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Pericentral Retinopathy and Racial Differences in Hydroxychloroquine Toxicity

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Purpose: To describe patterns of hydroxychloroquine retinopathy distinct from the classic parafoveal (bull's eye) maculopathy.

Design: Retrospective case series.

Participants: Patients from a large multi-provider group practice and a smaller university referral practice diagnosed with hydroxychloroquine retinopathy. Patients with widespread or "end-stage" retinopathy were excluded.

Methods: Review of ophthalmic studies (fundus photography, spectral-domain optical coherence tomography, fundus autofluorescence, multifocal electroretinography, visual fields) and classification of retinopathy into 1 of 3 patterns: parafoveal (retinal changes 2°–6° from the fovea), pericentral (retinal changes ≥8° from the fovea), or mixed (retinal changes in both parafoveal and pericentral areas).

Main Outcome Measures: Relative frequency of different patterns of hydroxychloroquine retinopathy and comparison of risk factors.

Results: Of 201 total patients (18% Asian) with hydroxychloroquine retinopathy, 153 (76%) had typical parafoveal changes, 24 (12%) also had a zone of pericentral damage, and 24 (12%) had pericentral retinopathy without any parafoveal damage. Pericentral retinopathy alone was seen in 50% of Asian patients but only in 2% of white patients. Patients with the pericentral pattern were taking hydroxychloroquine for a somewhat longer duration (19.5 vs. 15.0 years, $P < 0.01$) and took a larger cumulative dose (2186 vs. 1813 g, $P = 0.02$) than patients with the parafoveal pattern, but they were diagnosed at a more severe stage of toxicity.

Conclusions: Hydroxychloroquine retinopathy does not always develop in a parafoveal (bull's eye) pattern, and a pericentral pattern of damage is especially prevalent among Asian patients. Screening practices may need to be adjusted to recognize pericentral and parafoveal hydroxychloroquine retinopathy. *Ophthalmology 2015;122:110-116 © 2015 by the American Academy of Ophthalmology.*

Toxic retinopathy is a potential side effect of long-term hydroxychloroquine therapy, and the risk is dependent on a number of factors, including the daily dose, duration of use, and presence of kidney disease.[1,2] This change has been typically characterized as photoreceptor thinning that begins in a parafoveal ring and progresses over time to become a visible bull's eye retinopathy when the retinal pigment epithelium (RPE) becomes damaged. The damage may eventually spread into peripheral retina if the medication is not discontinued.[3] Toxicity is detectable in early stages (before RPE damage) through central visual fields, spectral-domain optical coherence tomography (SD-OCT), multifocal electroretinography (mfERG), and fundus autofluorescence (FAF). During a review of a large series of patients at high risk for retinopathy because of long-term exposure to hydroxychloroquine, we noticed a subset of patients with retinopathy that began outside the typical parafoveal zone and had a striking association with Asian ancestry. In this report, we demonstrate the features and demographics of this pericentral pattern of hydroxychloroquine retinopathy.

Methods

We reviewed the charts and imaging studies of patients from 2 sites: Kaiser Permanente in Northern California, an integrated health organization with a diverse population of approximately 3.4 million members, and a referral retina practice at the Byers Eye Institute at Stanford University. Institutional review board approval was obtained at both institutions. At Kaiser, we queried the pharmacy database to review all available ophthalmic studies for patients who had taken hydroxychloroquine for a minimum of 5 years. This yielded a dataset of 2657 patients, of whom 174 were judged to have toxic retinopathy (excluding diffuse end-stage disease) on the basis of distinctive abnormalities on visual fields or SD-OCT. The Stanford cohort included patients diagnosed with hydroxychloroquine retinopathy since 2009, when high-resolution SD-OCT imaging became available. At Kaiser, visual field tests were done using the Humphrey Analyzer (Carl Zeiss Meditec, Jena, Germany) and SD-OCT scans performed on the Spectralis (Heidelberg Engineering, Heidelberg, Germany). Patients at Stanford were studied with Humphrey visual fields, Cirrus SD-OCT (Carl Zeiss Meditec), and VERIS mfERG (Electro-Diagnostic Imaging Inc, Redwood City, CA) according to International Society for Clinical Electrophysiology of Vision standards[4] and ultra-widefield FAF (Optos North America, Marlborough, MA).

