of cerebral hemispheres bilaterally.

where no hyperintensity was observed on DWI in the regions of abnormal T2 signals in the cerebral white matter ranged between 1.4-1.7x10^{-3} mm^2/s consistant with slightly increased diffusion of water (Normal ADC values for white matter 0.82-1.24 x 10^{-3} mm^2/s (Figure 3).[4]

Multi-voxel H-MRS was performed with point-resolved spectroscopy (PRESS). Acquisition parameters were 1500/36 (TR/TE), 1500/136 (TR/TE), and 1500/272 (TR/TE). All spectra obtained from the abnormal white matter areas showed abnormal spectral peaks at 1.3 ppm in the region expected for lipids (Figure 4).

DISCUSSION

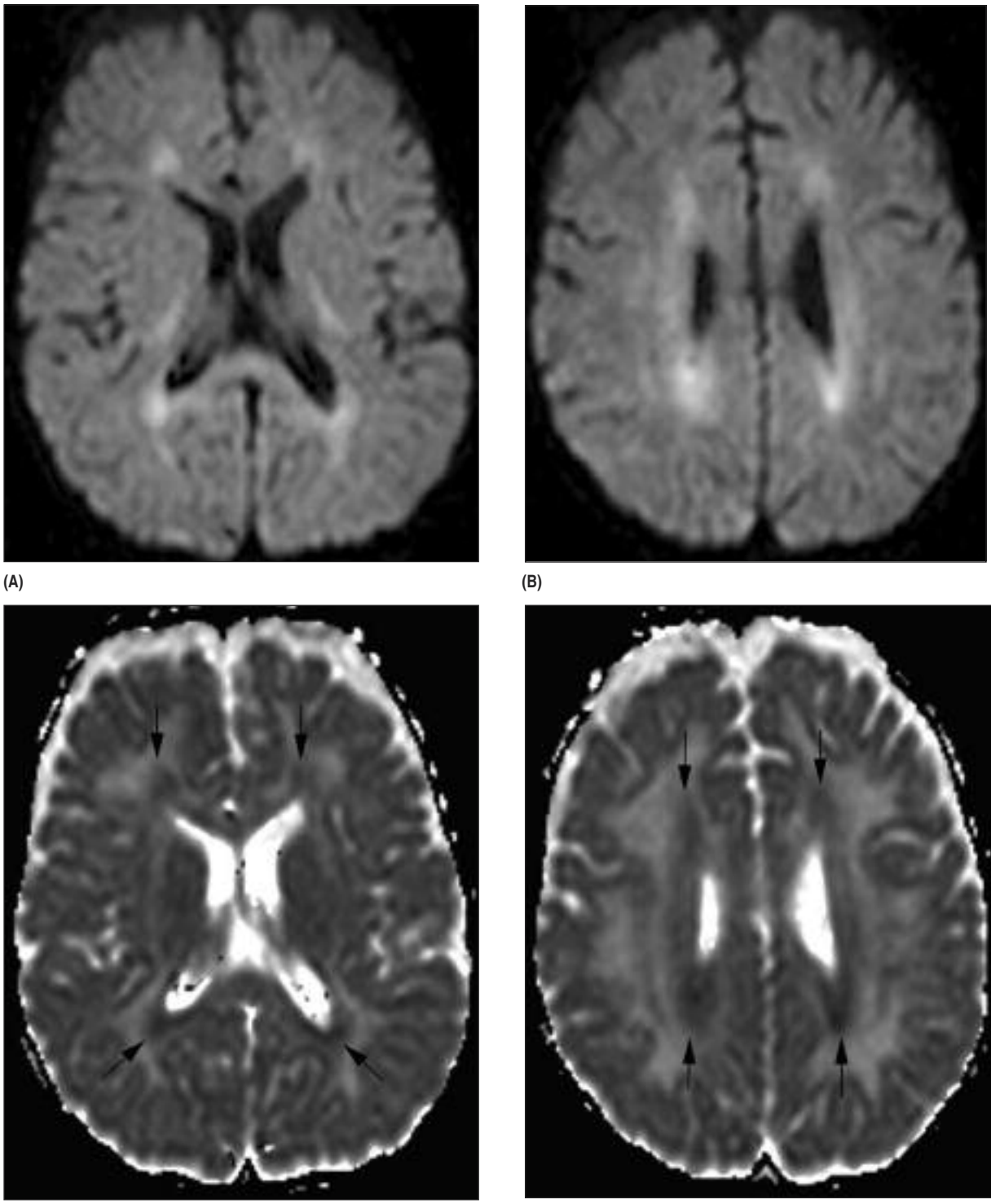
SLS is a rare autosomal recessive disorder characterized by the presence of congenital ichthyosis, spastic diplegia, mild to moderate mental retardation, and retinopathy. It was described in detail by Sjögren and Larsson in 1957.[1]

