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Peripapillary Retinal Nerve Fiber Layer Thinning in Patients With Autosomal Recessive Cone-Rod Dystrophy

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Abstract

PURPOSE—To evaluate peripapillary retinalnerve fiber layer (RNFL) thickness using spectral-domain optical coherence tomography (SD-OCT) in patients with autosomal recessive cone-rod dystrophy (CRD).

DESIGN—Cross-sectional study.

METHODS—Eleven patients (22 eyes) with CRD were studied, including 4 patients with identified *ABCA4* gene mutations. Peripapillary RNFL thickness was measured in 16 segments from 4 quadrants. The analyses were based on age- and disc size-adjusted normative data. An abnormal thinning was considered when RNFL thickness measurements were under the 5th percentile in at least 2 out of 4 segments in a quadrant. Mean RNFL thickness was quantitatively compared to normative data obtained from 134 subjects.

RESULTS—Eight patients (73%) had peripapillary RNFL thinning in at least one quadrant of at least one eye, including 3 out of 4 patients with known *ABCA4* gene mutations. Peripapillary RNFL thinning in the temporal quadrant was most commonly seen in 11 (79%) of 14 eyes with thinning in at least one quadrant. Significant thinning of the overall peripapillary RNFL was observed in CRD

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D. Conformity of author information The protocol was approved by an institutional review board of the University of Illinois at Chicago, and conducted in accordance with the principles of the Declaration of Helsinki and the HIPAA compliance. Informed consent was obtained from all patients.

A Table of Contents Statement: Using spectral-domain optical coherence tomography, 73% of autosomal recessive cone-rod dystrophy patients were observed to have peripapillary retinal nerve fiber layer thinning in at least one quadrant of at least one eye. The results confirm that the inner retinal structures can be affected in outer retinal disease. Careful evaluation of the inner retina may be important in determining the success rate of potential treatments, such as gene-directed therapy, for predominantly outer retinal diseases.

patients compared to that of controls (p=0.0002). Subgroup analysis showed that 8 (89%) of 9 patients who were older than 40 years had thinning in at least one quadrant of at least one eye.

CONCLUSIONS—Peripapillary RNFL thinning was commonly observed in our patients with autosomal recessive CRD. The results confirm that the inner retinal structures can be affected in outer retinal disease. Careful evaluation of the inner retina may be important in determining the success rate of potential treatments for predominantly outer retinal diseases.

INTRODUCTION

Cone-rod dystrophy (CRD) is a progressive inherited photoreceptor degenerative disease in which cone photoreceptor function is most often more impaired than rod photoreceptor function. Rod involvement occurs in concurrence with or subsequent to cone involvement.1 Patients characteristically present with impairment of color vision and visual acuity. Central scotomas are usually detected at an early stage, followed by various degrees of peripheral or midperipheral visual field defects. Electroretinogram (ERG) recordings typically show predominant loss in cone function, but reduction of a- and b-wave amplitudes for rods are also seen.2, 3 Fundus examination often shows various degrees of macular involvement, ranging from minimal and nonspecific pigmentary changes, a characteristic "bull's eye maculopathy", to a geographic atrophicappearing macular scar at a later stage.4 Diffuse peripheral or midperipheral pigmentary degenerative changes with waxy pallor of the optic disc and vascular attenuation similar to those seen in patients with retinitis pigmentosa (RP) are not infrequently observed.5 An initial history of photoaversion with an impairment of central vision and color vision is usually helpful for differentiating CRD from RP, in which nyctalopia and peripheral visual field loss are more prominent at an early stage.

