

Pericentral Hydroxychloroquine Retinopathy in Korean Patients

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Purpose: A pericentral pattern of hydroxychloroquine (HCQ) retinopathy recently has been recognized in the United States in patients of Asian heritage. We report on an investigation of this pericentral retinopathy within a Korean population.

Design: Retrospective, observational study.

Participants: Patients taking HCQ who were referred to ophthalmology for screening of HCQ retinopathy.

Methods: The medical records of patients were reviewed, including spectral domain optical coherence tomography, fundus autofluorescence, and visual fields.

Main Outcome Measures: Frequency of pericentral pattern of HCQ retinopathy and features of progression.

Results: Among 218 patients referred, 9 (4.1%) were diagnosed with toxicity. Of these, 8 had a predominantly pericentral pattern of retinal change, whereas only 1 had the classic parafoveal distribution of retinal damage. Progression of retinopathy was documented in 3 patients followed more than 12 months while taking HCQ. No progression was seen in 2 patients without retinal pigment epithelial (RPE) damage who were followed for at least 12 months after discontinuation of HCQ.

Conclusions: We found that a pericentral pattern of HCQ retinopathy was predominant among Korean patients, rather than the traditional (bull's eye) parafoveal pattern of damage. Retinopathy progressed while on the drug, but the progression stopped in patients with toxicity detected before RPE damage. These observations suggest the need for new approaches when screening for HCQ toxicity in Asian patients. *Ophthalmology* 2015;122:1252-1256 © 2015 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Hydroxychloroquine (HCQ) is widely used for the treatment of systemic lupus erythematosus, rheumatoid arthritis, and other rheumatologic diseases. Previous studies suggested that HCQ retinal toxicity was relatively rare¹; however, a recent report of patients who took HCQ for more than 5 years reported an overall prevalence of 7.5%.² Hydroxychloroquine retinal toxicity is generally irreversible and may progress even after cessation of drug.^{1,3} Thus, recognition of retinopathy at an early stage is important.

Hydroxychloroquine toxicity traditionally has been characterized as a parafoveal bull's eye retinopathy, evident in late stages as a ring of depigmentation about the fovea and in earlier stages as a tight ring scotoma on 10-2 fields^{4,5} or parafoveal thinning of the outer nuclear layer with breakup of the ellipsoid zone (EZ) and interdigitation zone (IZ) lines on spectral domain optical coherence tomography (SD OCT).⁶ However, a recent report based on a diverse group of patients in the United States found that patients of Asian heritage frequently developed retinopathy in a more peripheral or "pericentral" pattern.⁷

This new finding has not been confirmed in Asia. We reviewed the records of patients who were referred to a retina service in Seoul, Korea, for HCQ toxicity screening to determine the distribution of retinopathy. We also report the

progression of retinopathy while patients continued taking HCQ and after stopping the medication.

Methods

We reviewed the records of all patients who were referred for HCQ screening to the department of ophthalmology at the Asan Medical Center in Seoul Korea from 2011 to 2014. Data collected included age, sex, medical diagnosis, weight, refractive status, daily dose, duration of HCQ use, and cumulative dose of HCQ. The cumulative dose data were collected through an automated pharmacy system.

Detailed ophthalmic examination and ophthalmic ancillary tests included 10-2 or 30-2 visual fields (VFs) (Humphrey perimeter; Carl Zeiss Meditec Inc, Dublin, CA), SD OCT (Heidelberg Engineering, Heidelberg, Germany), and fundus autofluorescence (FAF) (Heidelberg Engineering). The SD OCT studies were read by 2 authors (D.H.L., Y.H.Y.), and a diagnosis of toxicity required agreement on the presence of bilateral discrete macular zones of EZ or IZ discontinuity. Patients were followed for a total of 6 to 30 months and for 2 to 18 months after retinopathy was diagnosed and the drug was discontinued. Several patients were checked with wide-angle FAF and swept-source optical coherence tomography to evaluate retinal structural changes outside the arcade. This study was approved by the Institutional Review Board and Ethics Committee of Asan Medical Center.