Ichthyosis is seen at birth and worsens with time. Congenital ichthyosis usually brings the patient to medical attention, whereas spasticity and mental retardation become apparent later in the first or second year of life. It usually presents after infancy as brownish verricous lichenified hyperkeratosis.[5] This skin appearance was present all over the body of our patient. Pruritus was an accompanying disabling feature and was always present. Our patient had no skin biopsy. We diagnosed the patient with clinical, laboratory, and imaging findings.

Ocular findings such as juvenile macular dystrophy have been described in SLS patients.[6] Unfortunately, ophthalmologic examination was not performed in our patient.

Spasticity becomes manifest at 4-30 months of age. The clinical spectrum is ranges from those who are confined to wheel-chair to those who can walk, but spastic gait is observed in these patients. Tendon reflexes are increased and Babinski reflexes may be positive bilaterally. The clinical problems (i.e. spastic gait, developmental delay, poor balance) in our patient were similar to other SLS patients reported in the literature.

Clinically, SLS is readily diagnosed, because the clinical findings are pathognomonic and are



(A) **(B)** **(C)** **(D)**

FIGURE 3: (A) & (B) Axial diffusion-weighted images and corresponding ADC maps **(C &D)** demonstrate slightly restricted diffusion in the periventricular white matter (arrows) and increased diffusion of water in the rest of the cerebral white matter, in the abnormal regions.

associated with negative simple laboratory test results. Other syndromes with dermatological and neurological findings are Rud syndrome, Refsum syndrome, maple syrup urine disease, Hartnup syndrome, CHILD (congenital hemidysplasia ichtyosis limb defects) syndrome, chondrodysplasia

