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Spectral-domain optical coherence tomography findings in Alström syndrome

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Abstract

Background—Alström syndrome is a multi-system recessive disorder caused by mutations in *ALMS1* gene. The aim of this study was to characterize morphological retinal changes in Alström patients using spectral-domain optical coherence tomography.

Methods—We studied volunteer patients attending the conference of Alström Syndrome International, a support group for affected families, using hand-held spectral-domain optical coherence tomography (SD-OCT) in an office setting. Patients had a clinical dilated retinal examination. Past medical records were reviewed.

Results—Twenty-two Alström patients (mean age 17 years, range 2 – 38 years, 12 males) were studied. OCT imaging demonstrated that central macular OCT changes are often mild during the first decade of life and gradually progress, demonstrating disruption of normal retinal architecture, and progressive loss of photoreceptors and retinal pigment epithelium with increased prominence of choroidal vasculature. Other changes found included hyperreflectivities in all retinal layers, severe retinal wrinkling, optic nerve drusen and vitreoretinal separation. Vision correlated with severity of OCT macular changes ($r=0.89$, $P=0.002$).

Conclusions—This study reports on OCT findings in a large group of patients with Alström syndrome. We document a panretinal gradual progression of retinal changes, which are often mild during the first years of life. Previously unreported observations include intraretinal opacities, optic nerve drusen and foveal contour abnormalities. Morphological retinal changes demonstrated

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by SD-OCT may help in understanding the pathophysiology of the disease and defining strategies for treatment such as gene therapy.

Keywords

Optical coherence tomography; Alström syndrome; ocular genetics

Introduction

Alström syndrome is a rare autosomal recessive ciliopathy caused by mutations in the *ALMS1* gene located at 2p12-13, with a prevalence of less than one per million in the general population.^{1, 2} The deficiency of ALMS1 protein affects cellular transport and structural support in many organs by a mechanism which is not completely understood. Manifestations include dilated cardiomyopathy, sensorineural hearing loss, insulin resistance, hyperinsulinemia, type 2 diabetes mellitus, and retinal degeneration. Life expectancy is reduced, rarely exceeding 40 years, usually the result of cardiac, renal, hepatic, or pulmonary failure.³ Great variability exists in onset, severity and progression of clinical symptoms, even within families harboring the same mutation.

The ophthalmic signs typically present in infancy with nystagmus, subnormal vision and photophobia. Rapidly progressive vision loss due to retinal dystrophy is usually observed throughout childhood. By the age of 10 years, most children have a visual acuity of counting fingers and by the second-to- third decade of life complete loss of vision is expected.⁴ On electroretinogram (ERG), there is initially decreased cone function followed later by rod involvement. Both systems usually yield undetectable ERG responses by the age of 5 years.⁵ Although no therapy currently exists for the progressive vision loss, early diagnosis by ophthalmologists is important for evaluation and treatment of potentially life threatening conditions, in particular cardiomyopathy, initiation of visual rehabilitation and genetic counseling.

The purpose of this study was to characterize the morphological changes of the retina in patients with Alström syndrome using spectral-domain optical coherence tomography (SD-OCT) in order to provide anatomic correlates which may help to elucidate the pathophysiology of the disease and define strategies for treatment such as gene therapy.

Methods

We studied volunteer patients attending the Alström Syndrome International (ASI) conference in Plymouth, Massachusetts. ASI provides support, medical consultation and a research locus for affected patients and their families. Patients were recruited by one of the authors (JDM), who is the Chair of the Scientific and Medical Advisory Board for ASI. All families attending the conference were given information about the study in advance of the meeting via the ASI newsletter and additional explanations were provided in the conference booklet upon registration. All attendees had the opportunity to meet with the recruiting author in person to discuss questions or concerns. Our ocular investigations were one arm of multifaceted research investigations being conducted at the conference. Patients could choose to enroll in all, one or selected projects offered at the conference. The choice to

participate or not did not affect the services and support available to the families. Written informed consent was obtained using a format that allowed patients/substitute decision makers to choose their level of participation. Consent forms were either read or translated to suitable media (e.g. via scanning, Braille) for the visually impaired. Patients did not receive any financial compensation for participating in this study. The study was approved by the Institutional Review Board of The Jackson Laboratory.

