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Segmentation of Retinal Layers in Sjögren–Larsson Syndrome

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In 1957, Sjögren and Larsson described an autosomal recessive syndrome in 28 individuals in northern Sweden who shared the clinical triad of congenital ichthyosis, intellectual disability, and spastic diplegia.¹ Ichthyosis is the first sign of Sjögren–Larsson syndrome (SLS, MIM 270200) and prompts medical evaluation, but the diagnosis of SLS is rarely considered until neurologic features appear later in infancy.

Macular crystalline inclusions, or “glistening dots,” are distinctive ophthalmic features that appear in infancy.² Jagell et al³ suggested that glistening dots constitute a fourth major clinical sign. The macular crystals may be absent in young infants and increase with age.² Although clinical symptoms present with variable severity, symptoms tend to stabilize by late childhood and remain stationary.⁴ Ophthalmologic evaluations may aid in distinguishing SLS from other neuroichthyotic syndromes. Sjögren–Larsson syndrome is rare and most reports are single cases that focus on the dermatologic or neurologic features. We studied 9 SLS patients to further characterize retinal findings in SLS.

Mutations in the *ALDH3A2* reduce enzyme activity of fatty aldehyde dehydrogenase (FALDH) resulting in accumulation of 16- and 18-carbon fatty aldehydes and alcohols thought to be responsible for the clinical symptoms. The FALDH oxidizes medium- and long-chain aliphatic aldehydes to fatty acids and is a critical component of the fatty alcohol nicotinamide adenine dinucleotide oxidoreductase complex of fatty alcohol metabolism. The diagnosis is made by measuring FALDH enzymatic activity in cultured fibroblasts and/or demonstrating pathogenic mutations in the *ALDH3A2* gene.

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Author Contributions

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Analysis and interpretation: Jack, Sadiq, Rizzo, Margalit

Data collection: Jack, Benson, Margalit

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We designed and conducted a prospective, observational case series (NCT01971957, www.clinicaltrials.gov). The institutional review board at the University of Nebraska Medical Center approved the study, which conformed to the Declaration of Helsinki and complied with all federal and state laws and regulations. Informed consent followed Health Insurance Portability and Accountability Act guidelines and was obtained from the patient or appropriate legal guardian. Only persons with an *ALDH3A2* mutation were enrolled. Exclusion criteria included patient or guardian failure to consent or inability to travel to the examination site. No patients met the exclusion criteria.

Manual segmentation of the central 2 mm through the anatomic foveal center was performed by an author (M.A.S.) experienced with Heyex Explorer Version 5.2 (Heidelberg Engineering, Heidelberg, Germany) and Spectralis HRA-OCT (Heidelberg Engineering). Fourteen eyes were imaged with optical coherence tomography. The 2 eyes from the patient with the macular pseudocyst were excluded due to disruption of retinal layers. Eleven normal eyes (age range, 19–25 years; mean, 22.81) were used for controls. The nonparametric Mann–Whitney test was used to test significance since the data were not of a normal distribution. Statistical analysis was performed using Excel (Microsoft, Redmond, WA) and MiniTab 16 (MiniTab, State College, PA).

Fluorescein angiography, fundus autofluorescence, and color fundus photography were performed using the P-200Tx (Optos, Dunfermline, Scotland). Fundus photography was also performed using the Visucam (Zeiss, Jena, Germany). Full-field electroretinography was performed according to standard protocols from the International Society of Electrophysiology of Vision using the Espion Visual Electrophysiology System (Diagnosys, Lowell, MA).

We studied 9 SLS patients (5 male, 4 female; age range, 3–23 years) with *ALDH3A2* mutations who exhibited generalized ichthyosis and spastic diplegia (Table 1; available at www.aaajournal.org). All patients exhibited photophobia, ichthyosis of the upper eyelid skin, and macular crystals. Symmetric, moderate vision loss ranging from logarithm of the minimum angle of resolution 0.14 to 0.57 (mean, 0.44 ± 0.15 ; Table 1) did not correlate with age (Pearson correlation coefficient of 0.11).

On examination and color fundus photography, macular crystals in our cohort were in a parafoveal distribution, varied in number and size, and were more evident on fundus photography than clinical examination, in part owing to photophobia and lack of cooperation (Fig 1; available at www.aaajournal.org). Retinal pigment epithelium atrophy was present in 10 of 18 eyes (56%; Fig 2; Table 1). One eye was found to have a pseudocyst (7.1%; Fig 2; Table 1).