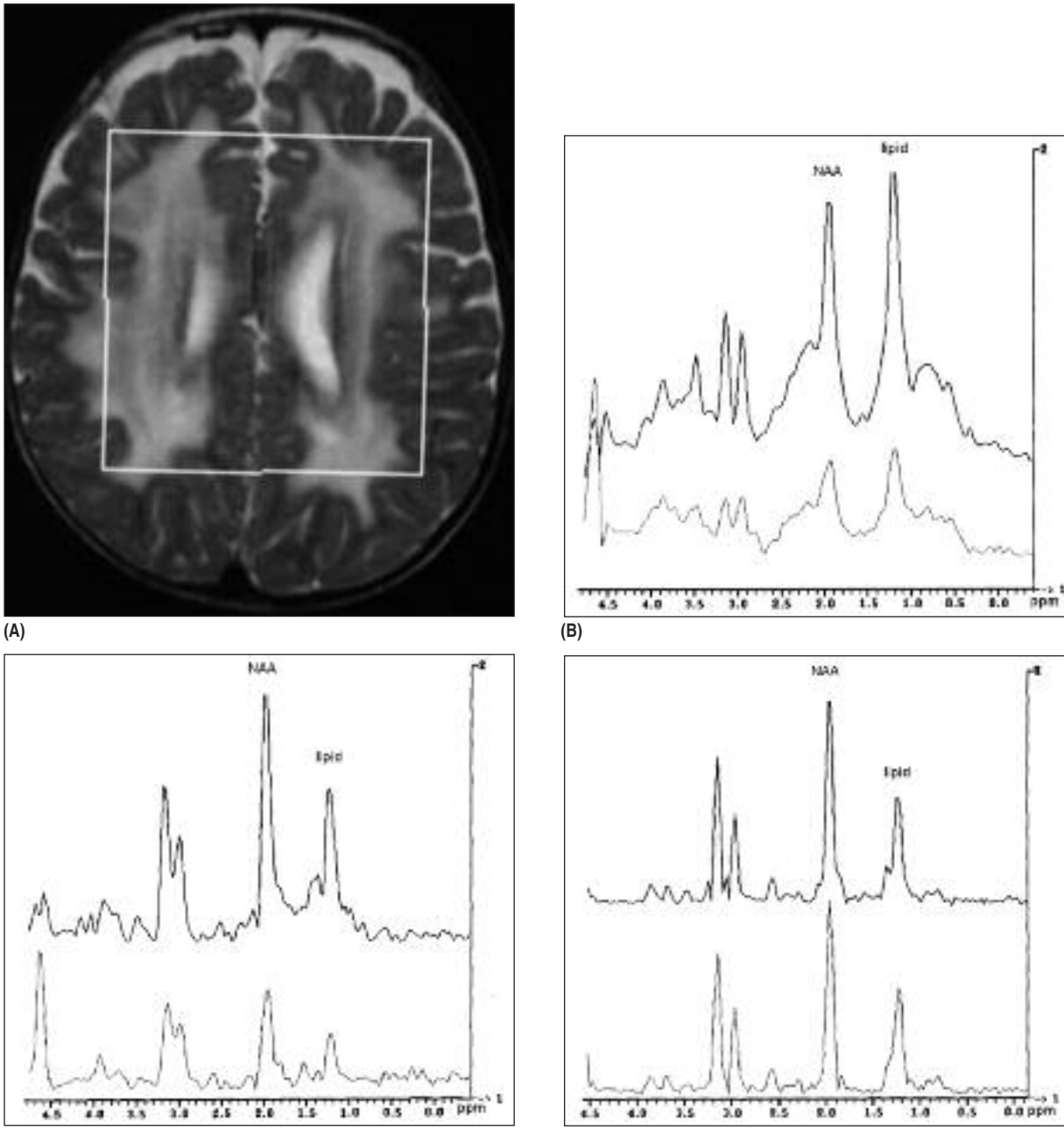


FIGURE 4: Reference image **(A),** Proton MR spectra obtained from cerebral white matter at TE: 36 msn **(B),** TE: 136 msn **(C),** TE: 272 msn **(D).** Note the presence of high, sharp lipid peak at 1.3 ppm that is apparent in all three MR spectra.

punctata, Dykes syndrome and X-linked ichthyosis. Ichtyosis, mental retardation, hypogonadism, polyneuropaty, epilepsy, small stature, and macrocytic anemia are features of Rud syndrome. Refsum syndrome is characterized by ichthyosis, polyneuritis, cerebellar ataxia, paresis of distal extremites, nystagmus, atypical retinis pigmentosa, deafness, increased protein in the cerebrospinal fluid, hexadenic acid in the serum. In CHILD syndrome and chondrodysplasia punctata patients, bone abnormalities and dysplasia are common. The features of maple syrup urine disease are myoclonia, quickly progressing mental deficiency, increased valine, leucine, isoleucine levels in the

blood, increased ketoacid levels in the urine. If untreated, death within the first few months of life is inevitable. In Dykes syndrome, cerebellar degeneration and hepatomegaly are associated with ichthyosis. For the diaognosis of Hartnup syndrome, hyperamino-aciduria, indicanuria, indolic aciduria and ataxia, pyramidal signs, nystagmus and dyplopia, mental retardation and seasonal photodermatitis are essential.[7,8] Because there is loss of myelin and ballooning of myelin sheaths in the cerebral white matter, moderate or severe mental retardation occurs in SLS. Epilepsy and speech disorders may be present. In the area of myelin loss, degeneration and loss of axis cylinders and astrocytosis are found. Myelin loss is also demonstrated in the pyramidal tracts of the brainstem and descending tracts of the spinal cord, including the lateral corticospinal and vestibulospinal tracts. Degeneration and loss of neurons are demonstrated in the cortex. Ascending tracts and cerebellar white matter are not affected.[7,9]

