Optical Coherence Tomography Characteristics of the Choroid Underlying Congenital Hypertrophy of the Retinal Pigment Epithelium

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Keywords

Congenital hypertrophy of the pigment epithelium ·
Choroid · Optical coherence tomography

Abstract

Purpose: This study evaluates and characterizes the choroid underlying congenital hypertrophy of the retinal pigment epithelium (CHRPE). **Methods:** Retrospective observational study of CHRPE at least 2 mm in diameter. Choroidal vascular architecture was qualitatively examined. Choroidal thickness was measured by 2 independent observers using enhanced depth imaging spectral domain optical coherence tomography. **Results:** Forty-six eyes of 46 patients with CHRPE were included. Thirty-two lesions had imaging sufficient for analysis. Haller's layer was healthy in 18 (56%), thin in 13 (41%), and absent in 1 (2%). Sattler's layer was atrophic in 30 (94%), and choriocapillaris was atrophic in 31 (97%). CHRPE with thinned Haller's layer had significantly larger diameter. The mean sub-CHRPE choroidal thickness was $82.4 \pm 7.9 \mu\text{m}$, compared to a thickness of $148.4 \pm 9.6 \mu\text{m}$ in the normal adjacent choroid ($p < 0.0001$). Mean retinal thickness overlying the CHRPE was $77.3 \pm 4.3 \mu\text{m}$, compared to a retinal thickness of $137.8 \pm 2.9 \mu\text{m}$ overlying the normal adjacent choroid ($p < 0.0001$). Sub-CHRPE choroidal thickness was a

mean of $56.2 \pm 3.1\%$ of the adjacent normal choroidal thickness. **Conclusion:** The underlying choroid CHRPE is thinner than the adjacent normal choroid. All layers of the choroid can be thin with a preference of the inner Sattler's and choriocapillaris layers.

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Introduction

As suggested by its name, the primary pathological finding in congenital hypertrophy of the retinal pigment epithelium (CHRPE) is tall retinal pigment epithelium (RPE) cells with increased size and number of pigment granules [1–4]. This corresponds with hyperreflectivity and thickening of the RPE on optical coherence tomography [3, 5–14]. It is also well recognized that the overlying retina is abnormal. Histopathology demonstrates atrophied, sometimes disorganized retina with photoreceptor degeneration [1–4]. Both time domain and spectral domain optical coherence imaging have confirmed these findings [3, 5–14].

However, the characteristics of the underlying choroid CHRPE are less well understood: comments exist in the literature but they are sparing and contradictory. Pub-

lished descriptions of the choroid underlying CHRPE range from no comment, to “normal” and “unremarkable” [1–3] to descriptions of parts of it being “missing in most areas” [4]. This study investigated a cohort of CHRPE lesions to better understand the characteristics of the underlying choroid, both in size and in morphologic features.

Methods

The Institutional Review Board of Memorial Sloan Kettering Cancer Center approved this retrospective observational study. The protocol adhered to the Health Insurance Portability and Accountability Act (HIPAA) and the Declaration of Helsinki. Patient identifying information was kept confidential. Due to the retrospective nature of this study, informed consent was not required for patient inclusion.

Patients and Setting

All data were collected from patient records at the Memorial Sloan Kettering Cancer Center outpatient ophthalmic oncology clinic.

Study Protocol

A consecutive retrospective chart review permitted us to identify 46 patients diagnosed with CHRPE in 46 eyes. A comprehensive ophthalmoscopic exam was performed on all eyes. For each CHRPE patient, demographic and clinical data were collected, including sex, age, ethnicity, iris color, lesion laterality, location, border configuration patterns, and the presence of associated lacunae, or halo.

