Autofluorescence and High-Resolution OCT Findings Revealed Ciliopathy in Senior-Loken Syndrome

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Abstract

To describe novel findings on fundus autofluorescence (FAF) and high-resolution optical coherence tomography (OCT) in a 27-year-old woman with the Senior-Loken syndrome (SLSN) emphasizing the photoreceptors' cilia appearance in the macula. The patient had renal transplantation early in life and poor visual acuity due to advanced autosomal recessive retinitis pigmentosa. FAF showed diffuse spots of decreased autofluorescence in the mid-periphery and a perifoveal ring of increased autofluorescence suggesting a bull's eye maculopathy. High-resolution OCT revealed a barely detectable inner-outer photoreceptor segment junction in the central macula corresponding to the area inside of the ring of increased autofluorescence, suggesting initial ciliary junction disorganization before photoreceptors death. Non-invasive technologies can monitor central photoreceptors ciliary anatomy enabling early detection of cell disorganization in diseases involving ciliopathy such as the Senior-Loken syndrome are concluded.

INTRODUCTION

Senior-Loken Syndrome (SLSN) is characterized by nephronophthisis resulting in end-stage renal disease associated with retinitis pigmentosa (RP).^{1–3} This association is observed in about 33% of nephronophthisis patients and the syndrome can be presented in two clinical forms: (I) juvenile, with severe renal dysfunction and severe RP; and (II) adult, with slow-progressive evolution.⁴

SLSN is a autosomal recessive disease caused mainly by mutation in the IQCB1 gene (also known as NPHP5), located on chromosome 3q21.1.5 IQCB1 encodes the protein nephrocystin-5, expressed in the connecting cilia of photoreceptors and in primary cilia of renal epithelial cells.^{5,6} In the retina, nephrocystin-5 co-localizes with retinitis pigmentosa GTPase regulator (RPGR) involved in both X-linked RP and Leber congenital amaurosis⁵ and it is responsible for epithelial cell integrity, resulting in renal cyst formation in cases of protein dysfunction in the kidneys.⁷

Progressive photoreceptor death in RP ultimately causes macular atrophy, which can be assessed in vivo by fundus autofluorescence (FAF) and high-resolution optical coherence

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tomography (OCT). FAF detects abnormal distribution of lipofuscin in the retinal pigment epithelium (RPE) derived from photoreceptor's outer segment phagocytosis.^{8,9} Abnormal accumulation or depletion of lipofuscin can manifest as increased or detectable instead of detected decreased autofluorescence image, respectively, helping to characterize inherited retinal disorders such as RP.¹⁰ In turn, high-resolution OCT delineates the ciliary junction between the inner and outer segments of the photoreceptors¹¹ and this junction presents as intact, absent or partially distinct, affecting visual acuity in different degrees in RP patients.¹²

We describe a case of SLSN in which fundus autofluorescence and high-resolution OCT imaging enhances visualization of the photoreceptor ciliary abnormalities in this disorder.

CASE REPORT

A 27-year-old woman presented with a complaint of progressive peripheral visual loss in the last 9 years. The patient's past medical history included renal transplantation at the age of 17 years due to kidney dysplasia causing end-stage renal disease. Her 17-year-old brother had the same visual complaints and funduscopy changes and he also had renal transplantation at the age of 5 years. Her parents were 4th degree cousins and she had an uncle and two great-grandmothers who all lost sight due to an unknown origin (Fig. 1).

Visual acuity was 20/80 in her right eye and 20/200 in her left eye and no nystagmus was present. On funduscopy examination, she had diffuse and mild atrophic RPE changes with mid-peripheral pigments clumps, relatively spared macula and diffuse vascular attenuation in both eyes. In her left optic disc some drusen were noted (Fig. 2). Fundus autofluorescence (FAF) showed diffuse spots of decreased autofluorescence in the mid-periphery and a perifoveal ring of increased autofluorescence (Fig. 3). An inner-outer photoreceptor segment junction was barely detected in the central macula (Fig. 4) on spectral-domain optical coherence tomography (SD-OCT), corresponding to the area inside of the ring of increased autofluorescence observed after image superimposition using a software in MatLab 2.0. Full-field electroretinogram (ERG) revealed attenuation in both scotopic and photopic responses and together with clinical findings suggested the diagnosis of retinitis pigmentosa. Family pedigree consistent with an autosomal recessive inheritance of retinitis pigmentosa in an association with early-onset renal failure defined the diagnosis of Senior-Loken syndrome.