Table 1. Comparison between the Patients with Toxicity and Those Without

Patient Characteristics, No. (%)	Retinal Toxicity	No Retinal Toxicity	P Value*
Female sex	9 (100.0)	182 (87.1)	0.61
Primary indication			
Systemic lupus erythematosus	6 (66.7)	148 (70.8)	0.72
Rheumatoid arthritis	3 (33.3)	52 (24.9)	0.70
Other	0	9 (4.3)	NA
Kidney disease [†]	2 (22.2)	40 (19.1)	0.69
Liver disease	1 (11.1)	13 (6.2)	0.46
Patient Characteristics, Mean (SD)			
Age (yrs)	54.1 (12.4)	46.2 (12.4)	0.06
HCQ daily dose (mg/kg)	4.2 (1.3)	3.8 (0.9)	0.17
Duration of HCQ use (mo)	115.8 (30.8)	99.8 (46.5)	0.31
HCQ cumulative dose (g)	991.9 (385.5)	729.8 (341.1)	0.03
Refractive error (D) [‡]	-0.19 (2.31)	-1.51 (2.52)	0.14

D = diopters; HCQ = hydroxychloroquine; NA = not available; SD = standard deviation.

*Fisher exact test or Student *t* test.

[†]Kidney disease defined as a period of >3 months with glomerular filtration rate <60 ml/min/1.73 m².

[‡]Average spherical equivalent, excluding patients with prior cataract or refractive surgery.

Results

Of 218 patients reviewed, 9 (4.1%) showed discrete EZ-IZ loss on SD OCT suggestive of HCQ toxicity. Although the mean age, daily dose, duration of use, and cumulative dose were all greater in the patients with toxicity compared with those without (Table 1), only the difference in cumulative HCQ dose was statistically significant ($P = 0.03$). Patients with toxicity were slightly less myopic on average than those without.

Table 2 shows demographic and dose information for the patients with toxicity. The patients with outer retinal changes consistent with HCQ retinopathy were separated into those with a pericentral or parafoveal pattern. Eight patients with outer retinal loss more than 7° from the fovea were classified as having pericentral retinopathy, whereas only 1 patient had outer retinal changes in the classic bull's eye pattern 2° to 6° from the fovea. Figure 1 illustrates the findings of pericentral retinopathy

(case 1), including 30-2 VFs. The pericentral pattern of toxicity was visible only at the periphery of 10-2 VF tests. Most of the patients tested with the 30-2 protocol showed some mid-peripheral losses, particularly in more advanced cases.

Because the SD OCT findings were unexpected or sometimes ambiguous at first examination (given the traditional description of parafoveal retinopathy), and the initial 10-2 fields were not revealing, some patients were followed while remaining on HCQ until damage was clearly evident on SD OCT. Figure 2 shows the progression of pericentral FAF in case 1. A hyperfluorescent zone in the inferior temporal area appeared 12 months after the initial study (10 years of HCQ therapy), and this zone enlarged and became more intense on repeat FAF 6 months later, at which time the patient discontinued HCQ. A wide-field FAF of this same patient 27 months after the initial study is shown in Figure 1.

Three of the patients were followed at least 12 months (maximum 24 months) while still taking HCQ. Figures 3 and 4

Table 2. Demographic and Dose Information for the Patients with Toxicity

Case Identifiers	Age (yrs)	Sex	Diagnosis	Weight (kg)	Mean Refractive Error (D)	HCQ Daily Dose/Weight (mg/kg)	HCQ Duration (mos)	HCQ Cumulative Dose (g)
Pericentral Pattern								
1	53	F	SLE	47	-0.69	4.3	134	1342
2	38	F	SLE	53	-5.44	7.5	96	1053
3*	34	F	SLE	48	-0.06	4.2	52	379
4 [†]	66	F	SLE	55	-1.75	3.6	98	396
5	67	F	RA	54	1.94	3.7	141	1115
6	55	F	SLE	64	-0.75	4.7	111	1054
7	67	F	RA	50	1.25	4.0	151	1099
8	60	F	RA	55	1.38	3.6	120	949
Parafoveal Pattern								
9	47	F	SLE	56	NA	3.6	139	1540

D = diopters; F = female; HCQ = hydroxychloroquine; NA = not available; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

*History of renal disease and liver disease.

[†]History of renal disease, LASIK, and intraocular lens surgery.

