Phenotypic Variability Among Adult Siblings With Sjögren-Larsson Syndrome

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Background: Sjögren-Larsson syndrome (SLS) is an early childhood–onset disorder with ichthyosis, mental retardation, spastic paraparesis, macular dystrophy, and leukoencephalopathy caused by the deficiency of fatty aldehyde dehydrogenase due to mutations in the ALDH3A2 gene (the gene that encodes microsomal fatty aldehyde dehydrogenase). Cerebral proton magnetic resonance spectroscopy in those with SLS demonstrates an abnormal white matter peak at 1.3 ppm, consistent with long-chain fatty alcohol accumulation.

Objective: To define the clinical course and proton magnetic resonance spectroscopic findings of SLS in adults.

Design and Setting: Case series in a tertiary care center.

Patients: Six siblings of a consanguineous Arab family with early childhood–onset SLS who carry the 682C→T mutation in the ALDH3A2 gene were reinvestigated in adulthood.

Results: The 6 affected siblings ranged in age from 16 to 36 years. All exhibited the typical clinical and imaging manifestations of SLS, but their severity markedly varied. Neurological involvement was apparently nonprogressive, and its severity showed no correlation with age. Cerebral proton magnetic resonance spectroscopy showed a lipid peak at 1.3 ppm, with decreasing intensity in the older siblings.

Conclusion: These observations document significant clinical variability and the nonprogressive neurological course of SLS in adult siblings with the same ALDH3A2 genotype, and demonstrate possible correlation of proton magnetic resonance spectroscopic changes with age, suggesting unknown pathogenic mechanisms to compensate for the responsible biochemical defect in this disease.

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JÖGREN-LARSSON SYNDROME (SLS) (Online Mendelian Inheritance in Man 270200) is an autosomal recessive disorder characterized by congenital ichthyosis, mental retardation, spastic paraparesis, and leukoencephalopathy. Additional manifestations include perimacular glistening white dots, photophobia, seizures, and the development of leg contractures. The neurological features of SLS appear in the first few years of life and then seem to stabilize. Most described patients have been children, and less is known about the long-term clinical course in adults.

Sjögren-Larsson syndrome is caused by mutations in the ALDH3A2 gene, which encodes microsomal fatty aldehyde dehydrogenase. Fatty aldehyde dehydrogenase deficiency results in impaired oxidation of long-chain fatty aldehydes to fatty acids. The consequent accumulation of fatty aldehyde precursors, including fatty alcohols, or the formation of aldehyde-modified macromolecules is postulated to affect the normal formation of multilamellar membranes in the stratum corneum and myelin, and to result in the symptoms. Cerebral proton magnetic resonance spectroscopy (1H-MRS) in those with SLS demonstrates an abnormal white matter peak, consistent with long-chain fatty alcohol accumulation, that emerges in infancy and coincides with retarded myelination. Although the severity of the neurological deficit may vary among SLS patients, little is known about genotype–phenotype correlations in this disease.

To further define the clinical course of SLS in adults and to determine the phenotypic variation among siblings, we investigated a large multiplex SLS family.

METHODS

Early clinical and computed tomographic imaging results in 6 affected siblings of a consanguineous Arab SLS family were previously published. The diagnosis was subsequently confirmed by finding reduced fibroblast fatty aldehyde dehydrogenase activity (4% of normal) in the proband and genetic linkage to chromosome 17p11.2 with identification of the 682C→T missense mutation in the ALDH3A2 gene. Homozygosity for 682C→T has been reconfirmed in all 6

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†This score indicates the following: 0, asymptomatic; 1, mild gait abnormality without functional limitation; 2, moderate gait abnormality without consistent use of an assistive device; 3, marked gait disturbance with consistent use of an assistive device; 4, marked gait problems with frequent use of a wheelchair; and 5, wheelchair bound (revised from data given by Willemsen et al2).

‡The echo time was 36 milliseconds.

Abbreviations: Cho, choline; Cr, creatine; F, frontal; FC, finger counting; 1H-MRS, proton magnetic resonance spectroscopy; MI, myo-inositol; MRI, magnetic resonance imaging; NAA, N-acetylaspartate; ND, not done; O, occipital; P, parietal; Pv, periventricular; T, temporal; WM, white matter; WMA, WM abnormalities; +, mild; ++, moderate; ++++, severe; –, not present.

The 6 affected siblings ranged in age from 16 to 36 years. All exhibited the major clinical features of SLS, but their severity varied (Table). Ichthyosis was generalized in distribution, and was most prominent over the trunk and extremities, but spared the head, palms, and soles. Although all patients exhibited spastic paraparesis, they differed in their ability to ambulate. Patients 1 and 2 also had mild hyperreflexia in the arms, and patients 2, 3, and 4 displayed an inappropriate emotional response, but none had seizures or signs of peripheral nerve involvement. The severity of cutaneous and neurological manifestations showed no apparent correlation with age. The number of macular glistening white dots tended to be higher in the older patients. This generally correlated with a decrease in visual acuity, suggesting progressive macular dysfunction. In contrast, the results of full-field electroretinography were normal, even in the oldest sibling, indicating that the extramacular retinal function remains preserved.