All patients had a diagnosis of Alström syndrome by accepted clinical criteria,³ and confirmed by molecular genetic testing. Ophthalmic and medical history was obtained from the medical records of the patients provided to ASI by the families. Visual acuity was graded on a scale from 0 to 3: 0=better than 20/40, 1=20/40 to 20/400, 2=20/800 to light perception, 3=no light perception. No further ophthalmic examination was done on site other than dilated funduscopy after which spectral domain optical coherence tomography (SD-OCT) images were obtained using the Envisu C2300 hand-held SD-OCT (Bioptigen, Research Triangle Park, NC). The technique used for obtaining OCT images with this instrument has been previously described.^{6–8} Examinations were conducted in a darkened room at the hotel, usually performed in the supine position, but in some patients the sitting position was the preferred method.

Measurement of foveal thickness was performed by an experienced OCT technician (EA) at the center of the foveal pit, from the deepest point of the pit to the level of the RPE using the caliper provided with the imaging software. Measurements were taken only in images in which the fovea was clearly identified by its characteristic features.⁹ A retina specialist (VK) experienced in interpretation of OCT images, and unfamiliar with clinical details of the patient, graded all foveal images as showing mild, moderate or severe changes. Mild changes (=1) were graded when OCT morphology was almost entirely normal, moderate (=2) when there was evidence of photoreceptors and RPE cell loss with preservation of retinal architecture and severe (=3) when there was complete loss of retinal morphology. Images that included the optic nerve were reviewed for evidence of optic disc drusen.

For statistical analysis purposes patients were divided into groups by decade of life. Statistical analysis was performed using Prism 6 software (GraphPad Software Inc., San Diego, CA). Descriptive statistics regarding age, sex, and frequency of systemic manifestations is provided. We used Pearson correlation coefficient test to examine the relationship between age and foveal thickness, and linear regression analysis was performed to correlate change in foveal thickness with increased age. A Spearman rank correlation test was calculated between visual acuity and grading of OCT scans. Analysis of OCT macular grades by age group was calculated with the nonparametric Kruskal-Wallis test. Images of the optic nerve were analyzed for the proportion demonstrating optic disc drusen. Statistical significance was tested at a two-tailed level of 0.05.

Results

Fifty-six Alström patients attended the 2013 ASI conference of which 32 (57%) consented to participate in our study. Patients with autistic spectrum behaviors that would likely preclude the ability to comply with OCT image acquisition and adults with known advanced

cataracts were not included in the study. Thirty-one percent (10/32) of consented patients were later excluded from analysis because they were unable to comply with OCT imaging instructions and had OCT images of poor quality. Mean age of the remaining 22 patients (12 males) was 17 years (range 2–38 years). All patients had at least one *ALMS1* mutation (Table 1). There were only 6/22 patients with homozygous mutations. Twelve patients harbored compound heterozygous mutations; most often in different exons. There were four patients in whom only one heterozygous mutation was found. The number of patients reported in this study is not sufficient to establish genotype-phenotype correlations. In addition, analysis of genotype-phenotype correlations ideally should be done on patients of approximately the same age. Ninety-one percent of patients (20/22) had hearing loss, 36.3% (8/22) had dilated cardiomyopathy, and 31.8% (7/22) had diabetes mellitus (Table 1).

Visual acuity ranged from 2/60 to no light perception. Children in their first decade of life had some useful vision and were usually able to read large print. Vision loss progressed during the second decade of life such that all patients older than 20 years were completely or nearly completely blind. Fundoscopic findings also demonstrated a pattern of progression. During the first decade and the beginning of the second decade of life the fovea was usually apparent, the internal limiting membrane (ILM) reflex was mildly reduced, no “bone spicule” pigmentary clumping was seen, vascular attenuation was mild, and optic atrophy, if present, was usually mild if present. “Bull’s eye” maculopathy was seen in patients 9 to 12 years old. From the middle of the second decade of life onward the fovea became progressively less apparent, the ILM reflex was lost, vascular attenuation became more severe, pigmentary clumping increased and optic atrophy became severe.