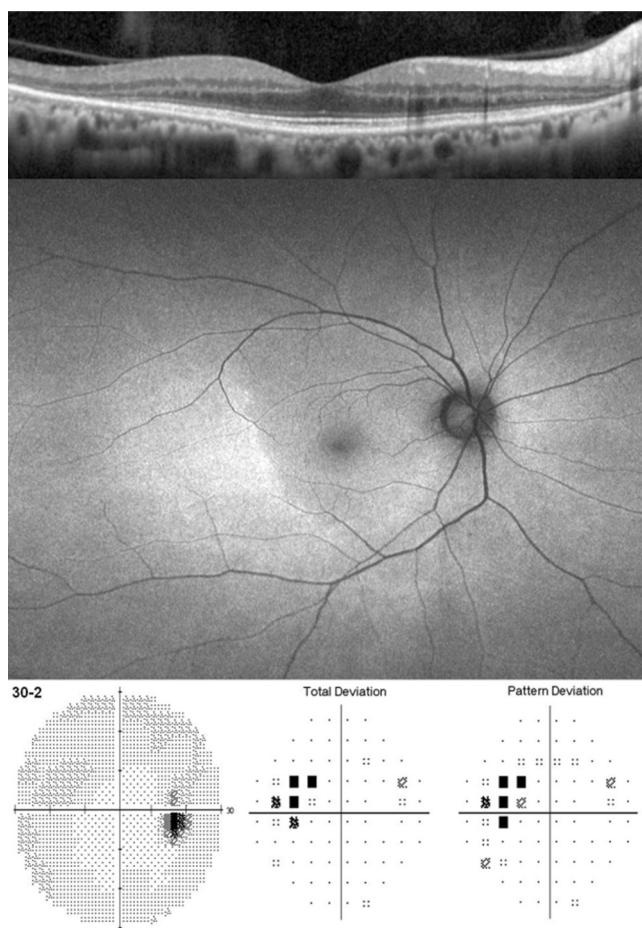


Figure 1. Case 1. **Top:** Horizontal spectral domain optical coherence tomography of the right eye, showing loss of the outer retina (ellipsoid zone and interdigitation zone) in the temporal retina. **Middle:** Wide-field fundus autofluorescence showing a broad area of hyperfluorescence in the inferotemporal macula. **Bottom:** 30-2 visual field (VF) with superonasal scotoma corresponding to the retinal changes. A 10-2 VF test showed normal results.

show the SD OCT pattern of retinal anatomic changes while on HCQ in cases 2 and 3, respectively, illustrating the pericentral origin of damage in these eyes. There was little outer retinal damage at the first screening visits, but upon repeat screening 1 to 2

years later, there is marked loss of the EZ and IZ in areas more than 7° eccentric from the fovea. Centripetal movement of the degeneration from a more peripheral origin is seen clearly in the left eye of case 2, which had some early thinning at baseline in the far temporal periphery of the SD OCT field.

Three patients with retinopathy were also followed for at least 12 months (maximum 18 months) after discontinuation of HCQ, which allows comparison of the degree of progression on and off the drug. Two patients, whose toxicity was detected before any retinal pigment epithelial (RPE) damage on SD OCT, showed no further loss of EZ or IZ structures after HCQ was stopped. **Figure 4** shows the right eye SD OCT of case 3, with clear progression while on the drug from 0 to 12 months (when the drug was discontinued), but no progression from 12 to 30 months. An additional patient with some RPE damage apparent on SD OCT (but not on FAF or fundus examination) was followed for 18 months after discontinuing HCQ and showed mild narrowing of the EZ. The patient with classic parafoveal retinopathy had marked RPE loss and showed prominent foveal thinning and progressive loss of EZ over 9 months of follow-up off HCQ.

