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Quantitative Assessment of Outer Retinal Layers and Ellipsoid Zone Mapping in Hydroxychloroquine Retinopathy

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Abstract

Background: To quantitatively assess outer retinal layers in eyes with hydroxychloroquine (HCQ) toxicity.

Methods: A retrospective case-control study was performed to identify eyes with HCQ retinopathy/toxicity at Cleveland Clinic. A clinical diagnosis of HCQ retinopathy was made based on clinical and imaging features including the presence of parafoveal ellipsoid zone (EZ) loss on spectral-domain OCT and visual field defects. All participants underwent macular cube scan using the Cirrus HD-OCT (Zeiss, Oberkochen, Germany). Quantitative assessment of outer nuclear layer/Henle fiber layer complex (ONL/HFL) metrics and EZ mapping were performed with a novel software platform and compared with age-matched controls. HCQ toxicity group was divided into three subgroups based on the severity.

Results: There were 14 eyes from 14 patients in HCQ toxicity group (mean age 57.0 ± 18.6 years), and 14 eyes from 14 subjects in age-matched control group (mean age 59.4 ± 18.6 years). Multiple outer retinal parameters including ONL/HFL-EZ volume, parafoveal ONL/HFL-EZ thickness and EZ-retinal pigment epithelium (RPE) volume were significantly reduced in all HCQ toxicity subgroups (early, moderate and advanced toxicity) compared with controls. Semi-automated layer segmentation tool produced en face representation of EZ-RPE mapping and

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allowed unique visualization of EZ attenuation in eyes with HCQ toxicity. The longitudinal analysis of HCQ toxicity group demonstrated progressive decline in some outer retinal parameters.

Conclusion: Hydroxychloroquine toxicity resulted in significant outer retinal layer volumetric thinning compared with controls. Quantitative assessment of outer retinal parameters and EZ mapping on SD-OCT may become a useful biomarker to identify and monitor HCQ toxicity.

Synopsis/Precis:

Quantitative assessment of outer retinal parameters on spectral domain OCT in patients with hydroxychloroquine toxicity exhibited significant outer retinal layer volumetric loss and allowed unique visualization of ellipsoid zone attenuation resembling Bull's eye appearance.

Keywords

Optical coherence tomography; hydroxychloroquine; hydroxychloroquine toxicity; Plaquenil; Plaquenil toxicity; ellipsoid zone

INTRODUCTION

Hydroxychloroquine (HCQ; Plaquenil®) retinopathy (i.e., HCQ toxicity) is a severe complication associated with HCQ intake that can cause irreversible vision loss. [1-3] Early detection of retinal toxicity is crucial since vision loss is usually permanent and cellular damage may progress despite discontinuation of treatment. [2 3] Although no ideal single test exists for identification of early toxicity, spectral-domain optical coherence tomography (SD-OCT) plays a critical role in identifying photoreceptor and retinal pigment epithelium (RPE) involvement that can be utilized for both screening and monitoring purposes. [2 4-6]

To date, several investigators have utilized SD-OCT in eyes with HCQ toxicity and qualitatively evaluated thinning of the outer retinal layers or attenuation of the ellipsoid zone (EZ), while others have quantitatively analyzed outer retinal thickness on SD-OCT topographic map. [7-10] This study aims to characterize HCQ toxicity using a newly developed assessment tool for retinal layer segmentation and mapping on SD-OCT. [11 12]

METHODS

This study was an IRB-approved retrospective case-control series. A medical records search was performed to identify subjects with HCQ toxicity based on clinical (e.g., visual field defects) and imaging features (e.g., parafoveal EZ loss). Macular cube scan was obtained using Cirrus HD-OCT (Zeiss, Oberkochen, Germany) with a raster scan pattern 512×128 A-scans covering a 6×6 mm area centered on the fovea. SD-OCT data was imported into a semi-automated layer segmentation tool for outer retinal mapping. [11 12] The software provides automated segmentation of the internal limiting membrane, outer boundaries of the outer plexiform layer (ONL), EZ band and RPE as shown in Figure 1. The generated segmentation lines were carefully reviewed by an image analyst, and segmentation errors were manually corrected. *En face* EZ topographic maps were generated to visualize overall EZ alterations, the severity of loss, and regional location.