CRDs are predominantly inherited in an autosomal recessive fashion, however, autosomal dominant[6, 7] and X-linked recessive transmissions have also been reported.[8, 9] Variations in multiple genes have been shown to cause this phenotype.[1] Mutations in the *ABCA4* gene account for 30-65% of autosomal recessive CRD.5, 10-12 The ABCA4 protein is a member of the ATP-binding cassette (ABC) superfamily whose products are transmembrane proteins involved in energy-dependent transport of a wide spectrum of substrates across cell membranes.[13] The *ABCA4* gene is transcribed exclusively in photoreceptors, and the protein transports vitamin A derivatives in the outer segment disc membranes.[14] Mutations in this gene have also been reported in patients with age-related macular degeneration,[15, 16] autosomal recessive Stargardt disease[17] and autosomal recessive RP.[18]

In 1987, Newman et al reported that clinically evident RNFL thinning could be detected on fundus photography in various diseases of the outer retina, including Best macular dystrophy, Leber congenital amaurosis, Stargardt disease, choroideremia, rodcone dystrophy and CRD. 19 However, an accurate observation of wedge-shaped RNFL defects on fundus examination is often technically difficult especially when detection is attempted against a background of generalized retinal pigment epithelial atrophy. More recent studies have shown that spectral-domain optical coherence tomography (SD-OCT) can be a sensitive tool to detect peripapillary RNFL thinning in patients with RP [20] and juvenile X-linked retinoschisis (XLRS) (accepted for publication in *Eye*). The purpose of our study was to evaluate peripapillary RNFL thickness measurements using SD-OCT in patients with autosomal recessive CRD, including those with known *ABCA4* gene mutations. The presence of RNFL defects in this group of patients would have potential impact on patient selection in future therapeutic trials.

METHODS

Subjects

This study included 4 patients with a diagnosis of autosomal recessive CRD and disease-causing variants in the *ABCA4* gene. An additional 7 patients who had the same clinical diagnosis, including 3 patients where no *ABCA4* mutations were detected by screening with single-strand conformation polymorphism analysis (SSCP), as well as 4 patients with unavailable genetic test results, were enrolled in the study. Genetic testing techniques were previously described.[5,21] Seven CRD patients with either positive or negative results for *ABCA4* gene mutations whose names were listed in our genetic database participated after receiving a telephone invitation. Other patients were prospectively recruited when seen in the Electrophysiology and Inherited Retinal Disease unit at the Illinois Eye and Ear Infirmary. The diagnosis of CRD was established based on clinical presentation and ERG findings. All patients were examined by two authors (SP and GAF).

Exclusion criteria included known optic nerve diseases or anomalies (glaucoma or glaucoma suspects, optic disc drusen, optic neuropathy, optic pit or coloboma), known other retinal diseases (diabetic retinopathy, hypertensive retinopathy), uveitis, intraocular pressure (IOP) higher than 20 mmHg or a previous history of ocular hypertension, refractive error of more than ± 6 D sphere or ± 3 D cylinder, previous intraocular or refractive surgery, a diagnosis of diabetes mellitus, and inability to hold reasonable fixation, or media opacity that precluded a high-quality OCT examination.

Data Collection, Ocular Examination and Psychophysical Tests

Patient characteristics were collected, including date of birth, gender, race, medical and ophthalmic history, onset of visual impairment, genetic testing results, as well as pedigree information. All patients underwent a comprehensive ocular examination, including best-corrected visual acuity (BCVA) measurement using either a Snellen projection chart or a Feinbloom Distance Test Chart for the Partially Sighted, slit-lamp examination, intraocular pressure measurement with Goldmann applanation tonometry, and dilated fundus examination with direct and indirect ophthalmoscopy. Color fundus photographs were obtained in all patients. Each patient underwent ERG testing obtained by either of two procedures previously described.[22, 23] The recording techniques adhered to an international standard for clinical electrophysiologic measurements.24 ERG measurements were compared with either 90% tolerance limits or to an appropriate range obtained from a normally sighted control population.

Optical Coherence Tomography

SD-OCT scanning was performed on all subjects using Optovue technology(RTVue Model-RT100 version 3.5; Optovue Inc., Fremont, CA). The NHM4 protocol was used for peripapillary RNFL analysis. Peripapillary RNFL thickness was measured at a diameter of 3.45 mm around the center of the optic disc with a total of 2,225 A-scans. The results were displayed in a color map using customized software with normative data adjusted for age and optic disc size. A peripapillary RNFL thickness map was shown as a numerical value and the color code in each of 16 segments for the 4 quadrants: superior (46 ° -135 °), nasal (316°-45 ° for the right and 136 ° -225 ° for the left), inferior ((226 ° -315 °), and temporal (136 ° -225 ° for the right and 316°-45 ° for the left). An abnormally thin RNFL was encoded yellow and red for values less than the 5^{th} and 1^{st} percentiles, respectively. RNFL measurements not considered as thin (the 5^{th} percentile or more) were demonstrated in green. Peripapillary RNFL thinning in an individual quadrant was considered when red or yellow coding presented in at least 2 out of 4 segments of the quadrant. An example is shown in the Figure (Right).