Previous optical coherence tomography studies demonstrated macular crystals and pseudocysts.⁵ Intraretinal hyperreflective bodies corresponding to crystals were seen primarily in the macular and foveal outer plexiform layer and inner nuclear layers.⁵ We obtained optical coherence tomography in 14 eyes of 7 patients (Fig 2; Table 1). Although present in all layers, the vast majority of macular crystals localized to the inner nuclear and outer plexiform layers. Segmentation of retinal layers was performed on the full retinal

thickness, on inner nuclear, and outer nuclear layers. These layers were selected because they were thought to better reflect the cellularity of the fovea. Also, histochemical studies indicate that FALDH is most active in the inner and outer nuclear and ganglion cell layers of the retina (Rizzo, unpublished observations, April, 2014).

Full retinal thickness was reduced by 22% ($P = 0.0015$), the inner nuclear layer was reduced by 30% ($P = 0.0023$), and the outer nuclear layer was reduced by 40% ($P = 0.0003$). The SLS cohort displayed retinal thinning despite being compared with a slightly older reference cohort. Thinning seemed to be most pronounced in the umbo, where there is normally a paucity of rods and inner retinal layers. This thinning suggests that there is outer retinal injury in SLS, which could be a result of direct toxicity, changes in structural integrity, loss of trophic factors, or altered development. Inner nuclear layer, outer nuclear layer, and full-thickness retinal thinning suggest multiple cell types are likely affected in SLS.

Fundus autofluorescence and fluorescein angiography showed retinal pigment epithelium atrophy. All 4 patients imaged using fundus autofluorescence demonstrated heterogeneous macular autofluorescence with crystals (Fig 1), which is consistent with a prior report describing reduced levels of central retinal macular pigment.⁴ All 4 eyes evaluated with fluorescein angiography were found to have window defects and crystals without the presence of leakage or an enlarged foveal avascular zone.

In this study, we report the characterization of the retinal layers using retinal segmentation in SLS in the largest case series originating from the United States. Limitations of our study include low disease prevalence and the ability of young patients to complete examinations requiring patient attention and cooperation. Larger studies that include emerging imaging strategies may shed additional light on the retinal findings associated with this unique metabolic syndrome.

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FIGURE 1.

Representative fundus photos and fundus autofluorescence from patients with sjögren-Larsson Syndrome. (Top) Fundus photographs demonstrating macular glistening dots (arrows) and RPE changes (black arrowhead) in the central macula. (Bottom) Fundus autofluorescence photographs showing heterogeneous hyper- and hypo-autofluorescence in the central macula (white arrowheads).

Figure 2.

Optical coherence tomography (OCT) through the fovea. Top left, Right eye demonstrating foveal retinal atrophy (white arrowheads). Top right, Right eye showing a foveal pseudocyst (asterisk) and macular glistening dots predominantly in the inner retinal layer (white arrows). Bottom left, Left eye with perifoveal loss of the innereouter segment junction and interruption of the external limiting membrane (black arrows), small pseudocyst (asterisk), foveal atrophy (white arrowhead), and macular glistening dots predominantly in the inner nuclear layer and outer plexiform layers (white arrow). Bottom right, Right eye with separation of retinal layers forming pseudocyst (asterisk), macular glistening dots in the inner nuclear layer (white arrows). All frames demonstrate the presence of macular glistening dots on the infrared images (white diamonds).

Table 1

Clinical Exam Findings

	Age	3	5	6	10	15	16	17	19	23	Mean	SD
Sex	M	F	F	M	M	F	M	F	F	M	44%	Female
LogMAR OD	UA	UA	UA	UA	0.4	0.54	0.096	0.54	0.48	0.48	0.42	0.17
LogMAR OS	UA	UA	UA	UA	0.48	0.6	0.176	0.48	0.48	0.48	0.45	0.14
Average LogMAR	UA	UA	UA	UA	0.44	0.57	0.136	0.51	0.48	0.48	0.44	0.15
Average IOP	UA	UA	UA	UA	UA	18.5	16	17	15	16	16.5	1.3
Horizontal C/D	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.7	0.3	0.3	0.42	0.15
Macular Glistening Dots	+	+	+	+	+	+	+	+	+	+	100%	
Atrophy	-	-	+	+	+	+	+	+	-	-	56%	
Pigmentary Changes	-	+	-	-	-	-	+	+	-	+	44%	
Cystoid Space	-	-	-	-	-	+	-	-	-	-	11%	

UA = Unable + = Present - = Absent