Data containing various outer retinal parameters as listed in Table 1 were subsequently exported and evaluated: “central subfield” and “parafoveal” were defined as a distance of 0.5 mm and 1.0 mm from the fovea, respectively. ONL/Henle fiber layer complex (ONL/HFL)-EZ represented the gap between inner boundaries of ONL/HFL to EZ band whereas EZ-RPE represented the gap between photoreceptor EZ band to RPE mitochondria zone.[13] The *en face* EZ-RPE topographic map provided calculations related to the percentage of total EZ attenuation (i.e., the measurement value of EZ-RPE thickness of 0 μ m) and partial EZ attenuation (EZ-RPE thickness <10 μ m and < 20 μ m). Outer retinal parameters were compared between eyes with HCQ toxicity and controls. The longitudinal assessment of outer retinal parameters in HCQ toxicity group was completed to evaluate outer retinal change over time with a follow-up visit of more than 6 months. Baseline was defined as the time of diagnosis or suspected HCQ toxicity. The right eye for each subject was utilized for analysis. Data are presented as the mean $\pm$ standard deviation. All *P* values were two-tailed, and *P* < .05 was considered statistically significant.

RESULTS

Overall, 14 right eyes from 14 patients were included in both HCQ toxicity group and the age-matched control group (baseline characteristics of patients are presented in Supplemental Table). In HCQ toxicity group, the mean age at presentation was 57.0 ± 18.6 years (range 17 to 90), the mean duration of drug exposure was 20.6 ± 15.0 years (range 2 to 45), and the mean daily dosing based on actual body weight (ABW) was 5.5 ± 1.6 mg/kg/day (range 3.4 to 8.6). Clinical severity of HCQ retinopathy based on Marmor’s grading scale at baseline visit was early disease in 5 eyes, moderate in 6 eyes, and advanced in 3 eyes, respectively.[14] The patient with the lowest dosing in each group (ABW 4.0/3.7/3.4 mg/kg/day) had either been taking the drug for over 20 years and previously been prescribed double the amount (ABW 6.7-8.0 mg/kg/day) or had chronic renal failure. The patient with the lowest duration of HCQ exposure in each group (2.6/3.5/2.0 years) was either overdosed based on ABW (8.1-8.6 mg/kg/day) or had chronic renal failure.

Multiple outer retinal parameters were significantly lower in HCQ toxicity group compared with control group as shown in Table 1, including ONL/HFL-EZ volume (1.97 ± 0.44 mm³ vs 2.86 ± 0.23 mm³, *P* < .001) and EZ-RPE volume (0.89 ± 0.24 mm³ vs 1.27 ± 0.18 mm³, *P* < .001) in the moderate disease subgroup. Also, the mean area of partial EZ attenuation was significantly higher in the HCQ toxicity group compared with controls. Representative cases of HCQ toxicity with EZ-RPE mapping are displayed in Figure 2A-O. Eight (57%) eyes exhibited EZ-RPE attenuation localized to the parafoveal area resembling bull’s eye appearance, and 2 (14%) eyes demonstrated diffuse, severe disruption.

The results of quantitative measurements analysis comparing two different visits are displayed in Table 2. Five eyes with early disease at baseline and three eyes with moderate disease were included. The mean visit interval was 28.5 ± 7.5 (range 17 to 39) months. There was a significant decrease in several ONL/HFL-EZ parameters at the follow-up visit including ONL/HFL-EZ volume in early disease. Figure 3 displays a representative case with HCQ toxicity of longitudinal progression.

DISCUSSION

In this report, a semi-automated layer segmentation tool successfully allowed quantitative assessment of outer retinal thickness/volume, percentage of EZ-RPE attenuation/loss, and produced *en face* representation of EZ-RPE mapping. It also allowed unique visualization of EZ attenuation in subjects with HCQ toxicity. In HCQ toxicity group, multiple outer retinal parameters were significantly reduced possibly indicating a loss of photoreceptors and RPE cells. Our study was in reasonable agreement with previous studies that demonstrated the progression of outer retinal thinning.[8 15] Meanwhile, the foveal EZ-RPE thickness showed a significant increase. It has been recently reported that HCQ suppresses the activity of an organic anion transporting polypeptide 1A2 (OATP1A2) expressed in the RPE, which mediates the uptake of all-trans-retinol, an essential process in the retinoid visual cycle.[16] It is possible that the increased EZ-RPE thickness at follow-up visit might be due to the functional recovery of remaining photoreceptors with elongation of the outer segment following cessation of HCQ intake.