We performed color fundus photography and ultrasonography on all eyes, and we recorded lesion diameters that were at the broadest segment visualized on ophthalmoscopy. We excluded any lesion <2 mm in diameter from the analysis. Heidelberg Spectralis HRA + OCT (Heidelberg Engineering, Germany) was used to obtain enhanced depth imaging optical coherence tomography (EDI-OCT) images. When EDI-OCT imaging was available, and of sufficient quality, images were reviewed to assess choroidal vascular architecture, as well as choroidal (CT) and retinal thickness (RT) both within and adjacent to the CHRPE lesion. The choroidal vascular architecture was assessed qualitatively for the structure of Haller’s layer (normal, thin, or absent) as well as the presence of atrophy of Sattler’s layer and the choriocapillaris. CT was measured using the digital caliper tool and defined as the vertical distance between the hyperreflective line of RPE/Bruch’s membrane complex on the inner margin, and the choroidal-scleral junction on the outer margin. We measured the RT, defined by the distance between the internal limiting membrane and the outer RPE at the border of Bruch’s membrane similarly. We measured CT and RT at the central-most point of the CHRPE and a point 500 µm outside the CHRPE on the same cross-sectional OCT image. Two independent observers (J.H.F., E.K.S.) performed all CT and RT measurements at each location, and all analysis was done using a mean of these 2 measurements.

Upon completion of the data collection, we removed all patient identifiers. Data were then saved on a password-protected Micro-

Table 1. Demographics of CHRPE patients ($n = 44$)

Age, years	
Mean	54.3
Median	55.5
Range	12–80
Gender, n (%)	
Male	22 (50)
Female	22 (50)
Ethnicity, n (%)	
White	33 (75)
Black	4 (9.1)
Hispanic	2 (4.5)
Asian	2 (4.5)
Other	3 (6.8)
Iris color, n (%)	
Blue	10 (27)
Brown	27 (73)

soft Excel file and subsequently uploaded to statistical software for analysis. All statistical analysis was conducted using Stata 13 (StataCorp LP, College Station, TX, USA).

Statistical Analysis

We compiled demographic and clinical data for all CHRPE lesions that met the study criteria. For the CT and RT measurements, Bland-Altman analysis was used to assess for agreement between observers. Further analysis used averages of the 2 CT and RT measurements at each location. We compared mean sub-CHRPE CT to the adjacent CT 500 µm from the edge of the lesion using a paired t test. We also compared RT overlying the CHRPE to the adjacent RT 500 µm from the edge of the lesion using a paired t test. The measurement was taken 500 µm from the edge of the lesion at the most posterior border and towards the macula (either nasal or temporal, depending on location), and from the same OCT horizontal scan as the CHRPE measurement. We established a cutoff for statistical significance at a p value of <0.05.

Results

We identified CHRPE lesions in 46 eyes (25 right, 21 left). Of these 46 CHRPE lesions, 44 met the inclusion criteria of 2 mm or greater. Table 1 summarizes the demographic data.

We identified 29 (63%) of the CHRPE in the equator, 10 (22%) in the equator, 5 (11%) in the macula-equator, and 2 (4%) in the ora. Intrinsic lacunae were present in 28 (61%) of lesions. We identified a characteristic optical halo in 43 (93%) at the edge of the lesion. There were 3 patterns of border configuration: round (29, 63%), scalloped (13, 28%), and torpedo (4, 9%). Table 2 summarizes information on the location and appearance of CHRPE lesions.

Fig. 1. These representative images demonstrate color fundus image (left) with corresponding optical coherence tomography (right) demonstrating atrophy of all choroid layers beneath the CHRPE within the overlying boundaries of the lesion.

Table 2. Location and appearance of CHRPE lesions

Laterality	
OD	24 (55)
OS	20 (45)
Diameter, mm	
Mean	7.98
Median	9
Range	2–14
Fundus location	
Macula-equator	5 (11.4)
Equator	9 (20.5)
Equator-ora	28 (63.6)
Ora	2 (4.5)
Lacunae	27 (61.4)
Halo	40 (90.9)
Border configuration	
Round	27 (61.4)
Scalloped	13 (29.5)
Torpedo	4 (9.1)

Data are shown as number of patients (%) or as stated.

