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Selective thinning of the perifoveal inner retina as an early sign of hydroxychloroquine retinal toxicity

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Learning objectives

Upon completion of this activity, participants will be able to:

1. Identify characteristic findings of hydroxychloroquine retinal toxicity
2. Describe the course of hydroxychloroquine retinal toxicity
3. Compare retinal thickness in patients treated with hydroxychloroquine and in control patients
4. Specify retinal layers particularly affected by treatment with hydroxychloroquine

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CLINICAL STUDY

Selective thinning of the perifoveal inner retina as an early sign of hydroxychloroquine retinal toxicity

S Pasadhika[1], GA Fishman[1], D Choi[2] and M Shahidi[1]

Abstract

Purpose **To evaluate macular thickness profiles using spectral-domain optical coherence tomography (SDOCT) and image segmentation in patients with chronic exposure to hydroxychloroquine.**

Methods **This study included eight patients with chronic exposure to hydroxychloroquine (group 1) and eight controls (group 2). Group 1 patients had no clinically evident retinal toxicity. All subjects underwent SDOCT imaging of the macula. An image segmentation technique was used to measure thickness of six retinal layers at 200 μm intervals. A mixed-effects model was used for multivariate analysis.**

Results **By measuring total retinal thickness either at the central macular (2800 μm in diameter), the perifoveal region 1200-μm-width ring surrounding the central macula), or the overall macular area (5200 μm in diameter), there were no significant differences in the thickness between groups 1 and 2. On an image segmentation analysis, selective thinning of the inner plexiform + ganglion cell layers ($P = 0.021$) was observed only in the perifoveal area of the patients in group 1 compared with that of group 2 by using the mixed-effects model analysis.**

Conclusion **Our study results suggest that chronic exposure to hydroxychloroquine is associated with thinning of the perifoveal inner retinal layers, especially in the ganglion cell and inner plexiform layers, even in the absence of functional or structural clinical changes involving the photoreceptor or retinal pigment epithelial cell layers. This may be a contributing factor as the reason most patients who have early detectable signs of drug toxicity present with paracentral or pericentral scotomas.**

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Keywords: hydroxychloroquine; perifoveal; parafoveal; ganglion cell; retinal toxicity; OCT

Introduction

Hydroxychloroquine, an anti-malarial medication, is useful in treating several forms of malaria as well as various rheumatologic diseases, such as rheumatoid arthritis (RA),[1] systemic lupus erythematosus (SLE), and dermatologic conditions.[2] Retinal toxicity is a well-known adverse effect associated with the use of chloroquine and hydroxychloroquine.[3] Although retinal toxicity is currently reported infrequently,[4,5] a careful monitoring for potential drug toxicity is necessary because it may lead to potentially severe and irreversible visual loss.

Retinal toxicity may be clinically evident as pigment mottling within the macular area or present with a characteristic bull's eye maculopathy.[6] The affected individuals may observe visual field defects which can occur before fundus changes.[7] Patients with macular pathology may experience a deficiency in their colour vision. In later stages of toxicity, atrophy of the retinal pigment epithelium (RPE) and neurosensory retina can spread centrifugally and become visible over the entire fundus. Retinal toxicity is generally irreversible and may be progressive despite discontinuation of medication.[8] Early detection and prompt discontinuation of medication may reverse retinal toxicity at an initial stage.[6] Multifocal electroretinography (mfERG) may be useful to detect the reduction of retinal cone function at an early stage of toxicity.[9] However, it is a

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relatively inconvenient and not always readily available test.

The mechanism of retinal toxicity is not yet well understood. Clinical characteristics, including pigmentary changes in the macular area, may have led some clinicians into believing that photoreceptors were primarily involved. Nonetheless, previous studies in animals with chronic exposure to chloroquine showed that the first histopathological changes were detected in the retinal ganglion cells.[10,11] Using spectral-domain optical coherence tomography (SDOCT), our recent study in humans showed that thinning of the peripapillary retinal nerve fibre layer (RNFL) and retinal ganglion cell axons were consistently observed in patients with fundus changes due to drug toxicity.[12] However, such thinning was not generally detected in those who had chronic exposure to hydroxychloroquine without fundus changes. Furthermore, a 7×7-mm macular scan analysis showed that the inner retina (RNFL + ganglion cell layer (GCL) + inner plexiform layer (IPL)) was selectively thin in those who had chronic exposure without clinically evident toxicity, compared to controls.