DISCUSSION

SLSN is an autosomal recessive condition characterized by nephronophthisis and retinitis pigmentosa. Nephronophthisis is a chronic disease with resulting formation of corticomedullary cysts and renal failure.¹³ Pathogenesis involves mutation in the nephronophthisis genes, expressed both in the sensitive cilia of renal epithelial cells and in the retinal photoreceptors connecting cilia.¹³

Even though different genes are associated with SLSN, nephronophthisis is a common feature. However, ocular involvement can present several phenotypes, including retinitis pigmentosa, congenital Leber amaurosis, nystagmus, amblyopia, Coats' disease, cataract, and keratoconus, according to the mutated gene.^{14–20}

NPHP1 gene (2q13) has been described in association with late-onset RP in a small percentage of patients.¹⁴ NPHP3 gene (3q22) mutation can cause profound vision loss with abolished ERG responses, nystagmus, abnormal pupillary reflexes, and retinal changes ranging from early-onset RP to Leber congenital amaurosis.¹⁵ Leber congenital amaurosis and late-onset RP have been associated with in loss-of-function alleles in NPHP4 gene

(1p36).^{16,17} Homozygous deletions in NPHP6 were described in association with tapetoretinal degeneration and Joubert syndrome.¹⁸ However, the most frequent gene related to SLSN is IQCB1 (NPHP5), manifesting early-onset RP in nearly 100% of cases.⁵

Our patient and her brother had renal transplantation early in life and poor visual acuity due to advanced RP. Consanguinity and autosomal recessive inheritance was observed in the family pedigree. Generalized photoreceptor dysfunction and typical vascular and peripheral retinal abnormalities of RP were present. Generally, these features often appear later in the disease process.¹³ The apparent clinically normal macula revealed photoreceptor damage on FAF, as stated by the fact that RP patients can manifest three different autofluorescence changes in the macula: (I) abnormal ring of increased autofluorescence surrounding the fovea; (II) abnormal central autofluorescence; and (III) neither ring nor central autofluorescence.²¹ FAF abnormality is a non-specific manifestation, suggesting increased RPE metabolic activity before photoreceptor death and RPE atrophy.²² Parafoveal ring of increased autofluorescence is a common finding in RP patients with different mutations¹⁰ and, besides, the RPGR gene, involved in X-linked RP, co-localizes with the IQCB1 protein in the photoreceptor cilia.⁵

Our patient had a parafoveal ring of increased autofluorescence, suggesting parafoveal rod dysfunction.²³ The relative preserved central autofluorescence corresponding to central cones was then morphologically assessed by high-resolution OCT. In the area within the hyperautofluorescent ring, the ciliary junction between inner and outer segments (IS/OS) was present, despite barely detectable, but outside the ring, neither IS/OS junction nor external limiting membrane (ELM) was observed. These findings are in agreement with the parafoveal rod dysfunction suggested by FAF, because the ELM can be used as a landmark to represent abnormalities in the photoreceptor's outer segment and the thickness between the ELM and retinal pigment epithelium is proportional to visual function.²⁴

Our findings show that initial ciliary disorganization in central macula occurs before photoreceptor cell death and outer segment loss. Ciliary disorganization is a novel finding, because usually the high-reflectance band corresponding to inner-outer segment junction is well-delineated and preserved within the autofluorescence ring.²¹

SLSN belongs to the group of ciliopathies and as understanding about its underlying genetic profile and pathophysiology emerges, a more effective treatment approach can be developed. In the ophthalmic field, new non-invasive diagnostic technologies as fundus autofluorescence and high-resolution OCT are helpful in the monitoring photoreceptor sensory cilia, making a more defined clinical parameter to gauge prognosis and efficacy in future therapies.

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Figure 1.

Family pedigree showing the patient (arrow pointing to black circle) and her brother (black square) with Senior-Loken Syndrome (SLSN). An autosomal recessive trait and consanguinity are observed. Her uncle (gray square) and two great-grand-mothers (gray circles) were blind due to an unknown cause and no history of renal disease was assessed.

Figure 2. Fundus image showing diffuse atrophic retinal pigment epithelium (RPE) changes, arteriolar attenuation and clinically spared central macula in both eyes. Mild hypopigmentation is noted in the right eye. Optic disc drusen and intraretinal pigment migration in the mid-periphery are observed in the left eye.

Figure 3.

Fundus autofluorescence showing diffuse areas of decreased autofluorescence corresponding to retinal pigment epithelium (RPE) atrophy and a ring of increased autofluorescence surrounding the fovea in both eyes. Highly-increased autofluorescence is seen on optic disc corresponding to drusen formation in the left eye.

Figure 4.

High-resolution optical coherence tomography (OCT) showing (A) a cross-section image of central macula from an age-matched control eye; the limits of the inner-outer segment (IS/OS) junction (arrows) corresponding to the area within the hyperautofluorescent zone patient's right eye (B) and left eye (C). OCT and autofluorescence images are consistent with photoreceptor IS/OS junction cilia disorganization. Nasally and temporally, neither IS/OS junction nor ELM is observed (outside the limits pointed by arrows), corresponding to the area outside the hyperautofluorescent ring. In the left eye (C), a highly reflective line in the inner surface of the retina (arrowhead) represents an epiretinal membrane. Retinal thickness values in microns are placed to the side of the corresponding eye.