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Case Report

End-stage crystalline maculopathy with retinal atrophy in Sjögren-Larsson syndrome: a case report and review of the literature

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***Abstract*:** Sjögren-Larsson syndrome (SLS) is a rare, autosomal recessive neurocutaneous disorder. It is caused by the inheritance of sequence variants in the *ALDH3A2* gene, which codes for fatty aldehyde dehydrogenase (FALDH). Universal signs of the condition are congenital ichthyosis, spastic paresis of the lower and upper limbs, and reduced intellectual ability. In addition to this clinical triad, patients with SLS experience dry eyes and decreased visual acuity caused by a progressive retinal degeneration. Examination of the retina in patients with SLS often reveals glistening yellow crystal-like deposits surrounding the fovea. This crystalline retinopathy often develops in childhood and is considered pathognomonic for the disease. The metabolic disorder typically shortens lifespan to half that of the unaffected population. However, now that patients with SLS live longer, it becomes increasingly important to understand the natural course of the disease. Our case describes a 58-year-old woman with advanced SLS whose ophthalmic examination illustrates the end-stage of the retinal degeneration. Optical coherence tomography (OCT) and fluorescein angiography confirm the disease is restricted to the neural retina with dramatic thinning of the macula. This case is unique since it is among the most advanced both in terms of chronological age and severity of retinal disease. While the accumulation of fatty aldehydes, alcohols, and other precursor molecules is the probable cause of retinal toxicity, a more complete understanding of the course of retinal degeneration may aid in the development of future treatments. The aim of our presentation of this case is to increase awareness of the disease and to foster interest in therapeutic research which may benefit patients with this rare condition.

Plain Language Summary

Eye issues in Sjogren-Larsson Syndrome

Sjögren-Larsson syndrome (SLS) is a rare, inherited condition that affects the skin and nervous system. It is caused by variations in a gene that controls the way fats are broken down in the body. The three key signs of the disease are (1) peeling, dry skin; (2) muscle stiffness and impaired movement of the arms and legs; and (3) reduced intellectual ability. Most signs of the condition appear shortly after birth. Genetic testing and counseling services can help patients and their families to understand what to expect with SLS. Caring for people with SLS requires teamwork by specialists like neurologists and physical therapists. Because eye problems are common, the early consultation of an eye doctor is also important. An eye examination can also confirm the diagnosis of SLS. SLS often causes the eyes to appear red, feel dry, or become irritated. This can make it hard to see

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in bright light. Decreased vision at night is also common. This is caused by the progressive loss of the central part of the retina which is needed to see fine details. Because SLS shortens lifespan, it is rare for anyone to reach the final stages of the disease. As patients with SLS are living longer, as illustrated by the individual in our case study, it becomes important to understand how the disease progresses. Unfortunately, treatments to restore vision are not yet available. Nevertheless, some protective measures can be taken. Eye examinations in early childhood are important for preventing damage to the eyes. Wearing glasses can improve vision, as well as protect eyes from accidental injury or falls. Eye drops can provide relief from dry eyes, and sunglasses can reduce glare and sensitivity to light. In the future, gene therapy may be used to treat SLS.

Keywords: ALDH3A2, crystalline retinopathy, eye, neurocutaneous disorders, retinal imaging, Sjögren-Larsson syndrome