Severe white matter signal intensity changes are observed in SLS patients on MRI. The corpus callosum may also be involved. It is known that cerebellar white matter is not affected.[10] In our case, there was severe white matter disease involving both cerebral hemispheres. The periventricular white matter abnormalities were confluent. These findings may suggest that hyperintense abnormalities on T2-weghted images arises or becomes apparent during the process of myelination. This is because the T2 abnormalities on brain MRI were very subtle at 8 months of age and were very extensive at 2 years of age. There was a progression of disease within two years. In addition, an abnormal high-signal intensity was observed in the splenium and genu of the corpus callosum on T2-weighted images. There was no abnormal contrast enhancement. No abnormal intensities were detected in the basal ganglia and cerebellum. Subcortical U fibers were spared. Because the basal ganglia and cerebellum were free of abnormal T2 signal, these regions, normal white matter and gray matter were not evaluated with MRS.

Miyanomae et al. first described the results of H-MRS in a 20-year-old bedridden patient with SLS. H-MRS (TR: 2000/ TE: 35) revealed a high-lipid spectral peak of 1.3 ppm.[11]

The spectra of 1.3 ppm and 0.9 ppm of H-MRS are thought to be assigned to the methylene and methyl groups of lipid, respectively. The presence of abnormal lipid signals has also been reported in patients with other degenerative disorders, including other peroxisomal disorders (Zellweger's syndrome) and multiple sclerosis. However, in these patients, the lipid peaks at 1.3 ppm and 0.9 ppm were less intense, broader, and visualized with only a short TE. Davie et al. speculated that they represented myelin breakdown products secondary to demyelination.[12,13] The spectral peak was observed only at 1.3 ppm in our patient. This peak was not probably related to myelin breakdown products due to its stability on long echo times. The spectral peak at 1.3 ppm in our patient was high and sharp, similar to NAA and probably reflected the accumulation of lipids because of the FALDH deficiency. FALDH catalyzes the oxidation of medium- and long-chain fatty aldehydes derived from fatty alcohols. Therefore, the accumulated lipids may be fatty alcohol or related metabolites.

To our knowledge, DWI characteristics in SLS patients have not been reported in the literature. ADC values in the regions of hyperintensities on DWI in the immediate periventricular white matter ranged between 0.65-0.78 $x10^{-3}$ mm^2/s consistant with slightly restricted diffusion of water. This slightly restricted diffusion may suggest active inflammatory process causing demyelination. However, the main pathologic findings in these patients are incomplete myelination instead of demyelination. The conventional MRI findings are also compatible with initially delayed and eventually permanently incomplete myelination.[14] In addition, there was no choline increase on H-MRS in our patient; this was against active inflammation consistant with active demyelination. Other than these small areas of restricted diffusion, ADC values were slightly increased (1.4-1.7$x10^{-3}$ mm^2/s) consisting of slightly increased diffusion of water in the abnormal areas in cerebral white matter. We speculate that the mild increase in ADC values might be due to the accumulation of mobile lipid molecules.

In addition, the presence of high ADC values of the white matter might be related to relatively increased molecular motion of water indicating disintigration of the white matter (somewhat loosening of the tissue) secondary to lack of myelination.

The peak at 1.3 ppm on H-MRS is narrow and also visible at a long TE of 136 and 272 msn. This finding suggests that the accumulated lipids are mobile molecules that move freely or within intercellular or intracellular droplets. Lipids located in lipid bilayers have a low mobility and lead to broad resonance at short TEs; these lipids are not visible at long TEs on H-MRS. Although neuropathologic examinations demonstrate severe axonal damage in SLS patients,[15] we did not find decreased NAA on H-MRS; this argues against extensive axonal damage.