Discussion

We found that a newly described pattern of pericentral HCQ retinopathy among Asian patients in the United States⁷ was more prevalent among Korean patients with toxicity, as opposed to the classic “bull’s eye” parafoveal pattern. This finding strengthens the suggestion that we may need to modify screening recommendations for HCQ toxicity in Asian patients.⁷

The American Academy of Ophthalmology has recommended regular ophthalmic screening for patients on long-term HCQ therapy.⁸ The 10-2 VF test has been highlighted as a key test for detecting the early HCQ toxicity because of its sensitivity in the central macula.^{5,9,10} However, very early VF damage may be confused with nonpathologic variations, and some patients do not perform fields reliably. Thus, the American Academy of Ophthalmology guideline emphasized the importance of adding objective testing such as SD OCT and multifocal electroretinography where available. The use of multifocal electroretinography for screening has been hampered by its limited availability and variable interpretation, and so the simultaneous use of VF and SD OCT tests is typically

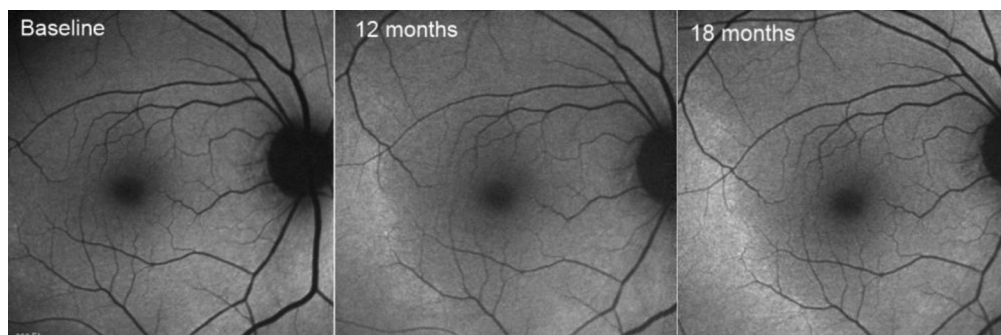


Figure 2. Case 1. Fundus autofluorescence images showing progressive hyperfluorescence in the inferotemporal macula while taking hydroxychloroquine (HCQ), which was discontinued after the 18-month study (11 years of HCQ therapy).

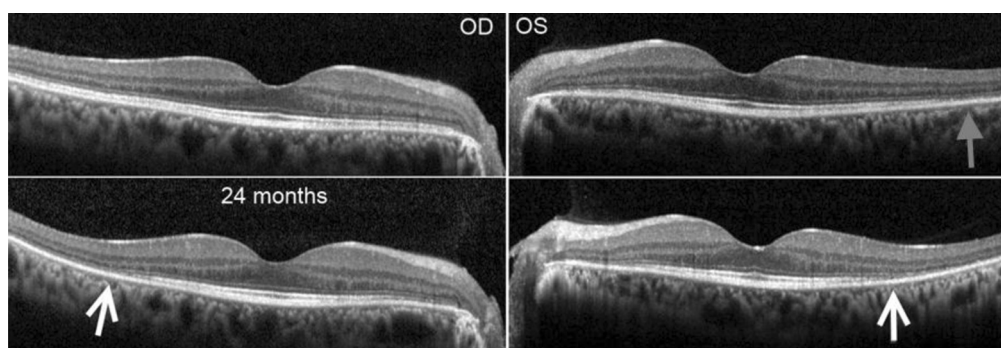


Figure 3. Case 2. Horizontal spectral domain optical coherence tomography images showing progressive centripetal loss of the outer nuclear layer (white arrows) over 24 months while taking hydroxychloroquine (8 years of therapy). The initial temporal change in the left eye (grey arrow) was not recognized as toxicity. OD = right eye; OS = left eye.

recommended to provide a balance of subjective and objective tests to detect and confirm HCQ toxicity.^{4,8}

Prior reports have shown a characteristic parafoveal loss of the photoreceptor EZ-IZ junction on SD OCT in HCQ retinal toxicity^{6,11} and have emphasized the necessity of recognizing early thinning on OCT that is typically just 2° to 6° off the center.⁴ However, most of the patients in the current study presented with outer retinal changes so far from the fovea that they might not have been detected with central VF testing or SD OCT scanning protocols that did not go beyond 10° of the macula. The majority of

our patients had EZ-IZ loss in perifoveal and even mid-peripheral areas that sometimes resembled the optical coherence tomography findings of patients with pericentral retinitis pigmentosa. Only 1 patient showed the classic bull's eye parafoveal damage.