Quantification of outer retinal changes in patients undergoing HCQ therapy may allow efficient assessment for the progression of HCQ toxicity. This technology may provide an additional tool for toxicity screening in the future, but more research is needed.

Our study is limited by retrospective nature of the study and small sample size with variable follow-up periods. Wide-field 9×9 mm volume scans may better allow the identification of pericentral photoreceptor changes in certain ethnic groups (e.g., Asians).[6] Also, in eyes with tilted OCT images, retinal thickness measurements may be exaggerated with broadened scan area coverage since the thickness was measured parallel to the vertical axis of the B-scans.[17 18] The development of mathematical adjustment may be warranted. Moreover, due to the optical properties of Henle's fiber layer, it is possible that eyes with OCT image tilt may have resulted in less consistent measurements in the ONL/HFL boundary.[17]

In conclusion, this study provides evidence of the potential value of quantitative outer retinal parameters and *En face* EZ-RPE mapping on SD-OCT as a quantitative biomarker in a clinical setting to diagnose and monitor HCQ toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Ellipsoid zone (EZ) mapping and horizontal OCT B-scan image of the right eye in the normative age-matched control group.

A, EZ-retinal pigment epithelium (RPE) *en face* topographical map. The red line indicates the location of horizontal B-scan. **B**, Macular map sector with an inner circle representing the macular radius of 0.5 mm (corresponds to “central subfield”) and an outer circle representing the macular radius of 1.0 mm (corresponds to “parafoveal”). **C**, Horizontal B-scan crossing the central fovea displaying semi-automatically segmented retinal layer boundaries. Each boundary was carefully reviewed, and segmentation errors were corrected manually. The internal limiting membrane (a, blue), the outer boundaries of the outer plexiform layer (b, green), EZ band (c, yellow), and RPE (d, turquoise). For retinal thickness measurement, three orange lines parallel to the vertical axis of the B-scan image are illustrated at the fovea, 1.0 mm nasal and temporal to the fovea. Orange figures indicate retinal thickness between the neighboring boundaries at each location.

Figure 2. Various levels of hydroxychloroquine (HCQ) toxicity based on *en face* ellipsoid zone (EZ)-retinal pigment epithelium (RPE) mapping appearance.

The farthest left column contains *en face* topographical mapping of EZ to RPE thickness. The image is mirrored across the horizontal axis to maintain consistency in presentation. Total EZ-RPE attenuation is shown in pink (A, F, K). The second left column contains a three-dimensional reconstruction of macular cube displaying retinal layer plane of EZ (green) and RPE (pink). The pink color in green demonstrates the area where EZ plane and RPE plane are identical indicating total EZ-RPE attenuation (B, G, L). The third left column contains horizontal B-scan crossing the central fovea with retinal thickness map (C, H, M). The second right, and the farthest right column contain fundus autofluorescence (D, I, N), and Humphrey visual field (10-2 E, 10-2 J, 24-2 O), all for comparison purposes. A-E, A right eye of a 53-year-old female with systemic lupus erythematosus (SLE) and nephrotic syndrome in mild toxicity subgroup. Daily HCQ dosing of 400 mg for 38 years (daily dosing based on actual body weight was 6.8 mg/kg/day). A focal EZ-EPE attenuation can be observed in the parafoveal lesion on *en face* EZ-RPE mapping. F-J, A right eye of a 61-year-old female with SLE in moderate toxicity group. Daily HCQ dosing of 400 mg for 45 years (daily dosing based on actual body weight was 5.4 mg/kg/day). Moderate and continuous EZ-RPE attenuation resembling bull's eye appearance can be observed in the parafoveal lesion on *en face* EZ-RPE mapping. K-O, A right eye of a 56-year-old female with SLE. Daily HCQ dosing of 400 mg for 40 years (daily dosing based on actual body weight was 4.5 mg/kg/day). Severe and diffuse EZ-RPE attenuation involving the fovea can be observed on *en face* EZ-RPE mapping.