In conclusion, the abnormal peak suggesting lipid accumulation at 1.3 ppm on H-MRS most probably suggests the diagnosis of SLS. Both slightly restricted and increased diffusion of water can be observed on DWI in SLS patients.

REFERENCES

1. Sjögren T, Larsson T. Oligophrenia in combination with congenital ichthyosis and spastic disorders. Acta Phychiatr Scand 1957;32 (Suppl 113):1-112.
2. Rizzo WB. Sjögren-Larsson syndrome: fatty aldehyde dehydrogenase deficiency In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill; 2001. p.2239-58.
3. Rizzo WB, Craft DA. Sjogren-Larsson syndrome. Deficient activity of the fatty aldehyde dehydrogenase component of fatty alcohol:NAD+ oxidoreductase in cultured fibroblasts. J Clin Invest 1991;88(5):1643-8.
4. Chan YL, Yeung DK, Leung SF, Chan PN. Diffusion-weighted magnetic resonance imaging in radiation-induced cerebral necrosis. Apparent diffusion coefficient in lesion components. J Comput Assist Tomogr 2003;27 (5):674-80.
5. Willemsen MA, IJlst L, Steijlen PM, Rotteveel JJ, de Jong JG, van Domburg PH, et al. Clinical, biochemical and molecular genetic characteristics of 19 patients with the Sjögren-Larsson syndrome. Brain 2001;124 (Pt 7): 1426-37.
6. Phanthumchinda K, Srimanuthipol K, Yodnophaklao P. Sjogren-Larsson syndrome. J Med Assoc Thai 1996;79(8):541-4.
7. Gomori JM, Leibovici V, Zlotogorski A, Wirguin I, Haham-Zadeh S. Computed tomography in Sjögren-Larsson syndrome. Neuroradiology 1987;29(6):557-9.
8. Mckusick VM, Francomano CA, Antonarakis SE. Mendelian Inheritence in Man. Catalogs of Autosomal Recessive, and X-linked Phenotypes. 9th ed. Baltimore: John Hopkins Univesity Press; 1990. p.3972.
9. Mulder LJ, Oranje AP, Loonen MC. Cranial CT in the Sjogren-Larsson syndrome. Neuroradiology 1987;29(6):560-1.
10. Willemsen MA, Van Der Graaf M, Van Der Knaap MS, Heerschap A, Van Domburg PH, Gabreëls FJ, et al. MR imaging and proton MR spectroscopic studies in Sjögren-Larsson syndrome: characterization of the leukoencephalopathy. AJNR Am J Neuroradiol 2004; 25(4):649-57.
11. Miyanomae Y, Ochi M, Yoshioka H, Takaya K, Kizaki Z, Inoue F, et al. Cerebral MRI and spectroscopy in Sjögren-Larsson syndrome: case report. Neuroradiology 1995;37(3):225-8.
12. Davie CA, Hawkins CP, Barker GJ, Brennan A, Tofts PS, Miller DH, et al. Serial proton magnetic resonance spectroscopy in acute multiple sclerosis lesions. Brain 1994;117(Pt 1):49-58.
13. Bruhn H, Kruse B, Korenke GC, Hanefeld F, Hänicke W, Merboldt KD, et al. Proton NMR spectroscopy of cerebral metabolic alterations in infantile peroxisomal disorders. J Comput Assist Tomogr 1992;16(3):335-44.
14. Willemsen MA, Van Der Graaf M, Van Der Knaap MS, Heerschap A, Van Domburg PH, Gabreëls FJ, et al. MR imaging and proton MR spectroscopic studies in Sjögren-Larsson syndrome: characterization of the leukoencephalopathy. AJNR Am J Neuroradiol 2004;25(4):649-57.
15. Sylvester PE. Pathological findings in Sjogren-Larsson syndrome. J Ment Defic Res 1969; 13(4):267-75.