Consistent with the clinical findings, all 4 siblings studied by MR imaging had symmetric cerebral white matter abnormalities, but their extent, distribution, and pattern varied (Table). Patchy T2-weighted and fluid-attenuated inversion recovery signal hyperintensities were observed in patient 3, whereas confluent lesions were present in patients 1, 4, and 6 and tended to correlate with their functional disability. Subcortical U fibers, cerebral gray matter, ventricular size, and the cerebellum seemed unaffected.

Table. Clinical and Laboratory Findings in the 6 Siblings With Sjögren-Larsson Syndrome Due to the 682C→T ALDH3A2 Gene Mutation*

<table>
<thead>
<tr>
<th>Variable</th>
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<th>3</th>
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<th>5</th>
<th>6</th>
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<td>33/M</td>
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<td>+ + +</td>
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<tr>
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<td>3</td>
<td>4</td>
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<tr>
<td>Maximal WMA score</td>
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<td>+ +</td>
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<td>1.2</td>
<td>0.7</td>
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</tr>
<tr>
<td>NAA/Cr ratio</td>
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<td>ND</td>
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<td>1.4</td>
<td>ND</td>
<td>1.6</td>
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<tr>
<td>Cho/Cr ratio</td>
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<td>ND</td>
<td>1.4</td>
<td>0.9</td>
<td>ND</td>
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<tr>
<td>M1/Cr ratio</td>
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<td>ND</td>
<td>0.9</td>
<td>0.8</td>
<td>ND</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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The most significant 1H-MRS finding was the presence of a prominent sharp lipid peak at 1.3 ppm in the affected cerebral white matter, with a decreasing lipid-creatine ratio in the older siblings (Table). This peak was visible at a short echo time in all the studies, but not at a long echo time in the 2 oldest siblings. A smaller peak at 0.9 ppm was also seen, and basal ganglia spectra were normal. Other metabolites seen on 1H-MRS did not correlate with age.

Comparison of the current clinical status with the more qualitative data 11 years earlier showed a similar distribution of the neurological deficit in individual patients and no apparent deterioration. All subjects reside in one village and consume a diet customary to their community.

COMMENT

To our knowledge, this is the largest described family with genetically confirmed SLS, and it provides a unique opportunity to define the intrafamilial clinical variation, particularly in adults. A previous study of this family in 1987, before the genetic defect in SLS was discovered, had a paucity of clinical information and used older imaging techniques. Therefore, longitudinal comparisons of the natural history of SLS in this family are limited. Several conclusions, however, may be drawn from these studies.

First, the neurological involvement in our adult SLS patients, based on physical examination, is apparently non-progressive, and its severity does not correlate with age. Although slow progression remains a possibility, prior observations in children with SLS tend to support this conclusion.

In this aspect, SLS could superficially resemble forms of cerebral palsy or other static encephalopathies of childhood. Obviously, most of the clinical and MR imaging disease burden in those with SLS is attained early in life. This may be the result of selective vulnerability of the brain to lipid abnormalities during myelin maturation.

Second, phenotypic variation, even among siblings, may be significant. Despite identical ALDH3A2 genotypes and apparently similar environmental exposures and diets, the affected siblings differed in the severity of cutaneous disease, neurological impairment, and brain imaging results. Most mutations in SLS are private, and there are few studies comparing the clinical disease among patients with the same ALDH3A2 genotype, either within or across kindreds. The clinical variation seen in our family suggests that additional unknown genetic or environmental factors exist to compensate for the responsible biochemical defect. Furthermore, distinct pathogenic mechanisms may act in different tissues to account for the discordance between cutaneous and neurological involvement and for the progressive macular dystrophy.

Third, the intensity of the cerebral 1H-MRS white matter lipid peak at 1.3 ppm was inversely correlated with the age of the siblings. Although this signal may fluctuate in intensity and we have no serial 1H-MRS data on individual patients or statistical confirmation, the decrease in the 1.3-ppm peak among older siblings was striking. Moreover, review of the published cerebral 1H-MRS data in a large series of SLS patients reveals a similar trend that was not previously noted. Because this peak is highly characteristic of SLS and probably represents accumulation of fatty alcohols or their metabolites beginning in infancy, it is tempting to speculate that its decline in adults reflects decreasing levels of the same lipids, indicating reduced activity of the disease. That the peak was not seen at a long echo time in the 2 oldest siblings is probably due to its low intensity. It is unlikely that the decrease in the lipid peak reflects progressive loss of myelin, because there was no apparent worsening of the MR imaging findings in the older siblings or of neurological symptoms with age.

The new observations in our SLS family suggest that the clinical course in some adults may reveal previously unknown pathogenic mechanisms of this disease.

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Author Contributions: Study concept and design: Lossos, Khoury, Rizzo, and Rosenmann. Acquisition of data: Lossos, Khoury, Rizzo, Gomori, Banin, Zlotogorski, Jaber, Argov, and Rosenmann. Analysis and interpretation of data: Lossos, Khoury, Rizzo, Gomori, Banin, Zlotogorski, Abramsky, Argov, and Rosenmann. Drafting of the manuscript: Lossos, Rizzo, and Rosenmann. Critical revision of the manuscript for important intellectual content: Lossos, Khoury, Rizzo, Gomori, Banin, Zlotogorski, Jaber, Abramsky, Argov, and Rosenmann. Obtained funding: Lossos, Banin, and Abramsky. Administrative, technical, and material support: Lossos, Khoury, and Abramsky. Study supervision: Lossos, Gomori, Zlotogorski, Abramsky, Argov, and Rosenmann.

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REFERENCES