Figure 3. A case example of hydroxychloroquine (HCQ) toxicity progression.

A 52-year-old female with systemic lupus erythematosus. The patient has been taking the drug 400 mg per day for 24 years. Daily dosing based on actual body weight was 7.1 mg/kg/day. **A-F** Longitudinal changes in *en face* ellipsoid zone (EZ)-retinal pigment epithelium (RPE) mapping (**A, D**), three-dimensional macular cube reconstruction (**B, E**), and horizontal B-Scan images (**C, F**) of an eye with moderate EZ attenuation due to hydroxychloroquine (HCQ) toxicity. SD-OCT performed at baseline (**A-C**) and a follow-up visit after 32 months (**D-F**). This patient continued HCQ intake for another 26 months after baseline. The severity of HCQ toxicity was a moderate disease at the baseline visit and advanced disease at the follow-up visit. Focal EZ-RPE attenuation is evident in the parafoveal lesion on *en face* EZ-RPE mapping (**B**), and increased area of total EZ-RPE attenuation can be observed at the follow-up visit (**D**). Enhanced choroid visualization suggestive of RPE atrophy and choroidal shadowing indicative of RPE proliferation on SD-OCT were absent at baseline (**C**) but became apparent at the follow-up visit (**F**).

Table 1.

Comparison of outer retinal parameters between HCQ toxicity group and control group.

	HCQ toxicity group			Control group <i>n</i> = 14
	Early <i>n</i> = 5	Moderate <i>n</i> = 6	Advanced <i>n</i> = 3	
Foveal ONL/HFL-EZ thickness (μm)	115.0 ± 9.0	94.2 ± 33.9 [*]	58.0 ± 4.9 [*]	126.4 ± 23.3
Central subfield ONL/HFL-EZ thickness (μm)	97.3 ± 11.8 [*]	78.4 ± 22.2 [*]	48.2 ± 14.0 [*]	113.7 ± 12.6
Central subfield ONL/HFL-EZ volume (mm ³)	0.076 ± 0.009 [*]	0.061 ± 0.017 [*]	0.038 ± 0.011 [*]	0.089 ± 0.010
Parafoveal ONL/HFL-EZ thickness (μm)	75.7 ± 12.9 [*]	55.2 ± 12.1 ⁺	42.6 ± 15.7 [*]	96.6 ± 11.0
Parafoveal ONL/HFL-EZ volume (mm ³)	0.238 ± 0.041 [*]	0.174 ± 0.038 ⁺	0.134 ± 0.049 [*]	0.304 ± 0.035
ONL/HFL-EZ Volume (mm ³)	2.55 ± 0.37 [*]	1.97 ± 0.44 ⁺	0.77 ± 0.19 [*]	2.86 ± 0.23
Foveal EZ-RPE thickness (μm)	47.3 ± 5.8	44.0 ± 4.1 [*]	30.0 ± 6.9 [*]	51.9 ± 8.3
Central subfield EZ-RPE thickness (μm)	38.9 ± 4.5	32.4 ± 6.0 [*]	18.9 ± 8.2 [*]	40.7 ± 6.3
Central subfield EZ-RPE volume (mm ³)	0.030 ± 0.003	0.025 ± 0.005 [*]	0.015 ± 0.006 [*]	0.032 ± 0.005
Parafoveal EZ-RPE thickness (μm)	31.0 ± 4.4 [*]	22.1 ± 5.7 ⁺	10.8 ± 5.3 [*]	37.7 ± 5.9
Parafoveal EZ-RPE volume (mm ³)	0.098 ± 0.014 [*]	0.069 ± 0.018 ⁺	0.034 ± 0.017 [*]	0.119 ± 0.019
EZ-RPE Volume (mm ³)	1.10 ± 0.09 [*]	0.89 ± 0.24 ⁺	0.27 ± 0.35 [*]	1.27 ± 0.18
EZ-RPE thickness < 20 μm, area coverage (%)	4.8 ± 3.8 [*]	19.5 ± 8.4 ⁺	81.6 ± 27.5 [*]	0.9 ± 2.5
EZ-RPE thickness < 10 μm, area coverage (%)	1.1 ± 1.2 [*]	9.9 ± 4.7 ⁺	70.7 ± 36.6 [*]	0.1 ± 0.1
EZ-RPE thickness = 0 μm, area coverage (%)	0.8 ± 1.1	7.4 ± 4.3 ⁺	65.8 ± 36.6 [*]	0.1 ± 0.1

Abbreviations: EZ, ellipsoid zone; HCQ, hydroxychloroquine; ILM, internal limiting membrane; ONL/HFL, outer nuclear layer/Henle fiber layer; RPE, retinal pigment epithelium.