The OCT machine provided internal fixation. However, most of the patients with CRD had poor visual acuity and were unable to see the fixation target. They were asked to direct their gaze in a direction to facilitate visualization of their optic disc. Each peripapillary RNFL scan was completed within 0.39 seconds, while the patients maintained their eye position. Only scans with good centration were included for analysis. The scans with low or irregular signal strength index (SSI) and visibly misaligned segmentation lines were excluded. Three scans were performed in each eye to ensure reproducibility. When an initial set of 3 scans was not reproducible, additional scans were performed to provide at least 3 high-quality scans with acceptable reproducibility of the color coding in at least 2 out of 3 scans in each eye. A total of 17 patients with autosomal recessive CRD underwent OCT examination; however, high-quality images could not be obtained from 4 patients with *ABCA4* mutations and 2 patients with pending genetic testing results. Included for analysis were data from the remaining 11 patients with high-quality OCT images.

Additional macular scans were also performed using the MM5 protocol, which is presented as 5×5 mm macular thickness maps with results compared to color codes based on age-similar customized normative data. Scan acquisition time required for each of the MM5 scans was 0.78 seconds.

Data Analysis

Peripapillary RNFL thickness was analyzed in each quadrant based on the color codes which, as mentioned, were referenced to customized normative data adjusted for age and optic disc size. Mean circumferential peripapillary RNFL thickness from all 4 quadrants in each eye was quantitatively compared to normative data which were obtained from 268 eyes of 134 control subjects (mean age of 44.1 ± 15.5 years). These normative data were provided from the analyzer. The thickness measurements from our patients with CRD were analyzed compared to those of the normal subjects using an unpaired Student *t*-test. Probability values under 0.05 were considered statistically significant.

RESULTS

Twenty-two eyes of 11 patients were included in this study. Patient characteristics are shown in Table 1. Mean (SD) age of the patients was 47.7 (18.9) years, with a median of 54.4 years (range 10.9-68.8 years). Female patients predominated (64%). Caucasians were the majority (64%), followed by African American (18%) and Palestinian (18%). Visual acuity ranged from 20/50 to counting fingers, with mean logMAR acuity of 1.43 (equivalent to 20/540). Mean (SD) of IOP was 14.8 (1.7) mmHg (range, 11-17 mmHg). Four patients from different families (numbers 1-4) were found to harbor plausible disease-causing mutations in the *ABCA4* gene (Table 1). No *ABCA4* variants were found in three patients after screening with SSCP, three patients refused to have blood tests for genetic evaluation, and a genetic result was pending in one patient.

Color Code Referenced Peripapillary RNFL Analysis

Eight (73%) of 11 patients showed peripapillary RNFL thinning using our criteria of at least one quadrant in at least one eye, including 3 (numbers 1-3) out of 4 patients (numbers 1-4) who harbored plausible disease-causing variations in the *ABCA4* gene (Table 2). Of the 8 patients with thinning, 6 had thinning in both eyes, and 2 had thinning in one eye. There were 4 patients who had thinning in 2 or more quadrants in at least one eye. Interestingly, 3 patients with a known *ABCA4* gene mutation had thinning in 2 or more quadrants in both eyes. There were 14 (64%) of 22 eyes which presented with peripapillary RNFL thinning in at least one quadrant. Thinning in the temporal quadrant was most commonly seen in 11 (79%) of 14 eyes, followed by the nasal (7 eyes, 50%), inferior (5 eyes, 36%), and superior quadrants (4 eyes,

29%). The presence of RNFL thinning was not necessarily symmetrical. All patients were older than 40 years old, except for 2 patients (numbers 10-11). Peripapillary RNFL thinning, in at least one quadrant of at least one eye, was seen in 8 (89%) of 9 patients whose ages were greater than 40 years.

