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Ophthalmic Findings in Late Stage Sjogren-Larsson Syndrome

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Abstract

Purpose—To report spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF) documentation of late stage macular findings associated with Sjogren-Larsson Syndrome in three adult siblings.

Methods—Three adult siblings with Sjogren-Larsson Syndrome underwent ophthalmic examination and imaging.

Results—Crystalline maculopathy and subretinal deposits, presumably lipofuscin accumulation, with macular atrophy were present in varying degrees in all three adult siblings.

Discussion—In adults with Sjogren-Larsson Syndrome, crystalline retinopathy can progress to macular atrophy and the appearance of lipofuscin accumulation.

Keywords

Crystalline retinopathy; Fundus autofluorescence; Muller cell; Sjogren-Larsson Syndrome; Spectral domain optical coherence tomography

Introduction

Sjogren-Larsson Syndrome (SLS) is a rare, autosomal recessive disorder with an estimated prevalence of <0.4 per 100,000. This neurocutaneous disorder presents as congenital ichthyosis, spasticity, and mental retardation.¹ By age two, ophthalmic changes are generally present and progress with age. SLS is caused by a defect in lipid metabolism, due to a microsomal fatty aldehyde dehydrogenase enzyme (FALDH) deficiency. The consequent accumulation of fatty aldehydes and fatty alcohols disrupts white matter myelin and the barrier functions of the stratum corneum.^{2–4}

Ophthalmic manifestations can involve all retinal layers, including the accumulation of undigested lipid metabolites in retinal ganglion cells, secondary to FALDH deficiency. The formation of foveal and parafoveal crystals is associated with the degeneration of Muller cells in the inner retina, and eventually, retinal pigment epithelium compromise from

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lipofuscin accumulation, leading to progressive RPE atrophy.⁵⁻⁶ Macular pigment (lutein and zeaxanthin) is reduced in the fovea in SLS and is likely caused by a reduction in carotenoid accumulation and Muller cell dysfunction.⁷ Patients may complain of photophobia and reduced visual acuity (VA), secondary to Muller cell compromise, retinal thinning, photoreceptor dysfunction, and RPE atrophy.

We present the first reported spectral domain optical coherence tomography and fundus autofluorescence documentation of lipofuscin accumulation and RPE atrophy, which are advanced macular findings associated with Sjogren-Larsson Syndrome, in three non-consanguineous Caucasian adult siblings.

Case Report

Three siblings (35, 38, and 42- years-old) presented with congenital ichthyosis, spasticity, and mental retardation. The diagnosis of Sjogren-Larsson Syndrome (SLS) had been made at prior institutions during childhood and included confirmatory genetic testing. A detailed ophthalmologic examination included assessment of best-corrected visual acuity (BCVA), slit-lamp examination, fundoscopy, and extensive fundus imaging using standard color fundus photography, auto-fluorescence (FAF) and near-infrared reflectance imaging (Heidelberg HRA2), and spectral domain optical coherence tomography (SD-OCT; Heidelberg Spectralis OCT).

Patient 1

A 35-year-old woman presented with best-corrected visual acuity (BCVA) of 20/50 OU with mild myopia. On adnexal exam scaling of her upper lids was noted. Anterior segment exam was normal as was her peripheral retinal exam. Her optic nerves appeared healthy. On macular evaluation, intraretinal crystals were present OU along with retinal pigmentary changes and atrophy. These changes were symmetrical between the two eyes, except for more prominent lipofuscin accumulation in the right macula (Figure 1A). Fundus autofluorescence imaging revealed scattered areas of hyperautofluorescence, corresponding to pigmented areas of the macula and signifying areas of increased lipofuscin. Additional areas of hypoautofluorescence signified regions with RPE atrophy (Figure 1B). Spectral domain OCT showed crystals in the outer plexiform layer (OPL), inner plexiform layer (IPL), and nerve fiber layer OU, and pseudocystic atrophy in the right eye. Areas of ellipsoid zone disruption and retinal pigment epithelium (RPE) disruption are noted along with subretinal deposits, presumably lipofuscin accumulation OU (Figure 1C–D). Decreased central retinal thickness (CRT) was also appreciated OU.