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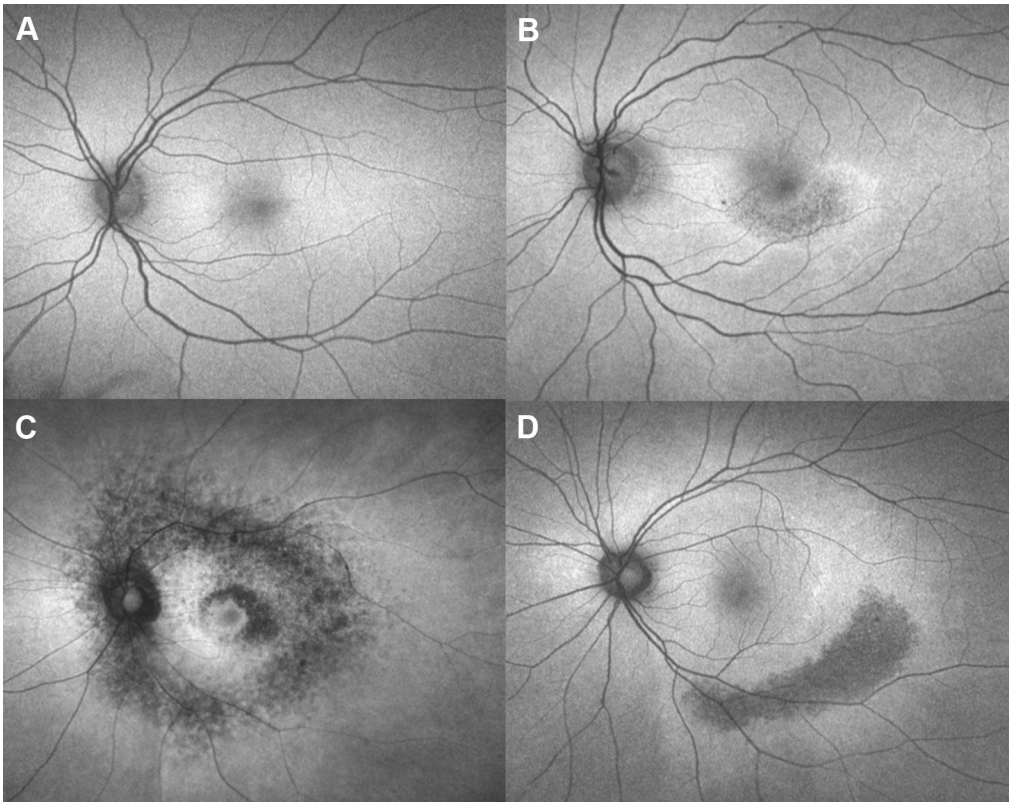

Figure 1. Comparison of a normal fundus and hydroxychloroquine retinopathy patterns using detail from ultra-widefield autofluorescence: normal **(A)**, parafoveal pattern **(B)**, mixed pattern **(C)**, and pericentral pattern **(D)**.

Cases diagnosed with toxic retinopathy were characterized according to the distribution of retinal damage: *parafoveal pattern*, with photoreceptor and sometimes RPE disruption in a ring 2° to 6° from the center of the fovea; *pericentral pattern*, with damage localized 8° or more from the center of the fovea; or *mixed pattern*, with evidence of retinal changes in both the parafoveal and pericentral areas, often with a zone of relatively normal retina in between. These different patterns are illustrated in Figures 1 and 2, showing FAF and SD-OCT changes. Patients also were characterized according to the severity of damage: *Mild toxicity* was defined as patchy photoreceptor loss on SD-OCT or isolated defects on visual fields; *moderate toxicity* was defined as photoreceptor damage and scotomas comprising a partial or full ring; and *severe toxicity* involved RPE damage visible on SD-OCT or hypofluorescence on FAF.

Patients were divided into racial groups of Asian (including East Asian, Southeast Asian, and Filipino), black, Hispanic, white, and other (including East Indian). Comparisons between groups were performed using the Student *t* test for continuous measures and Fisher exact test for categoric measures, and all reported probability values are 2-sided. Odds ratios were derived using logistic regression. Statistical analyses were performed only on the larger unselected Kaiser population.

Illustrative Cases

Case 1

Pericentral retinal dystrophy? A 42-year-old Chinese woman (5 feet 2 inches, 49 kg) with systemic lupus erythematosus took 400 mg/day of hydroxychloroquine for 8 years and then 200 mg/day for another 2 years. She had no visual symptoms, but an outside physician noted a limited ring of retinal degeneration near the inferior arcade of both eyes (Fig 1D). Our examination showed normal central maculae but symmetric bilateral arcuate zones of retinal atrophy and RPE pigment change (Fig 3). The damage was evident in visual fields and confirmed on SD-OCT and with mfERG. This pattern of degeneration would be atypical of late-onset retinal dystrophy, and given her high-dose exposure to hydroxychloroquine is most consistent with toxicity.

Case 2

Retinitis pigmentosa? A 67-year-old Korean women (5 feet 1 inch, 57 kg) took 300 to 400 mg of hydroxychloroquine per day for rheumatoid arthritis for 14 years. She had normal 30-2 visual fields after 4 years of therapy (Fig 4), but after 13 years showed bilateral ring scotomas most prominent between 10° and 20° from the fovea. She was given a diagnosis of retinitis pigmentosa sine pigmento by an outside physician in 2003 but was also advised to discontinue hydroxychloroquine. We believe her imaging studies, and the rapid development of a narrow pericentral ring (without peripheral degeneration), to be more consistent with hydroxychloroquine retinopathy.

Case 3

Glaucoma? An 81-year-old black woman (5 feet 4 inches, 65 kg) took 400 mg per day of hydroxychloroquine for alopecia for 17 years. She was being treated for possible glaucoma with initial intraocular pressures in the mid-20s and cup-to-disc ratios of 0.6,