Because patients with initial stages of hydroxychloroquine retinal toxicity often present with partial paracentral or complete pericentral ring scotomas,[6,7] we hypothesized that retinal anatomical changes may be observed initially in the perifoveal area. This study expanded on an initial study by more specifically identifying which region of the macula and cellular levels in the inner retina were selectively thin. Using an image segmentation technique,[13] we were able to define retinal structures into six separate cellular levels compared to two levels in our previous study. In addition, we were able to evaluate retinal thickness in selected areas of the macula. The ability to stratify cellular layers more comprehensively allowed us to better identify which retinal layers were more specifically affected in our previously evaluated cohort of patients.[12] This study can provide a more comprehensive insight into the retinal structural changes that occur in hydroxychloroquine retinal toxicity, which in turn, may lead to earlier detection with the use of more sensitive screening procedures.

Materials and methods

Patients

Eight female patients (16 eyes) with a history for chronic use of hydroxychloroquine for at least 5 years (group 1) and eight (16 eyes) visually normal, age-similar, race-matched female controls (group 2) were included in this study. The study was conducted in the Electrophysiology and Inherited Retinal Disease unit at the Illinois Eye and Ear Infirmary. Three patients were prospectively recruited from the electrophysiology unit, and three patients attended a comprehensive eye clinic at the University of Illinois at Chicago. Two additional patients participated after obtaining a telephone invitation. All patients were examined by two authors (SP and GAF). This study followed the Declaration of Helsinki Principles and was approved by an institutional review board at the University of Illinois. Informed consent was obtained from all participants.

Exclusion criteria included known optic nerve diseases or anomalies, glaucoma or glaucoma suspects, known retinal diseases, uveitis, intraocular pressure higher than 20 mm Hg or a history of ocular hypertension, refractive error of more than ± 6 D sphere or ± 3 D cylinder, previous intraocular or refractive surgery, and media opacity that precluded a high-quality OCT examination.

Ocular examination and psychophysical tests

All participants underwent a comprehensive ocular examination, including best-corrected visual acuity (BCVA) measurement using the Early Treatment Diabetic Retinopathy Study chart (The Lighthouse Long Island City, NY, USA), slit-lamp biomicroscopy, Goldmann applanation tonometry, colour vision testing using Ishihara Psuedoisochromatic Plates (Kanehara Shuppan Co. Ltd, Tokyo, Japan), and dilated fundus examination. The patients in group 1 underwent visual field testing using the Humphrey 10-2 program (Zeiss Humphrey Systems, Dublin, CA, USA) and evaluation by mfERG (VERIS; Electro-Diagnostic Imaging, San Mateo, CA, USA). The protocol for the mfERG technique was previously described.[14] Data collection included date of birth, race, gender, ocular and medical history, duration of drug exposure, dosages, as well as previous and current body weight.

Scan acquisition and image segmentation

Spectral-domain optical coherence tomography imaging was performed using Optovue technology (RTVue Model-RT100 version 3.5; Optovue Inc., Fremont, CA, USA). Internal fixation was used to facilitate OCT image acquisition. Macular scans were performed using the Radial Lines protocol, which provided twelve, 6-mm scans centred at the fovea. Scan acquisition time required for each of the Radial Lines scans was 0.27 s. The scans had a depth resolution of 3 μm per pixel and spatial resolution of 6 μm per pixel.

Horizontal and vertical SDOCT images from the Radial Lines scans were exported in TIF format. Automated image segmentation and analysis were performed using

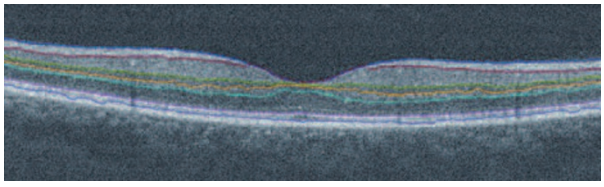

Figure 1 An example of a vertical scan through the foveal centre in a control subject, showing a retinal layer segmentation technique applied to spectral-domain optical coherence tomography (SDOCT) image. The retina is segmented with seven boundary lines into six layers, including retinal nerve fibre layer (RNFL), ganglion cell + inner plexiform layers (GCL + IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer + photoreceptor inner segments (ONL + PIS), and photoreceptor outer segments (POS) (from top to bottom).