Patient 2

The 38-year-old man presented with BCVA of 20/70 OD and 20/60 OS and mild hyperopia. Scaling was noted on bilateral upper lids. Anterior segment, optic nerve, and peripheral retinal examination were all normal. Macular evaluation revealed intra-retinal crystals and RPE changes in the fovea and para-foveal zones. One pigmented nidus of lipofuscin accumulation was noted in each macula superotemporal to the fovea (Figure 2A). Hyperautofluorescence was noted in the fovea and in the few areas of lipofuscin

accumulation OU on FAF imaging (Figure 2B). Crystals were noted in the OPL and IPL OU and pseudocystic atrophy was present OU along with significant retinal thinning, ellipsoid zone (EZ) disruption and a subretinal deposit OU on SD-OCT (Figure 2C). Central retinal thickness was reduced OU. Atrophic changes and lipofuscin deposits were less prominent compared to Patient 1.

Patient 3

The 42-year-old woman presented with BCVA of 20/70 OD and 20/80 OS with mild myopia. No lid scaling was present. Anterior segment, optic nerve, and peripheral retinal examination were all normal. Macular evaluation revealed fewer intraretinal crystals compared to her younger siblings and more prominent pigmentary changes and atrophy OU. General fundus pigmentation was lighter than her siblings as well (Figure 3A). FAF showed foveal hyperautofluorescence surrounded by a ring of hypoautofluorescence punctuated by areas of increased lipofuscin and hyperautofluorescence (Figure 3B). Fewer crystals were present relative to her siblings on SD-OCT, but EZ and RPE disruption were more prominent, as were areas of subretinal deposits, presumably lipofuscin accumulation (Figure 3C).

Discussion

This report demonstrates advanced SLS maculopathy in three adult siblings in the second largest family with genetically confirmed SLS, and the first from non-consanguineous origins. All three patients developed diplegic spasticity requiring walkers. The two oldest siblings were first discussed in a dermato-pathology paper in 1982.⁸ Considering no prior ophthalmic findings were recorded, a longitudinal comparison was not possible.

A crystalline maculopathy of varying severity was present in these three adult siblings. Crystals can be appreciated in any retinal layer but are usually most prominent in the outer and inner plexiform layers of the retina in patients with SLS. Considering that the Muller cell body is located in the inner nuclear layer with processes extending into the outer limiting membrane and inner limiting membrane of the inner retina, crystals found in this distribution could be considered a marker of Muller cell damage.⁹ Crystal formation has been documented in SLS patients as young as 3 years old and seems to be a relatively early step in pathogenesis.¹⁰

Muller cells function as support cells for other cells in the retina as they phagocytose outer segments shed from cones and defend against oxidative stress.⁹ They also act as optical fibers within the retina, without which photophobia could be exacerbated, as occurs in SLS patients. Muller cell dysfunction can also contribute to a loss of macular pigment, which is a feature of SLS maculopathy. Loss of macular pigment can lead to an increase in oxidative stress as well.

A consequence of the fatty aldehyde dehydrogenase enzyme (FALDH) deficiency in SLS is an accumulation of fatty aldehydes and fatty alcohols in several body tissues, including the retina. This accumulation of lipid and/or the secondary oxidative byproducts from lipid metabolism may result in Muller cell dysfunction. Muller cell damage could also further

compromise the retina's ability to metabolize and remove excess lipid and minimize the production of oxidative byproducts. Muller cell compromise can lead to neuronal apoptosis and photoreceptor damage, clinically demonstrated as pseudocystic atrophy, retinal thinning, increased lipofuscin, and RPE atrophy. These macular findings are the end-stage changes in SLS maculopathy that are present in varying degrees in our three adult patients.

Retinal crystals in this particular distribution and the atrophic retinal changes (IS/OS and RPE disruption) appear similar to those found in type 2 idiopathic macular telangiectasia and tamoxifen retinopathy, meaning that all three conditions may involve Muller cell dysfunction as an early step in a pathway which culminates in retinal atrophy. Unlike type 2 idiopathic macular telangiectasia and tamoxifen retinopathy, SLS maculopathy features subretinal deposits (presumably lipofuscin accumulation) late in the disease progression.