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Introduction

Sjögren-Larsson syndrome (SLS; OMIM 270200) is a metabolic disorder with neurocutaneous features inherited in an autosomal recessive fashion. It is caused by deficiency of an enzyme fatty aldehyde dehydrogenase 3 family member A2 [ALDH3A2; fatty aldehyde dehydrogenase (FALDH); OMIM 609523] which is responsible for catalyzing the oxidation of long-chain aldehydes (called fatty aldehydes) to fatty acids as a part of lipid metabolism.[1] The disease is characterized by a clinical triad of congenital dry (icthyptic) skin, symmetric spastic di- or tetraplegia, and leukoencephalopathy leading to reduced intellectual ability in early childhood.[1,2] It was first described in 1957 in 28 individuals from several highly consanguineous families in a remote area of northern Sweden.[3] SLS has a unique ocular phenotype that typically appears early in life.[4] Fundus abnormalities consist predominantly of depigmented, pale areas in the macular region associated with glistening perifoveal crystal-like deposits.[5] The pathogenesis of retinal changes is not fully understood, although several theories have been proposed related to toxicity from the accumulation of fatty aldehydes and fatty alcohols caused by dysfunction of ALDH3A2.[4,6] Here, we report a patient with end-stage retinopathy due to SLS.

Case description

A 58-year-old woman with a history of SLS was referred for retinal evaluation because of several months of bilateral shadows in her vision. Her medical history was significant for chronic ichthyosis, bilateral muscle weakness and spasticity in the legs and ankles, Hashimoto's thyroiditis, and mild intellectual disability since childhood. Her surgical history included bilateral heel cord lengthening at age 2, an appendectomy after a ruptured appendix at age 6, and removal of abdominal adhesions to correct a bowel obstruction at age 9. Her ocular history included myopia, keratoconjunctivitis sicca, reduced central acuity, nyctalopia, and photophobia. The patient used bilateral short-leg orthoses and was able to walk short distances with a rollator walker. For longer distances, she relied on a power-assist wheelchair. She required significant assistance with activities of daily living and lived in a group home. She also regularly attended a day program where she participated in exercises and activities. At home, she reported performing self-stretches in bed with her ankle-foot orthotics off that had been prescribed by a physical therapist. The patient's medications included ammonium lactate (12%) cream, Cetaphil® moisturizing lotion, and Eucerin® cream applied topically daily, as well as oral supplementation with 500 mg calcium and 2000 IU of Vitamin D taken daily.

Examination revealed a thin, anxious woman with mildly impaired speech. Her corrected visual acuity was 20/200 in the right eye and 20/80 in the left. She was able to identify all 11 Ishihara color plates. Pupils were reactive without afferent pupillary defect. Ocular motility was normal