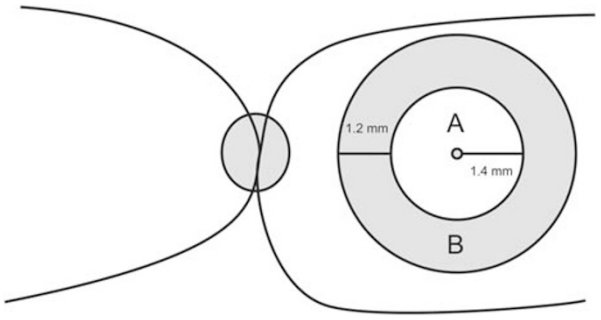

Figure 2 Cartoon shows the central macular area (A) and perifoveal area (B), as referred to in this study.

a dedicated software program developed in Matlab (The Mathworks Inc., Natick, MA, USA) and previously described.[12] The program enabled the measurement of the thickness profiles for six retinal layers (Figure 1): RNFL, GCL + IPL, inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer and photoreceptor inner segments (ONL + PIS), and photoreceptor outer segments (POS). Thickness measurements were averaged at 200 μm intervals along 6 mm lengths of the Radial Lines scans.

Data analysis

In each scan, the foveal centre was identified as the location on the thickness profile corresponding to the minimum retinal thickness (or thinnest retina). Thickness in central, perifoveal, and overall macular areas (Figure 2) was calculated by averaging 15, 14, and 27 measurements on thickness profiles, respectively, from both vertical and horizontal scans. The central macular area was 2800 μm in diameter (approximately 10°), centred at the foveal centre. The perifoveal area was defined as a 1200-μm-width ring surrounding the central macular area. The overall macular area was 5200 μm in diameter, centred at the foveal centre. Thickness measurements in the central macular and perifoveal areas obtained from images in group 1 (patients) were compared to those obtained in group 2 (controls). Mixed-effects models were used to compare all layers between the two groups simultaneously, while accounting for potential interpersonal correlations. Statistical significance was accepted at $P<0.05$.

Results

Demographic characteristics

The mean age in groups 1 and 2 were 54.9 ± 11.0 (range, 35–68 years) and 53.7 ± 10.5 years (range, 34–70 years), respectively. There were no statistically significant differences in ages between the groups ($P=0.836$). In each group, six and two subjects were Caucasian and African American, respectively.

Patients in group 1 were exposed to hydroxychloroquine from 6 to 35 years (median, 10 years). Six patients in group 1 had a diagnosis of SLE, one had RA, and one had juvenile idiopathic arthritis. Maximum daily doses of hydroxychloroquine ranged from 3.14 to 9.26 mg/kg per day (median, 6.56 mg/kg per day). Total accumulative doses ranged from 792 to 2628 g (median, 1651 g).

Ocular examination and psychophysical tests

All subjects had normal anterior segment and fundus examinations. Corneal verticillata was not observed in any of the participants. Both groups had a mean logMAR BCVA of 0.0 (equivalent to 20/20). Intraocular pressure ranged from 12 to 18 mm Hg. Each subject in both groups had normal colour vision screening (21 out of 21 Ishihara plates). Humphrey 10-2 visual field testing results were normal in all group 1 patients. All patients in group 1 underwent mfERG testing; however, reliable results were not obtained in two patients due to technical issues during recordings. Of the remaining six patients, five had normal mfERG results in all six rings compared to a visually normal age-similar population, whereas one had a reduction in amplitude in two of the six rings for the right eye and in five of the six rings for the left eye.

Image segmentation analysis

Table 1 shows the mean thickness measurements for each of six retinal layers and total retinal thickness in the central macular, perifoveal, and overall macular areas, in groups 1 (patients) and 2 (controls). There were no

Table 1 Mean retinal thickness measurements in each retinal layer in group 1 (with exposure to hydroxychloroquine) compared with those of group 2 (controls)