Macular OCT images demonstrated foveal thinning accompanied by loss of photoreceptors and retinal pigment epithelium (RPE, Figure 1). Other changes noted included marked parafoveal outer nuclear layer (ONL) thinning, which was apparent even in young patients with earliest disease (Figure 1A). Based on our grading methods of macular OCT changes, we found a median grade of 0.5 in the first decade of life, 1 in the second decade of life, and 2 in the third decade and older. Kruskal-Wallis analysis showed that OCT grades by age group were statistically different ($P=0.009$). Disruption of the morphology of the foveal architecture was a typical feature in older patients. Severity of foveal OCT changes was correlated with vision ($r=0.89$, $P=0.002$). Based on the 13/22 patients with sufficient data for analysis we found that foveal thickness was poorly correlated with age ($r=-0.44$, $P=0.13$).

OCT images of the retina peripheral to the macula showed progressive loss of the normal retinal architecture with age, loss of photoreceptors, loss of RPE and prominent choroidal vasculature (Figure 2). Hyperreflectivities in all retinal layers causing shadowing and severe wrinkling of the retina are OCT features seen only in older patients (Figure 3). Out of the eight patients who had OCT scans of the optic nerve, three (38%) had evidence of optic disc drusen; however, none of the drusen identified on OCT were seen with indirect ophthalmoscopy, perhaps in part because of the challenges of clinical examination in this setting on these sometimes difficult patients with poor fixation.

Discussion

We report the largest study, to our knowledge, of ocular OCT in patients with Alström syndrome. Ocular involvement typically begins in early infancy and includes reduced visual acuity, nystagmus and photodysphoria.⁵ Progressive deterioration of vision occurs throughout childhood, usually reaching light perception only during the second decade of life, although variations in rate of progression can occur, even within families harboring the same mutation.^{4, 10} We found similar results, with most patients retaining useful vision in their first decade of life, being able to read large print, an ability that was typically lost in their teens. We found that vision loss was correlated to the degree of disruption of normal retinal morphology demonstrated on OCT. Our findings suggest that vision loss correlates with loss of photoreceptors, thinning of the fovea and loss of retinal stratification seen on OCT. Previous reports identified cilia dysfunction in photoreceptors in Alström, causing a defect in rhodopsin transport and loss of vision.¹¹ Typical electrophysiologic changes include early cone-dysfunction followed later by rod involvement.¹²

The earliest fundus changes in eyes of Alström patients include a nonspecific granularity of the midperipheral retina.¹³ Bull's eye maculopathy is often seen in older patients, as confirmed in our study as well.¹⁰ Narrowing of the retinal vessels, atrophy of the RPE with development of "bone spicules" pigmentary clumping, and increased visibility of the choroidal vasculature were typically seen with advanced age. Other reports described atrophy and drusen of the optic nerve in Alström patients.^{5, 14} Our youngest patient with optic nerve drusen was 4 years old.

We are aware of only one other publication using OCT in Alström syndrome.¹³ The authors studied a 5-year-old boy and demonstrated mild thinning of the macula, and evidence of retinal immaturity consisting of a single layer of short thick cones and rods as well as immature short outer segments. In our study we did not find these findings. However, it is possible that the cause for this difference is the fact that none of our Alström patients had the genetic mutation of the patient presented by Vingolo et al.¹³ Genotype-phenotype variability is possible and remains to be shown in this condition.

Our study highlights the progressive retinal changes seen in Alström patients over time; however, since this is a cross sectional study of patients with many different genotypes it may well be that the rate of progression is genotype dependent. Patients in the first decade of life demonstrated loss of photoreceptors and RPE cells while retinal stratification was preserved. As photoreceptors degenerated, there is residual "debris" appearing as hyperreflective clumps at that layer (Figure 3), presumably composed of degenerated photoreceptors or migrated RPE cells,¹⁵ very different from the more discreet intraretinal hyperreflectivities seen in the third and fourth decades in the other retinal layers. Beginning in the second decade of life there was a more widespread loss of photoreceptors and RPE cells, and loss of normal layering. In the third and fourth decades of life there was severe disruption of normal retinal architecture with wrinkling of the inner retina and hyperreflectivities in all retinal layers. Typically, there was preservation of the inner nuclear layers. Although reduced in number, photoreceptors were not yet completely lost. Similar age progressive disruption of normal retinal layering with accumulation of hypertrophic RPE