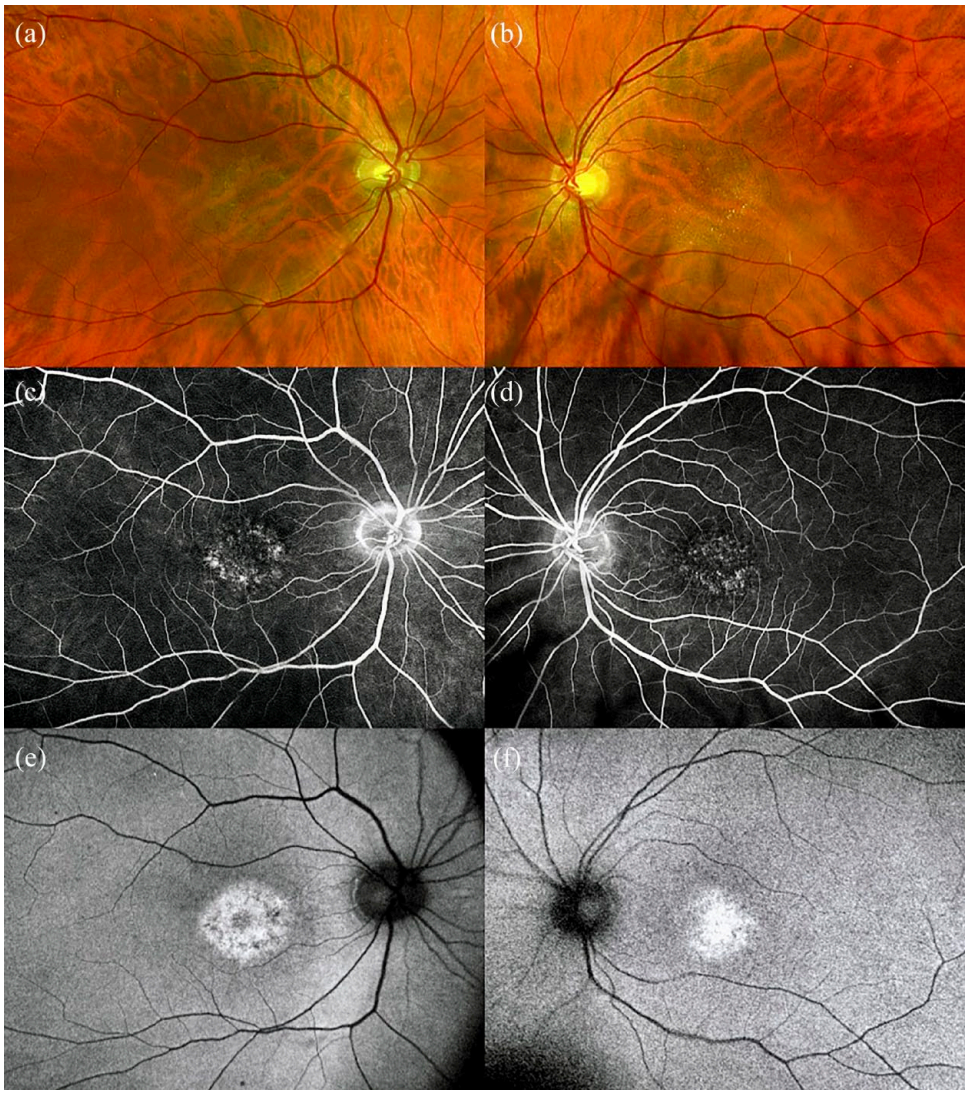

Figure 1. Fundus imaging of both eyes of a patient with end-stage Sjögren-Larsson syndrome (SLS). Fundus photographs of the (a) right and (b) left eyes show depigmented, pale areas in the central macula associated with faint yellow parafoveal crystalline deposits more numerous in the left than the right eye. Fluorescein angiography reveals staining of the inclusions in the (c) right and (d) left eyes. Fundus autofluorescence images illustrate hyperfluorescence with a speckled hypo-autofluorescence pattern in the parafoveal region of both the (e) right and (f) left eyes.

and visual fields were full to confrontation. Intraocular pressure was within normal limits in both eyes. Slit-lamp examination of the anterior segment was unremarkable except for bilateral nuclear sclerosis. Dilated fundus examination revealed depigmented, pale areas of atrophy of the central macula in both eyes associated with glistening crystal-like deposits consistent with a crystalline maculopathy (Figure 1(a) and (b)). Both optic discs were normal with a cup-to-disc ratio of 0.35 in the right eye and 0.4 in the left eye. Fluorescein angiography revealed stippled hyperfluorescence in the parafovea with staining of the crystalline macular deposits (Figure 1(c) and (d)). Fundus autofluorescence demonstrated parafoveal hyperfluorescence with a speckled hypo-autofluorescence pattern in both eyes (Figure 1(e) and (f)). Optical coherence tomography (OCT) demonstrated central macular atrophy with ellipsoid zone (EZ) band loss associated with cystoid degeneration and vitreomacular traction in both eyes (Figure 2). Physical limitations prevented psychophysical and electrophysiological testing.