Non-Color Code Referenced Peripapillary RNFL Analysis

Table 3 shows mean thickness of the peripapillary RNFL in each quadrant and in overall circumferential thickness. The overall peripapillary RNFL thickness measurements of our patients were compared with those from the 268 eyes of 134 control subjects. There was no statistically significant difference in ages between our cohort of patients and the controls (mean age of 47.7 + 18.9 versus 44.1 + 15.5, $p = 0.468$). By comparing our patients to controls, there was a statistically significant reduction of the thickness in the overall peripapillary circumferential RNFL measurements in the patients ($p = 0.0002$). When evaluating each quadrant separately, a statistically significant reduction in peripapillary RNFL thickness was observed in the temporal ($p < 0.0001$), nasal ($p = 0.003$) and inferior quadrants ($p = 0.005$).

Macular Scan Analysis

The mean central 1-mm macular thickness was calculated using data from 18 eyes of 9 patients. The macular thickness measurements from two patients (numbers 3 and 10) were excluded due to misaligned segmentation lines automatically drawn by the OCT program. The central macular thickness ranged from 108 to 262 μm, with a median of 168 μm. There was a statistically significant difference in mean central macular thickness between CRD patients and controls (175.2 ± 42.1 μm versus 265.8 ± 23.9 μm, $p < 0.0001$).

DISCUSSION

Using SD-OCT, in previous studies from our group we found that peripapillary RNFL thinning may be observed in patients with certain inherited retinal diseases, including RP[20] and XLRS (accepted for publication in *Eye*). The presence of peripapillary RNFL thinning of at least one quadrant in at least one eye was seen in 44% and 42% of patients with RP and XLRS, respectively, compared to 73% of patients with CRD in this study.

Scan centration at the optic disc is a key factor for an accuracy of OCT peripapillary RNFL measurement. Although the OCT machine provides internal fixation which facilitates scan acquisition, most of our patients were unable to see the fixation target. In our study, because of this issue with patient fixation, high-quality scans were obtained in 11 (65%) out of 17 patients who were examined. We cannot rule out the possibility that the 6 patients excluded from analysis might have had similar or even more advanced RNFL thinning than those presented. Therefore, our results may have possibly underestimated the prevalence of peripapillary RNFL thinning in autosomal recessive CRD patients.

In autosomal recessive CRD patients, the peripapillary RNFL thinning was most prominent in the temporal quadrant. This might, in part, be explained by the cone distribution in the posterior pole and the fact that most patients with CRD primarily present with macular involvement and its related symptoms prior to more apparent changes in the peripheral retina. Nonetheless, impairment of visual acuity did not always parallel the presence of such thinning in the temporal quadrant. For instance, patient number 5 retained visual acuity of 20/50 in one eye, despite an observation of peripapillary RNFL thinning in the temporal quadrant.

The results from our studies confirm that inner retinal structures may be affected in outer retinal degenerative diseases. However, the mechanism currently remains unclear. We speculate that this might result from either transsynaptic degeneration or, yet to be identified, a mechanism

by which there is a more direct involvement of inner retinal layers as a consequence of outer retinal photoreceptor cell degeneration.

Our study suggests that peripapillary RNFL thinning is commonly observed in patients with autosomal recessive CRD, including those with identified *ABCA4* gene mutations. The data also show that patients in an older age group are more likely to have peripapillary RNFL thinning than are younger patients, which is consistent with a similar observation in patients with XLRS. The degrees of thinning were usually similar between both eyes of the same patient, although asymmetry was also observed. Evaluation of the inner retinal structures using SD-OCT may have relevance in determining the success rate of potential treatments, such as the use of retinal neurotrophic factors or gene-directed therapy, for primarily outer retinal diseases.

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Biographic sketch

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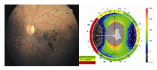

FIGURE.