Central subfield is equivalent to a distance of 0.5 mm from the fovea (inner circle).

Parafoveal is equivalent to a distance of 1.0 mm from the fovea (outer circle).

Statistical analysis conducted with Mann-Whitney U test.

^{*} Statistical significance of $P < .05$ against the control group.

⁺ Statistical significance of $P < .001$ against the control group.

Table 2.

Longitudinal comparison of outer retinal parameters between baseline and follow-up visit in HCQ retinopathy group.

	HCQ toxicity group					
	Early		<i>P</i>	Moderate		<i>P</i>
	Baseline <i>n</i> = 5	Follow-up visit <i>n</i> = 5		Baseline <i>n</i> = 3	Follow-up visit <i>n</i> = 3	
Foveal ONL/HFL-EZ thickness (μm)	115.0 ± 9.0	93.8 ± 8.3	.010	118.0 ± 27.9	108.2 ± 3.0	.624
Central subfield ONL/HFL-EZ thickness (μm)	97.3 ± 11.8	85.2 ± 9.1	.066	93.5 ± 19.2	77.3 ± 7.6	.192
Central subfield ONL/HFL-EZ volume (mm ³)	0.076 ± 0.009	0.067 ± 0.007	.065	0.073 ± 0.015	0.061 ± 0.006	.191
Parafoveal ONL/HFL-EZ thickness (μm)	75.7 ± 12.9	67.7 ± 8.7	.062	60.2 ± 15.6	50.1 ± 9.6	.329
Parafoveal ONL/HFL-EZ volume (mm ³)	0.238 ± 0.041	0.213 ± 0.027	.062	0.189 ± 0.049	0.158 ± 0.030	.329
ONL/HFL-EZ Volume (mm ³)	2.55 ± 0.37	2.30 ± 0.33	< .001	2.12 ± 0.56	1.92 ± 0.38	.383
Foveal EZ-RPE thickness (μm)	47.3 ± 5.7	52.0 ± 7.5	.009	44.3 ± 5.6	50.8 ± 5.2	.370
Central subfield EZ-RPE thickness (μm)	38.9 ± 4.5	39.7 ± 6.5	.613	36.4 ± 3.3	36.0 ± 4.8	.670
Central subfield EZ-RPE volume (mm ³)	0.030 ± 0.003	0.031 ± 0.005	.615	0.029 ± 0.003	0.028 ± 0.004	.661
Parafoveal EZ-RPE thickness (μm)	31.0 ± 4.4	30.9 ± 3.3	.924	25.3 ± 5.6	21.0 ± 4.4	.087
Parafoveal EZ-RPE volume (mm ³)	0.098 ± 0.014	0.097 ± 0.010	.924	0.080 ± 0.018	0.066 ± 0.014	.087
EZ-RPE Volume (mm ³)	1.10 ± 0.09	1.11 ± 0.07	.855	1.05 ± 0.14	0.83 ± 0.14	.063
EZ-RPE thickness < 20 μm, area coverage (%)	4.8 ± 3.8	4.1 ± 3.4	.571	13.8 ± 7.3	29.5 ± 13.1	.082
EZ-RPE thickness < 10 μm, area coverage (%)	1.1 ± 1.2	0.7 ± 0.8	.555	6.0 ± 1.2	15.9 ± 8.7	.156
EZ-RPE thickness = 0 μm, area coverage (%)	0.8 ± 1.1	0.4 ± 0.7	.506	3.7 ± 2.0	12.2 ± 8.0	.150

Abbreviations: EZ, ellipsoid zone; HCQ, hydroxychloroquine; ILM, internal limiting membrane; NS, not significant; ONL/HFL, outer nuclear layer/Henle fiber layer; RPE, retinal pigment epithelium.

Statistical analysis conducted with paired t-test.

Figures in bold text are statistically significant at *P* < .05.