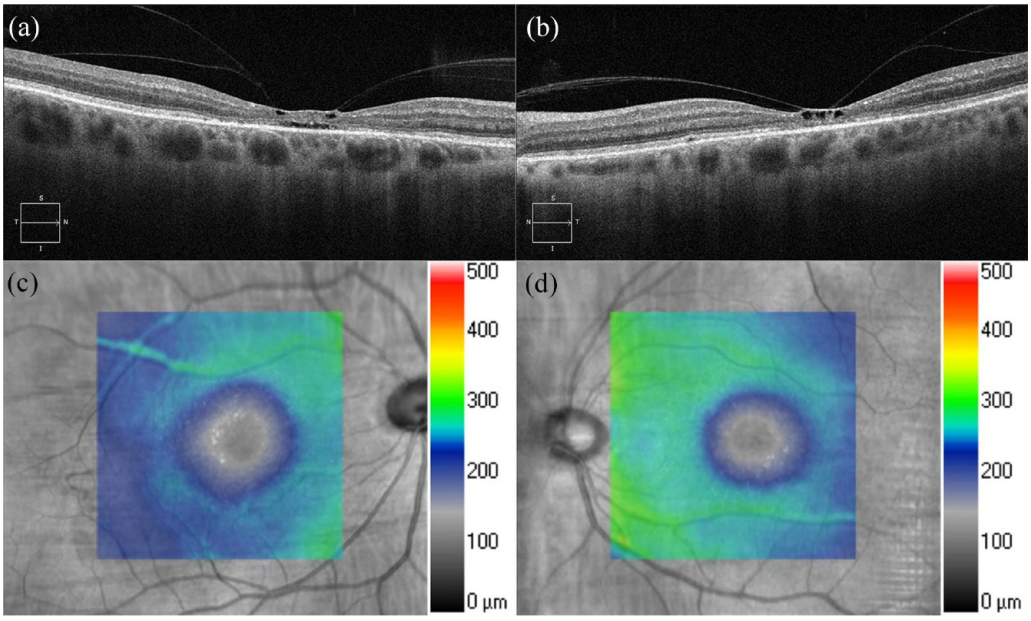

Figure 2. Imaging of the macula of a patient with end-stage Sjögren-Larsson syndrome (SLS). Horizontal high-definition (4096 A-scans) 6 mm spectral domain optical coherence tomography (SD-OCT) scans centered on the fovea of the right (a) and left (b) eyes (Cirrus software version 11.5.2.54532; Carl Zeiss Meditec, Inc. Dublin, CA). Outer retinal loss involves the parafovea of both eyes associated with cystoid macular degeneration. There is vitreomacular traction in both eyes with vitreous syneresis. A thin serous detachment of the macula is evident in the right eye. A distinct lack of reverse shadowing demonstrates the relative sparing of the retinal pigment epithelium layer. *En face* macular thickness maps (colored) derived from the 6 mm macular cube (512 × 128 macular cube) overlying the corresponding near-infrared reflectance fundus image (36° × 30°) centered on the fovea of the right (c) and left (d) eyes, respectively. Central macular thickness was significantly decreased to 118 µm on the right and 119 µm on the left.

Our study adheres to the tenets of the Declaration of Helsinki and was deemed exempt by the Institutional Review Board of the Lahey Hospital (Burlington, MA) by virtue of being a single case report. The patient involved provided written informed consent to publish all related medical data and images.

Discussion

The prevalence of SLS is estimated at 1 per 250,000 individuals worldwide, and as high as 8.3 per 100,000 individuals in certain regions of Sweden with high consanguinity.[7] Although Sjögren and Larsson never described the ocular findings associated with the syndrome that bears their names, SLS is associated with characteristic ophthalmic features including parafoveal crystalline deposits, photophobia, and progressive macular dystrophy which limits visual acuity.[1,4] Identification of these yellow-white glistening deposits and at least two of the elements of the clinical triad is pathognomonic for SLS.[4]

Understanding of the natural history of retinopathy in patients with SLS is limited by the rarity of the condition,[7] variation in penetrance of fundus abnormalities,[4,5] as well as by the severity of the associated neurologic, motor, and cognitive limitations.[8] Life expectancy in patients with SLS is generally decreased, with some estimates suggesting that it can be as little as half that of the unaffected population,[9,10] ranging from as few as 15 years in men to 26 years in women.[11] However, many of these estimates are based on patients who were historically institutionalized, which may independently contribute to reduced survival. Nevertheless, the shortened lifespan of patients with SLS, and variation of phenotype even between members of the same family,[12,13] also limits the ability to identify and monitor retinal abnormalities.[5] The systemic features of the disease often make it difficult to care for SLS patients and may hinder their performance of perimetry or other specialized testing, such as electroretinography. Hence, our case report of a patient who has far exceeded the average life expectancy of most

patients with SLS is quite unique because it demonstrates the ophthalmic findings associated with end-stage SLS retinopathy.