Fundus photograph (Left) of the left eye from a patient with autosomal recessive cone-rod dystrophy (patient number 2) which shows generalized retinal pigment epithelial atrophic changes, pigment clumping at the posterior pole, peripapillary region and midperiphery, vascular attenuation, without clinically-apparent optic disc pallor. Peripapillary retinal nerve fiber layer thickness measurements (Right) from the same eye were considered abnormally thin in three quadrants including, the nasal (4 out of 4 segments with red encoding), superior (3 out of 4 segments with yellow encoding) and temporal quadrant (2 out of 4 segments with yellow encoding).

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TABLE 1

Demographic Characteristics and Ocular Examination in Patients with Autosomal Recessive Cone-Rod Dystrophy

Subject No.	Age (years)	Gender	Race	Genetic Testing Results for the *ABCA4* Gene	Visual Acuity		Fundus Findings	
					OD	OS	Macula	Pigmentation
1	60	Female	Caucasian	IVS40+5 G>A & cys54tyr exon 3, heterozygous	20/400	20/400	Pigment clumping	Posterior pole, midperiphery
2	59	Female	Caucasian	glu328stop exon 8 & val767asp, heterozygous	3/200	3/400	Pigment clumping	Posterior pole, midperiphery
3	44	Male	Caucasian	ala1038val exon 21 & leu541pro exon 12, heterozygous [a]	5/400	5/200	Pigment clumping	Periphery
4	54	Female	African American	val989ala exon 20, heterozygous	20/400	CF	Pigment clumping	Posterior pole, peripapillary
5	42	Male	Palestinian	None detected [b]	20/50	20/400	Drusen-like lesions, hypopigmentation	-
6	45	Female	Palestinian	None detected [b]	20/70	20/200	Drusen-like lesions, hypopigmentation	-
7	63	Female	African American	None detected [b]	20/200	20/200	Geographic atrophic lesions	-
8	69	Female	Caucasian	No genetic testing	2/400	2/700	Pigment granularity	-
9	62	Female	Caucasian	Pending	20/200	20/400	Bull's eye-like lesions	-
10	16	Male	Caucasian	No genetic testing	10/300	10/200	Geographic atrophic lesions	-
11	11	Male	Caucasian	No genetic testing	10/120	10/160	Bull's eye-like lesions and pigment granularity	Few at midperiphery

CF = counting fingers; OD = right eye; OS = left eye; "-" = absent

[a] These two variants constitute a complex allele

[b] Screening with single-strand conformation polymorphism analysis (SSCP)

TABLE 2

Quadratic Distribution of Peripapillary Retinal Nerve Fiber Layer Thinning in Patients with Autosomal Recessive Cone-Rod Dystrophy Based on Color-Coded Referenced Normative Data

Subject No.	Side	Superior	Nasal	Inferior	Temporal
1	OD	+	-	-	+
	OS	-	+	-	+
2	OD	-	+	+	+
	OS	+	+	-	+
3	OD	+	+	+	+
	OS	+	+	+	+
4	OD	-	-	-	-
	OS	-	-	-	-
5	OD	-	-	-	+
	OS	-	-	-	+
6	OD	-	-	+	-
	OS	-	-	-	-
7	OD	-	-	-	+
	OS	-	-	-	-
8	OD	-	+	-	-
	OS	-	+	+	-
9	OD	-	-	-	+
	OS	-	-	-	+
10	OD	-	-	-	-
	OS	-	-	-	-
11	OD	-	-	-	-
	OS	-	-	-	-

“+” = present; “-” = absent

TABLE 3

Mean Circumferential Retinal Nerve Fiber Layer Thickness in Autosomal Recessive Cone-Rod Dystrophy (CRD) Patients Compared to That of a Control Population

Quadrant	CRD Patients (μm, mean ± SD)	Controls (μm, mean ± SD)	P-Value
Superior	125.04 ± 31.09	129.03 ± 17.83	0.347
Nasal	68.69 ± 25.48	78.43 ± 13.54	0.003[a]
Inferior	128.31 ± 30.11	139.78 ± 17.08	0.005[a]
Temporal	62.27 ± 16.93	79.63 ± 12.03	<0.0001[a]
Overall	96.08 ± 23.44	106.72 ± 11.34	0.0002[a]

[a]Statistically significant