Table 3. Choroidal and retinal thickness on EDI-OCT

	Central CHRPE	500 μ m outside CHRPE margin	<i>p</i> value ^a
Choroidal thickness, μ m			
Mean	82.4	148.4	<0.0001*
SE	7.9	9.6	
95% CI	66.2–98.6	128.8–168.0	
Range	25–292	82.5–38.5	
Retinal thickness, μ m			
Mean	77.3	137.8	<0.0001*
SE	4.3	2.9	
95% CI	68.5–86.0	132.0–143.7	
Range	33–118	104.5–182.5	

EDI-OCT, enhanced depth imaging optical coherence tomography; CHRPE, congenital hypertrophy of the retinal pigment epithelium; SE, standard error of the mean; CI, confidence interval. ^a Paired *t* test. * Statistical significance.

Of the 44 CHRPE lesions that met inclusion criteria, 32 (70%) had EDI-OCT imaging sufficient for analysis. Haller's layer was healthy in 14 (44%), thin in 17 (53%), and absent in 1 (2%). Sattler's layer and the choriocapillaris were atrophic in 31 (97%).

Bland-Altman analysis for interobserver consistency concerning CT and RT measurements on EDI-OCT was as follows: for all choroid measurements, mean measurement difference was 6.1 μ m (95% CI 1.5–10.7) with constant variability around the mean (limits of agreement –30.7 to 42.8) with no observable trend. For all retinal measurements, the mean difference was –0.36 μ m (95% CI –43.8 to 3.1) with constant variability around the mean

(limits of agreement –28.3 to 27.6) with no observable trend. We used averages of all measurements without concern for variability that would affect the validity or significance of statistical testing. Results on RT and CT are depicted in Table 3.

The mean sub-CHRPE CT was 82.4 $\pm$ 7.9 μ m, compared to a thickness of 148.4 $\pm$ 9.6 μ m in the normal adjacent choroid (*p* < 0.0001). The sub-CHRPE CT was a mean of 56.2 $\pm$ 3.1% of the adjacent normal CT, with a mean difference of 66 $\pm$ 6.3 μ m (range 23–216 μ m). Lesion location and border configuration did not correlate with CT. Figures 1 and 2 depict EDI-OCT of a thin choroid within the boundaries of the CHRPE lesion. Figure 1

Fig. 2. These representative images demonstrate color fundus image (left) with corresponding optical coherence tomography (right) depicting atrophy of the inner choroidal layers, while Haller's layer is maintained (albeit distended).

shows atrophy of all choroid layers, while Figure 2 is an example where Haller's layer is healthy. The mean RT overlying the CHRPE was $77.3 \pm 4.3 \mu\text{m}$, compared to an RT of $137.8 \pm 2.9 \mu\text{m}$ overlying the normal adjacent choroid ($p < 0.0001$). The RT overlying the CHRPE was a mean of $56.3 \pm 3.1\%$ of the adjacent retina in the area outside of the CHRPE, with a mean difference of $60.5 \pm 4.5 \mu\text{m}$ (range 0–106.5 μm).

There was no significant difference in the CT in CHRPE with thinned/absent versus normal Haller's layer. However, CHRPE with thinned or absent Haller's layer had significantly larger diameter compared to CHRPE with normal Haller's layer (8.78 vs. 6.53 mm, p value = 0.04).

Discussion

In our cohort of CHRPE, the underlying CT was significantly less than the CT of the adjacent normal fundus. The mean sub-CHRPE CT was approximately half the thickness (mean of 66 μm less) of the adjacent normal fundus. This finding was similar to the proportion of overlying retinal atrophy, which was also approximately half the thickness (mean 60 μm less) of the adjacent normal fundus. Lesion location and border configuration did not appear to correlate with these results, in this cohort.

EDI-OCT may identify gradient from small and medium vessels in the inner choroid to larger vessels in the outer choroid. It is possible to segment this gradient into choriocapillaris, Sattler's and Haller's layers, respectively. In our cohort, the majority (97%) of the lesions demon-

strated attenuated or unidentifiable inner choroid (in the choriocapillaris and Sattler's layer). In contrast, the outer Haller's layer was healthy in 44% and either atrophied (53%) or absent (2%). This finding suggests the thinning of the underlying choroidal CHRPE has a preference for impacting the inner choroid. Alternatively, the persistent larger vessels visible on OCT may represent dilated smaller vessels: long-term evaluation of these lesions and or histopathological correlations may clarify this answer.