The characteristic intraretinal deposits in SLS typically appear in the first year of life and steadily increase in number through the second decade of life, concentrated in the parafovea.[4] However, in adults there is wide variation in the total number of intraretinal crystals, with new deposits forming and older inclusions disappearing dynamically.[14] Imaging with fundus autofluorescence typically reveals characteristic hyper- and hypo-autofluorescent foci and fluorescein angiography displays a mottled hyperfluorescent pattern without leakage,[4,6] as illustrated by our case. Studies using OCT demonstrate that these reflective deposits accumulate primarily in the inner retina, especially in the outer plexiform layer and inner nuclear layers.[14] It is not known whether variations in the extent of crystalline retinopathy are caused by genetic or environmental factors.[4,14–16]

As the disease progresses, the maculae of patients with SLS increasingly thins and becomes deficient in macular pigments, leading to a loss of central acuity.[4,6,17] It is not known whether the loss of macular pigment, composed primarily of lutein and zeaxanthin, is the result of decreased uptake, increased turnover, or a consequence of the loss of cells containing these carotenoids in the retina.[4,6] The depletion of these antioxidants may expose the retina to increased photo-oxidative damage, thereby contributing to retinal degeneration. Another non-mutually exclusive theory is that progressive retinal atrophy results from dysfunction of Müller glia, presumably through oxidative damage, or the buildup of toxic metabolites.[4]

In contrast with the progressive and severe degeneration of the retina in the central macula, the retinal pigmentary changes are comparatively mild. Nevertheless, studies have identified the accumulation of lipofuscin within retinal pigment epithelial cells in patients with SLS, confirmed by both autofluorescence[6,18] and ultrastructural studies.[19] However, the distinct lack of hypertransmission on OCT imaging of the macula in our case indicates that degeneration in SLS is limited to the neural retina and may not progress to involve atrophy of retinal pigment epithelium, even in advanced stages of the disease. Nevertheless, these changes probably contribute to impaired visual performance under low-light conditions. Finally, the results of electroretinography studies are usually normal early in the disease.[4] While visual evoked potentials are often absent or delayed in patients with SLS, these changes are attributed to leukoencephalopathy rather than to an optic neuropathy.[4]

The pathogenesis of retinal changes in SLS is not well understood. The leading hypothesis is that deficiency in the function of ALDH3A2 leads to the accumulation of fatty aldehydes and fatty alcohols.[4,6] ALDH3A2 is known to be expressed in the mammalian retina.[20] It is not known why this leads to damage concentrated in the parafoveal region. Ubiquitous in human tissues, the loss of function occurs from the inheritance of either a homozygous or compound heterozygous variant of the gene.[21] Fatty aldehydes are potentially toxic molecules that can form covalent Schiff base adducts with free amino groups in membrane lipids such as phosphatidylethanolamine or impair the function of cellular enzymes.[22] ALDH3A2 is also involved in epidermal lipid synthesis, and its deficiency can result in a disruption of the function of the stratum corneum as a water barrier.[1] This predisposes patients to keratoconjunctivitis sicca, which affected our patient.