To the best of our knowledge we offer the first documentation of spectral domain optical coherence tomography and fundus autofluorescence findings of lipofuscin accumulation and RPE atrophy in advanced stage Sjogren-Larsson Syndrome maculopathy in three non-consanguineous Caucasian adult siblings. The maculopathy in this condition likely involves Muller cell dysfunction and has similar features to type 2 idiopathic macular telangiectasia and tamoxifen retinopathy, suggesting a common pathway that culminates in retinal atrophy. Reclassification of these conditions and potentially others based on Muller cell dysfunction rather than the presence of retinal crystals may be indicated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Summary

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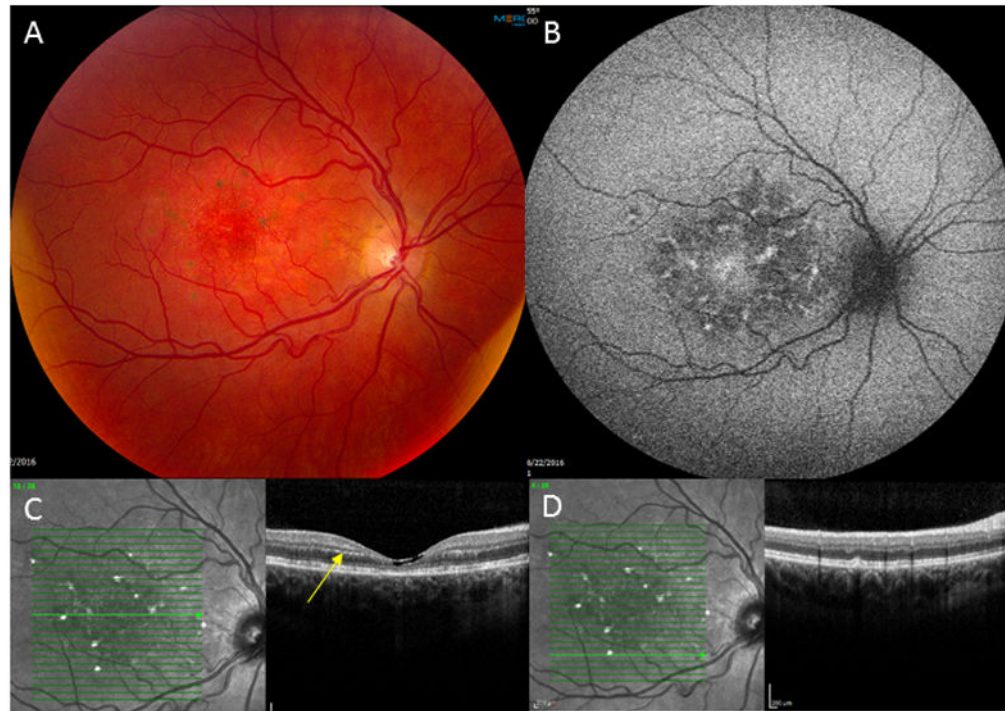


Figure 1.

A—Fundus photo OD showing intraretinal crystals in the macular region along with retinal pigmentary changes and atrophy. Several hyperpigmented spots of greater lipofuscin accumulation can be seen. B—Fundus Autofluorescence OD showing scattered hyperfluorescence consistent with pigmented regions of the macula and areas of increased lipofuscin accumulation, and patchy hypofluorescence indicative of RPE atrophy. C—SDOCT with crystals (yellow arrow) noted in the OPL, IPL, and nerve fiber layer OD. Additional regions of EZ and RPE disruption with subretinal lipofuscin accumulation is appreciated. Foveal pseudocystic atrophy is also appreciated. D—Subretinal (presumably lipofuscin) deposit.