Macular area/layers	*Group 1 (mean ± SD, μm)*	*Group 2 (mean ± SD, μm)*	P-*value*[a]
Central			
NFL	15.76 ± 3.22	16.93 ± 2.23	0.562
GCL + IPL	73.00 ± 6.01	73.38 ± 8.93	0.849
INL	28.95 ± 4.00	29.24 ± 3.16	0.884
OPL	30.89 ± 6.80	32.80 ± 1.94	0.347
ONL + PIS	91.27 ± 9.07	90.60 ± 3.23	0.739
POS	34.95 ± 3.47	33.42 ± 2.75	0.451
Total	274.81 ± 17.61	276.38 ± 12.73	0.838
Perifoveal			
NFL	34.95 ± 4.89	37.83 ± 5.25	0.097
GCL + IPL	70.02 ± 4.41	74.26 ± 5.46	0.021[b]
INL	30.66 ± 2.48	32.84 ± 2.38	0.202
OPL	27.41 ± 5.54	28.26 ± 1.94	0.608
ONL + PIS	77.57 ± 8.38	75.20 ± 3.02	0.166
POS	33.46 ± 2.76	33.07 ± 3.16	0.816
Total	274.06 ± 12.41	281.46 ± 5.69	0.132
Overall			
NFL	24.54 ± 3.57	26.50 ± 3.12	0.232
GCL + IPL	70.28 ± 4.55	72.47 ± 5.83	0.185
INL	29.41 ± 2.90	30.57 ± 2.38	0.474
OPL	29.09 ± 5.61	30.39 ± 1.50	0.420
ONL + PIS	84.96 ± 8.30	83.39 ± 2.62	0.333
POS	34.28 ± 2.85	33.38 ± 2.66	0.574
Total	272.57 ± 13.74	276.70 ± 6.11	0.441

NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; PIS, photoreceptor inner segments; POS, photoreceptor outer segments.
[a]From mixed-effects models.
[b]Statistically significant.

significant differences in thickness measurements of each layer in the central and overall macular areas. However, there was a statistically significant reduction in thickness measurements of the GCL + IPL ($P = 0.021$) only in the perifoveal area using mixed-effect models.

Discussion

In 1978, Rosenthal *et al*[10] reported that histopathological changes of inner and outer retinal structures could be observed in rhesus monkeys with chronic exposure to chloroquine, even in the absence of clinically evident retinal changes on fundus photography, fluorescein angiography, or electroretinography. The earliest pathological change was an accumulation of cytoplasmic granules in ganglion cells, which was followed by ganglion cell degeneration with shrunken cells and pyknotic irregular nuclei. At later stages, degeneration of photoreceptor and RPE cells was subsequently observed.[10] A previous histopathological study in a human eye with chronic exposure to chloroquine showed cytoplasmic inclusion bodies most prominently in the ganglion cells, but also some accumulation in IPL, INL, and RPE cells. Only minimal photoreceptor cell loss was detected.[15] Our recent SDOCT study also showed that thinning of inner retinal structures may be observed before clinically detectable structural and functional changes.[12]

Characteristic signs of retinal toxicity related to the use of chloroquine or hydroxychloroquine include paracentral or pericentral scotomas and a bull's eye maculopathy, shown as bilateral pigmentary changes of the macula with relative sparing of the central fovea. The mechanism to explain these clinical signs remains unclear. There has been initial speculation that cone photoreceptors, which are most dense in the macular region, are primarily involved in the course of toxicity. However, retention of central visual acuity and preservation of colour vision in some patients who have a bull's eye maculopathy[7] are inconsistent with this hypothesis. Our image segmentation results suggest that ganglion cells, and possibly also bipolar cells, are initially affected. It is known that not only cones are most dense in the macular area, but also that several layers of ganglion cells are present outside the foveal centre. We speculate that hydroxychloroquine may accumulate in ganglion cells throughout the retina; however, significant SDOCT changes were detected in the perifoveal area where ganglion cells are most populated. This may explain why most of the patients with early toxicity present with paracentral or pericentral scotomas, even though a bull's eye maculopathy may be absent. With progression of toxicity, reduction in mfERG amplitudes and a bull's eye maculopathy may become apparent. In addition, an impairment of central visual field sensitivity, visual acuity, and colour vision is clinically detectable due to subsequent degeneration of photoreceptor and RPE cells. Kellner *et al*[16] showed that parafoveal RPE loss was observed in two patients with chloroquine retinopathy using fundus autofluorescence.

Interestingly, image segmentation results did not show significant RNFL thinning in the perifoveal area. This is consistent with our previous observation that peripapillary RNFL thinning is absent in the patients who have chronic hydroxychloroquine exposure without fundus changes, but may be present in those with fundus changes related to drug toxicity.[12] This observation may imply that RNFL thinning follows significant ganglion cell degeneration.

Thinning of the GCL and a decrease in visual functions should theoretically occur in concurrence with or follow degenerative loss of ganglion cells. The degree of

ganglion cell degeneration that is sufficient to produce clinical symptoms or a detectable abnormality on psychophysical testing is essentially unknown. In glaucoma, retinal structural changes may precede clinically detectable functional abnormalities.[17] Similarly, inner retinal thinning was observed, although none of the patients in our study had apparent Humphrey visual field defects at this stage. Further studies are warranted to establish the time course for development of retinal structural and functional changes in patients with hydroxychloroquine retinal toxicity.