In the central nervous system, deficiency in the function of ALDH3A2 interferes with the production and integrity of myelin, including in the brain and spinal cord of patients with SLS.[2,4,23] This may contribute to the neurologic features of the disease, including abnormalities in visual evoked potentials.[4] Magnetic resonance imaging (MRI) of the brain often reveals a gradual development of abnormalities starting as soon as the first year of life manifesting as white matter changes, along with mild ventricular enlargement, diffuse brain atrophy, and hypoplastic corpus callosum.[24] Interestingly, in one case report, F18-fluorodeoxyglucose positron emission tomography showed low glucose metabolism in the basal ganglia and thalami of a 13-year-old young woman with SLS who had as of yet an unremarkable MRI.[23] Cerebral proton magnetic resonance spectroscopy (^{1}H-MRS) of patients with SLS typically show lipid accumulation in the cerebral white matter beginning in the first year of life.[25] Yet there is little to no correlation between white matter findings on MRI, patient age, or clinical symptoms,[24] suggesting changes in gray matter and spinal cord contribute to the neurologic phenotype.[4] Neuroimaging was not obtained in our patient.

Molecular studies have implicated more than 90 bi-allelic variations in the ALDH3A2 gene on chromosome 17p11, but the extent to which these sequence variants lead to a deficiency in enzymatic activity is quite variable.[13,16,22,26–28] Population genetic studies show allelic clusters specific to Europe,[15,26,29,30] South America,[31] and the Middle East.[27] Although a pedigree analysis was not performed for our patient, there was no reported family history of SLS, or consanguinity. Nonetheless, there can be significant clinical variation in patients, even among siblings who share a common sequence variant.[12,13,26] This heterogeneity has made it difficult to recognize genotype–phenotype associations in SLS. Although to date no explanation has fully accounted for why some individuals have more mild phenotypes, possible explanations have been proposed to include revertant mosaicism[32] or compensatory, alternative metabolic pathways upstream of the defect in FALDH that allow some individuals to escape the metabolic defect.[33]

No specific therapies for SLS currently exist. Treatment is limited to the management of symptoms and physical therapy to counteract spasticity and to preserve mobility.[34] Ichthyosis is managed by using moisturizing creams. Keratoconjunctivitis sicca is managed with lubricating ophthalmic drops. Ongoing investigations exploring the utility of adopting a low-fat diet, the use of bezafibrates, carotenoids, and gene therapy.[4,35] While a small, open-label study reported that reduced leukotriene formation via the 5-lipoxygenase inhibitor zileuton may reduce pruritus,[36] a larger double-blind, placebo-controlled study of zileuton in ten SLS patients was unable to discern efficacy.[37] Nevertheless, there is good reason to investigate further the possibility that the reduction of aldehyde adduct formation could prevent progressive damage to the retina.[38,39] Of note, our patient had not been placed on a specialized diet or regimen of antioxidants or vitamins. Critical for managing the progression of the disease is the early recognition of signs and symptoms that can point to the condition and lead to confirmatory testing. Ophthalmologists are able to play a valuable role in the diagnosis of the disease by detecting the pathognomonic retinal findings. This facilitates early detection of the disease, followed by treatment to decrease associated morbidity. In the future, gene therapy may be a potential option for the treatment of SLS.[38]

Conclusion

In summation, we present a patient with the end-stage retinal degeneration that accompanies the crystalline retinopathy associated with SLS. The features of parafoveal crystalline deposits, photophobia, and progressive central macular thinning associated with decreased central visual acuity, confirmed by multimodal imaging, provide a more complete picture of this rare retinal condition in its late stages than has previously existed in the literature. Building on this enhanced appreciation of the effects of this disease on the eye, the ophthalmologist should be able to play a more proactive role in making a timely diagnosis and setting in motion an early application of treatment.

Declarations

Ethics approval and consent to participate

Our study adheres to the tenets of the Declaration of Helsinki and was deemed exempt by the Institutional Review Board of the Lahey Hospital (Burlington, MA) by virtue of being a single case report.

Consent for publication

The patient involved provided written informed consent to publish all related medical data and images.

Author contributions

Lester H. Lambert: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Noreen Shaikh: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Jeffrey L. Marx: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – review & editing.

David J. Ramsey: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

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Availability of data and materials

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