cells within the inner retina have been described in patients with Bardet-Biedl syndrome due to mutations in *BBS1* and *BBS10*,¹⁶ which like the mutated gene in Alström syndrome, *ALMS1*, are involved with cilia function. Animal models have shown that loss of photoreceptors that occur in many hereditary retinal diseases, including ciliopathies, may initiate a common cascade of events that alters retinal structure and physiology, which can lead to a common retinal appearance despite different mutated genes.^{17, 18} In advanced disease stages there was marked thickening of the remaining inner retina after total photoreceptor loss, reminiscent of other retinal degenerations.¹⁹

To our knowledge pathological findings were reported in a single case of 32-years-old Alström patient,¹⁴ that showed “bone spicule” retinal pigmentation, and giant optic nerve drusen on clinical examination. Preretinal fibrosis, hypocellularity of the ganglion cell, inner nuclear and outer nuclear cell layers, absence of photoreceptors outer segments, absent RPE, clumps of pigment laden cells, and areas of chorioretinal scarring, including atrophy and drusen of the optic nerve, were seen microscopically. Our OCT scans of comparably aged patients revealed many similar findings.

A limitation of this study was that OCT imaging was unable to obtain useful images in 31% patients. Some patients were unable to comply even with manual restraint or could not fixate well enough for satisfactory image acquisition. Since the clinical course of the patients we imaged was similar to that reported in the literature, we do not believe this would create a bias in data collection, as the main reason for failure to image was behavioral rather than a manifestation of nystagmus or ocular abnormalities. We also acknowledge that OCT is not a true histologic analysis and some findings must be interpreted with caution until the true cellular anatomic correlates are known.

Early diagnosis of Alström syndrome has significant clinical and prognostic implications. Once the disorder is recognized, patients must be monitored for possible associated medical conditions, which if not recognized can lead to severe morbidity and even death.³ Since OCT findings in the initial stages of the disease are mild, this imaging tool will likely not suffice as a stand-alone diagnostic test. It does appear to have utility in following the progression of the disorder and perhaps identifying targets and responses to potential treatments such as gene therapy. We have shown that a progressive pattern of disruption of the normal retinal morphology in Alström eyes that matched the declining vision. This suggests a possible “window of opportunity”: treatment delivered early enough in life may be able to preserve normal retinal morphology and function, preventing the currently inevitable complete vision loss. Previously demonstrated in other genetic retinal dystrophies, gene therapy when administered at a younger age resulted in greater improvement in vision.²⁰ Our data suggest that a similar effect might be achieved in Alström syndrome.

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List of abbreviations

SD-OCT	spectral-domain optical coherence tomography
ERG	electroretinogram
RPE	retinal pigment epithelium
ONL	outer nuclear layer
ASI	Alström Syndrome International

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Figure 1.

Changes of foveal morphology demonstrated on OCT scans of three Alström patients of different ages. A (patient #2, right eye): 4 year old showing a mildly abnormal foveal contour with an easily recognized stratification of retinal layers. Photoreceptors remain preserved; however, evidence of outer nuclear (ONL) layer thinning exists and there is no external limiting membrane even in the very center of the fovea. Foveal thickness (red bar) is 168 μm . B (patient #10, right eye): 12 year old demonstrating deepening of foveal pit, a more advanced loss of foveal photoreceptors, and greater central than far perifoveal ONL loss. Foveal thickness (red bar) is 249 μm . C (patient #18, right eye): 30 year old

demonstrating advanced stages of foveal changes with extremely deep fovea (40 μm thick, red bar) almost to the retinal pigmented epithelium (RPE), complete loss of photoreceptors and increased backscattering suggesting thinned RPE.

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Figure 2.

(A) Peripheral retina of a 2-year-old patient (patient #1) demonstrating normal retinal stratification, intermittently poor signals from the inner and outer photoreceptor layers, and normal retinal pigmented epithelium (RPE) and choroid. (B) In contrast, the retinal morphology of this 36-year-old patient (patient #20) shows complete loss of normal retinal stratification, loss of photoreceptors, retinal surface irregularity, and increased backscattering suggesting thinning of RPE causing increased visibility of choroidal vasculature.