Because this peripheral pattern was not an expected presentation of HCQ retinopathy, a number of patients were followed until the cause of damage became clear. Continued use of HCQ (for at least 1 year) showed a steady centripetal progression of EZ-IZ disruption and FAF hyperfluorescence. There was also further loss of the EZ after stopping the drug in eyes with RPE involvement. In contrast, patients who discontinued HCQ therapy at an earlier stage of retinopathy (no RPE damage) did not show significant progression. This is an important observation because it demonstrates the speed with which retinopathy damage can occur while taking HCQ and the importance of detecting damage before progression into the fovea. Our series is too small for firm conclusions, but these observations are consistent with prior reports that there is little or no progression of EZ-IZ loss in patients with parafoveal retinopathy before RPE disruption.¹²

Hydroxychloroquine binds to melanin in the RPE and causes lipid complex accumulation, enzyme inhibition, free radical generation, and ion disturbances in the retina.^{13–19} However, the pathophysiology of the retinal toxicity and its central distribution are not clearly understood, nor is there an obvious explanation for the disparity in the retinal location between white and Asian patients. An increased risk in patients with more retinal pigment seems unlikely because black patients do not seem predisposed to the peripheral pattern,⁷ nor is myopia likely because the average refractive error was low among the patients with toxicity (and a review of the data from an American study⁷ showed no correlation with refractive status). Unusual dosing is not a factor because only 1 patient with retinopathy had received excessive daily dosage relative to a recent report that suggested lower risk at <5 mg/kg.² One study has suggested that aberrations in the *ABCA4* gene may predispose to HCQ toxicity,²⁰ although this has not been corroborated. Patients in that study would have been mostly of European ancestry, and perhaps future genetic studies will help to clarify the impact of racial differences on patterns of toxicity.

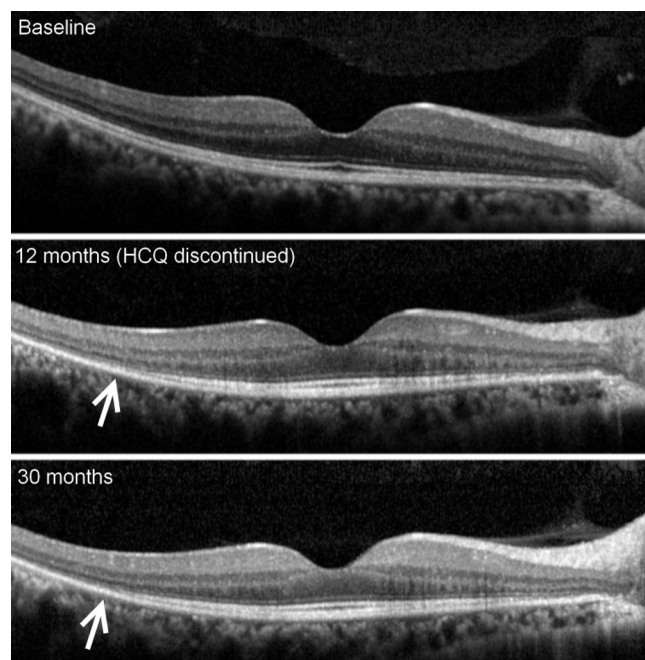


Figure 4. Case 3. Horizontal spectral-domain optical coherence tomography images from the right eye showing different degrees of progression on and off hydroxychloroquine (HCQ) in a patient with renal disease. The baseline examination (top) was performed after 3 years of HCQ therapy and showed no outer retinal damage. A loss of outer retinal structures temporally was seen 12 months later (middle, white arrow) was visible, and HCQ was discontinued. There was no evidence of further progression (bottom, white arrow) over the next 18 months off the drug.

In conclusion, the pattern of early HCQ toxicity differs between Korean patients and patients of European descent. Most Korean patients show pericentral rather than parafoveal photoreceptor damage, and the toxicity progresses in a centripetal fashion toward the fovea while on the drug. However, in both groups, progression appears to stop if the medication is discontinued at an early stage of retinopathy. On the basis of these observations, we propose that screening protocols for detecting HCQ toxicity in Korean and other Asian patients include wide-field examinations, such as 24-2 or 30-2 VF protocols, wide-field FAF, or SD OCT with at least 30° scans.

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Abbreviations and Acronyms:

EZ = ellipsoid zone; **FAF** = fundus autofluorescence; **HCQ** = hydroxychloroquine; **IZ** = interdigitation zone; **RPE** = retinal pigment epithelial; **SD OCT** = spectral domain optical coherence tomography; **VF** = visual field.

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