We realize that there is a theoretical possibility that SLE and other rheumatological diseases, themselves, may have an impact on retinal structures. Nonetheless, we excluded any patients with other abnormal fundus findings, including perivascular sheathing, retinal haemorrhages, and exudates. A more ideal control group might have been patients, with the same rheumatological diagnoses for the same period of time, who did not have a history of hydroxychloroquine exposure. However, in the absence of glaucoma or retinal vascular disease, we would not have anticipated inner retinal thinning solely from rheumatological diseases.

Because we aimed to detect an initial change of retinal microstructures related to chronic use of hydroxychloroquine, in this study we included only patients without symptoms and signs of hydroxychloroquine retinal toxicity. Several reports previously described abnormal OCT findings, including parafoveal thinning[18,19] and abnormalities in the parafoveal photoreceptor inner segment/outer segment junction[19] in patients with chloroquine or hydroxychloroquine retinal toxicity. However, those patients with noticeable OCT changes had clinical symptoms, visual loss, visual field defects, colour vision deficiency, or abnormal mfERG findings. In this study, all subjects had a normal inner segment/outer segment junction, and we were unable to differentiate perifoveal inner retinal thinning in SDOCT images between patients and controls by eye.

In summary, the use of SDOCT technology and image segmentation algorithms enhance the ability to detect early thickness abnormalities in retinal layers. We believe that the development of higher-resolution imaging technique with automated segmentation protocols will be useful to detect initial change of perifoveal GCLs. Because clinically detectable signs of toxicity, including visual field defects, colour vision deficiency, or fundus changes, are usually irreversible once they occur, longitudinal monitoring of perifoveal inner retinal thickness may have clinical relevance to detect earlier structural changes from hydroxychloroquine or chloroquine retinal toxicity before clinically evident functional impairment.

Summary

What was known before

- Peripapillary retinal nerve fibre layer thinning was consistently seen in patients who presented with retinal lesions compatible with anti-malarial toxicity.
- Selective thinning of the inner retina in the 7×7 mm posterior pole was observed in those without clinically apparent fundus changes.

What this study adds

- Because patients with initial stages of hydroxychloroquine retinal toxicity often present with partially paracentral or complete pericentral ring scotomas, we hypothesized that retinal anatomical changes may be initially observed in the perifoveal area.
- We were able to define retinal structures into six separate cellular levels by using an image segmentation technique. In addition, we were able to evaluate retinal thickness in selected areas of the macula.
- Using spectral-domain OCT, only the ganglion cell layer and inner plexiform layer complex in the perifoveal area were affected in the patients with hydroxychloroquine exposure compared to controls.

Conflict of interest

The authors declare no conflict of interest.

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Selective thinning of the perifoveal inner retina as an early sign of hydroxychloroquine retinal toxicity

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1. Which of the following retinal findings is most characteristic of hydroxychloroquine toxicity?

A Increases in the retinal pigment epithelium
B Focused involvement at the fovea
C Bull's eye maculopathy
D Sparing of the ganglion cell layer

2. Which of the following statements about retinal toxicity related to hydroxychloroquine is most accurate?

A Visual field defects never precede fundus changes
B A loss of color vision is common
C Retinal toxicity usually improves with time
D Retinal toxicity always ceases with withdrawal of hydroxychloroquine

3. Which of the following statements about measurements of total retinal thickness in study participants is most accurate?

A Hydroxychloroquine was associated with reduced thickness in the central macula and reduced macular thickness overall
B Hydroxychloroquine was associated with reduced thickness in the central macula only
C Hydroxychloroquine was associated with reduced overall macular thickness only
D Hydroxychloroquine was associated with neither reduced thickness in the central macula nor reduced overall macular thickness

4. Which of the following retinal layers appeared to be most affected by treatment with hydroxychloroquine?

A Ganglion cell layer plus inner plexiform layer
B Nerve fiber layer
C Photoreceptor inner segments
D Inner nuclear layer

Activity evaluation

1. The activity supported the learning objectives.

Strongly disagree				Strongly agree
1	2	3	4	5

2. The material was organized clearly for learning to occur.

Strongly disagree				Strongly agree
1	2	3	4	5

3. The content learned from this activity will impact my practice

Strongly disagree				Strongly agree
1	2	3	4	5

4. The activity was presented objectively and free of commercial bias.

Strongly disagree				Strongly agree
1	2	3	4	5