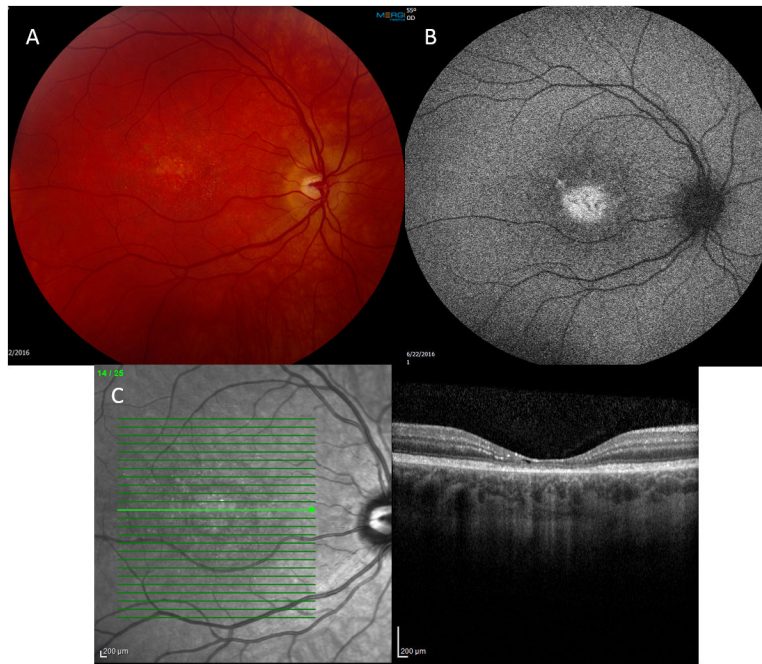


Figure 2.

A—Fundus photo OD with milder crystalline deposition and RPE atrophy than Patient 1. A single nidus of dark pigmentation secondary to lipofuscin accumulation is noted in the superotemporal region of the macula (arrow). B—FAF with hyperfluorescence from lipofuscin accumulation. C—SDOCT OD shows crystalline maculopathy and pseudocystic atrophy with significant retinal thinning.

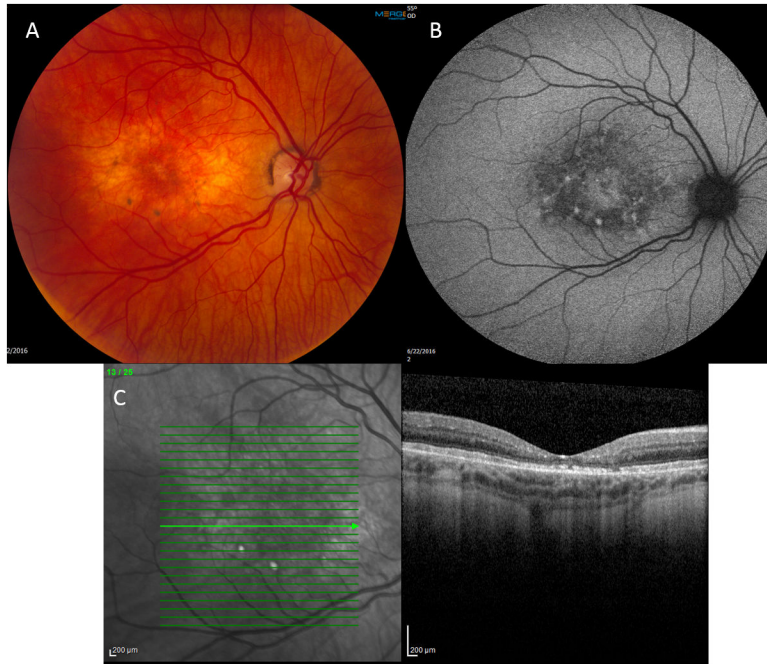


Figure 3. A—Fundus photo OD with prominent pigmentary changes and retinal atrophy, and diffuse fundus hypopigmentation. B—FAF shows foveal hyperfluorescence and a ring of hypofluorescence. C—SDOCT reveals fewer crystals relative to the patient’s siblings. There is prominent EZ and RPE disruption, and subretinal (presumably) lipofuscin accumulation.