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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 rare[1]; 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.

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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 m^2.
‡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.