It is possible to speculate that the interface of the RPE impacts the inner choroid, owing to its proximity to these layers; akin to the aberration in the outer retina, which is also close to the deranged RPE cells. In CHRPE, it is unclear what the inciting event is, including the time course or association in the retinal or choroidal thinning. With the increased use of enhanced depth imaging, entities that are known to be pathologic to the retina and RPE are now discovered also to involve choroidal abnormalities. For example, Best vitelliform macular dystrophy, Stargardt disease, age-related macular degeneration, and retinitis pigmentosa are all examples of ophthalmic diseases primarily involving the retinal/RPE complex, which have also been found to involve choroidal abnormalities [15]. With the RPE acting as the interface between the retina and choroid, it is not surprising that its irregularity implicates both the overlying and underlying structures. It could also be conjectured that CHRPE are primarily a choroidal disease and the striking RPE and retinal findings are secondary to that.

The published literature describes the unusual features of the overlying retina and RPE in CHRPE lesions [1–14]. The RPE cells are known to be taller with increased pig-

ment, and the overlying retina to be atrophied (mainly the outer retina). However, the published literature has mixed reports on the condition of the underlying choroid, some of which are contradictory to our findings. In histopathology reports of CHRPE using light and electron microscopy, the majority either make no mention of the choroid [3, 16] or refer to it as “unremarkable” [2], or only make reference to the inner choroid, calling the choriocapillaris “intact” or “normal” [1]. Parsons et al. [4] describe the histopathology of a CHRPE where the choriocapillaris is “missing from most areas.”

With the use of optical coherence tomography, descriptions of the choroid evolved in line with the improved, deeper imaging techniques. Time-domain OCTs were found to have disturbed optical transmission because the heavy pigment of the CHRPE shadowed the choroid [6, 9, 10]. Spectral-domain OCT reported a similar limitation [7, 8], although one report described “excavation” of the choroid beneath a CHRPE lesion [11]. Even with the use of enhanced-depth OCT, authors have noted the heavy pigment of the CHRPE makes the sclerochoroidal junction poorly discernible [14]; although increased light transmission in lacunae offers improved imaging in associated areas and with most OCT modalities [5].

The most extensive published appraisal of the underlying choroid was investigated in 18 CHRPE lesions by Fung et al. [12]. They reported, “the choroid was identical in thickness and vascular appearance under the CHRPE.” However, they compared the sub-CHRPE choroid to the choroid that was “immediately outside” the lesion margin, specifically at 50 μm . In contrast, the present study compared the choroid 500 μm from the CHRPE margin, with the belief that the choroid at this distance was more representative of the normal fundus, but minimally influenced by location-dependent variations in CT.

In summary, our cohort of CHRPE lesions reveals choroidal thinning in proportion to atrophy of the overlying retina. By optical coherence tomography, all layers of the choroid can be thin, although we found a propensity for attenuation of the inner choroid layers. It calls into question whether the origins of CHRPE derive from pathology in choroid, retina or the RPE. Now that we have entered an era of using higher-resolution optical coherence tomography, our findings warrant confirmation by other cohorts.

Statement of Ethics

Subjects have given their written informed consent, and the study was approved by the Memorial Sloan Kettering Institutes Research Committee on human research.

Disclosure Statement

The authors have no proprietary interest and no conflict of interest.

Funding Sources

This study was supported by The Fund for Ophthalmic Knowledge, The New York Community Trust, Research to Prevent Blindness, and Cancer Center Support Grant (P30 CA008748). The sponsor or funding organization had no role in the design or conduct of this research.

Author Contributions

J.H.F.: conceived of the idea, data acquisition, data analysis, composed the manuscript; E.K.S.: data acquisition, data analysis, critical review of the manuscript; M.G. and R.F.: data acquisition, critical review of the manuscript; D.H.A.: data analysis, critical review of the manuscript.

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