Figure 3. Intraretinal hyperreflectivities and outer retinal debris causing shadowing in a 38-year-old patient (patient #22). Prominence of the choroid is also seen.

Figure 4. Retinal morphology of a 9-year-old patient (patient #7), demonstrating wavy contour of the retina, loss of photoreceptors and retinal pigment epithelium with increased choroid visualization.

Table 1

Systemic and genetic findings of Alström patients

Patient Number	Age (years)	Obesity	Diabetes	Hearing loss	Cardiomyopathy	ALMS1	
						Allele 1	Allele 2
1	2	Yes	No	Mild	No	c.10483C>T p.Gln3495*	c.10483C>T p.Gln3495*
2	4	Yes	No	Normal	Yes	c.4156dupA p.Thr1386Asnfs*15	ND
3	5 [‡]	Yes	No	Normal	No	c.2930_2933dup p.Ser979fs	c.10265del p.Pro3422fs
4	8	Yes	No	Mild	No	c.10483C>T p.Gln3495*	ND
5	8	Yes	No	Mild	No	c.4156dupA p.Thr1386Asnfs*15	c.4156dupA p.Thr1386Asnfs*15
6	9	Yes	Insulin resistance, no diabetes	Mild-moderate	Yes	c.5145T>G p.Tyr1715*	c.3754C>T p.Gln1252*
7	9	Yes	No	Mild	No	c.4917_4920delTAAA p.Asn1639Lysfs*4	c.3518C>G p.Ser1174*
8	10	Yes	Insulin resistance, no diabetes	Severe-profound	No	c.10775delC; p. Thr3592Lysfs*6	ND
9	10	Yes	No	Mild-moderate	No	c.6436C>T p.Arg2146*	ND
10	12 [‡]	Yes	Yes	Mild-moderate	Yes	c.2930_2933dup p.Ser979fs	c.10265del p.Pro3422fs
11	13	Yes	Yes	Severe-profound	No	c.3251_3258delCTGACCAG p.p.Ala1084Aspfs*3	c.4917_4920delTAAA p.Asn1639Lysfs*4
12	14	Yes	No	Moderate-severe	No	c.2676delT p.Gly893Aspfs*41	c.2159delG p.Arg718Lys
13	15	Yes	Yes	Moderate	No	c.10539_10557ins(n)19 p.His3512fs	c.11416C>T p.Arg3806*
14	19	Yes	Insulin resistance, no diabetes	Moderate	No	Deletion of exon 17	c.5145T>G p.Tyr1715*
15	20	Yes	No	Moderate	Yes	c.7376_7379delATAG p.Asp2349Alafs*59	c.7376_7379delATAG p.Asp2349Alafs*59
16	24	Yes	Yes	Moderate	Yes	c.11651_11652insGTTA p.Asn3885Leufs*9	c.4823delA p.Lys1608Argfs*9
17	25	Yes	Yes	Moderate-severe	Yes	c.4213G>T p.Glu1405*	c.4213G>T p.Glu1405*
18	30	Yes	Yes	Moderate	No	c.11385delT p.Phe3795Leufs*38	c.3153C>A p.Tyr1051*
19	30	Yes	No	Moderate	Yes	c.11385delT p.Phe3795Leufs*38	c.11385delT p.Phe3795Leufs*38
20	36	Yes	Yes	Moderate-severe	Yes	c.7942C>T p.Gln2648*	c.9163A>T p.Lys3055*
21	36	Yes	Yes	Yes (undetermined degree)	No	c.10483C>T p.Gln3495*	c.5283delA p.H1762fs*24
22	38	Yes	No	Severe-profound	No	c.7374_7375delAG p.Asp2459*	c.7374_7375delAG p.Asp2459*

[‡]These two patients are brothers;

Continued sequencing to identify the second mutated allele was not done. Identification of one of the mutated alleles in combination with appropriate phenotypic features confirmed the diagnosis.³

ND = not done.

◆ Degree of hearing loss: Normal <19 dB, Mild: 20–40 dB, Moderate: 41–70 dB, Severe: 71–95 dB, Profound: >95 dB;