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.

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 (mERG), 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 mERG (Electro-Diagnostic Imaging Inc, Redwood City, CA) according to International Society for Clinical Electrophysiology of Vision standards and ultra-widefield FAF (Optos North America, Marlborough, MA).
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 woman (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,
showed marked outer retinal thinning in a ring zone 10 to 20° from the fovea, with a zone of retinal pigment epithelial clumping most prominent inferiorly. Given her long-term exposure to hydroxychloroquine, the loss of outer retinal structures and visual field changes are most likely a manifestation of toxicity.

Results

During an initial review of the Kaiser patients at risk for toxic retinopathy because they had taken hydroxychloroquine for a minimum of 5 years, we noticed that a subset of patients had a distinctive pattern of retinal damage most prominent in the pericentral rather than parafoveal macula. Similar patients were noted in the smaller Stanford practice. Examples of this pericentral pattern are illustrated in Figures 1 and 2 and the case presentations. The widefield FAF images in Figure 1 and OCT images in Figure 2 demonstrate the difference between the classic parafoveal pattern of toxicity and the pericentral pattern. Some patients showed a mixed pattern of both parafoveal damage and pericentral damage, often with relatively normal retina in between (Figs 1C and 2C). The pericentral damage often began inferiorly.

Overall, 12% (24/201) of our patients with toxic hydroxychloroquine retinopathy had a pericentral pattern of damage, and an additional 12% (24/201) showed a mix of parafoveal and pericentral changes. Both the Kaiser and the Stanford practices had a significant proportion of Asian patients (17% and 26%, respectively) representative of the Northern California populations they serve. After tabulating the racial distribution of patterns of retinopathy (Table 1), we found in both practices (one general, the other referral) a striking racial predilection for pericentral damage among the patients of Asian ancestry. In the larger Kaiser population, the odds ratio for an Asian patient to show a pericentral pattern rather than parafoveal pattern was 27.1 (95% confidence interval, 9.0–82.8; P < 0.01). In fact, of the Asian patients at Kaiser who were diagnosed with hydroxychloroquine toxicity, 55% displayed a purely pericentral pattern of retinopathy compared with only 2% of whites. A pericentral or mixed pattern of retinopathy was seen in 83% of Asians and 9% of whites. A similar racial disparity was seen in the Stanford population. In the Kaiser population, the pericentral pattern was not associated with the primary medical indication for hydroxychloroquine therapy, and it was seen only in female patients, but there were too few male patients in the study to reach a conclusion about sexual distribution. Black and Hispanic patients both showed predominately parafoveal damage, although there was a suggestion that they might be slightly more likely than whites to develop a pericentral or mixed pattern of retinopathy.

The distribution of the various patterns of retinopathy was influenced by the severity of the toxicity at diagnosis (Table 2). Among all of our patients, the parafoveal pattern was fairly evenly distributed between patients diagnosed at a mild, moderate, or severe stage of toxicity, whereas 92% of patients with a mixed or pericentral pattern were diagnosed at a stage of moderate or severe toxicity.

Table 3 shows that Kaiser patients with the pericentral pattern of retinopathy on average took a greater cumulative dose of hydroxychloroquine (2186 vs. 1813 g, P = 0.02) and were on the medication for a longer duration (19.5 vs. 15.0 years, P < 0.01). However, as noted earlier, patients with the pericentral pattern were diagnosed at a later stage of toxicity.

Discussion

Much of the literature on hydroxychloroquine retinopathy has emphasized the specificity of parafoveal (bull’s eye) damage as a sign of this drug toxicity. Although this remains an excellent and relatively specific clinical finding, especially in a predominantly white population, it should no longer be considered as the unique presentation of retinal toxicity. There is also a pattern of pericentral retinal damage (typically in the region of the arcades) that affects Asian patients primarily but can be seen in all races.

Our patient populations have a significant proportion of Asian patients (Table 1), which helped us become aware of this new pattern of hydroxychloroquine toxicity. In our combined practices, 12% of patients had purely a pericentral pattern of retinopathy, and an additional 12% had a mixed pattern. These numbers will vary with the demographics of a given practice, but demonstrate that this pattern will not be
uncommon in a racially diverse population. However, the relative distribution of parafoveal versus pericentral damage within a racial group such as Asians or whites should be independent of the proportion of that race in a practice. We found that a high percentage of Asian patients show a pericentral or mixed pattern of hydroxychloroquine retinopathy, whereas this pattern is rare among whites. The similarity of racial distribution for these fundus patterns in our 2 patient populations helps confirm the conclusion that these patients do represent hydroxychloroquine toxicity and that racial ancestry is an important factor in the clinical presentation of retinopathy. Hispanics and blacks showed

Figure 3. Case 1. Top to bottom: Fundus images show granular pigmentary changes in a pericentral ring pattern most prominent inferiorly. 30-2 Visual fields (threshold and pattern deviation plots) show partial ring scotomas approximately 10 to 20 degrees from fixation. Multifocal electoretinograms (retinal views) show loss of signal inferiorly most severely at 10 to 15 degrees eccentricity, with no suggestion of parafoveal functional loss. The standard 20° fundus autofluorescence (FAF) image from the left eye can be compared with the widefield view in Figure 1D. The area of retinal pigment epithelium (RPE) degeneration (dark stippling) is seen only in the lower right corner of the standard FAF, but the bright ring of hyperfluorescence separating the normal and abnormal zones of the retina is seen more clearly. This ring corresponds to the abrupt thinning of the photoreceptor layer in the spectral-domain optical coherence tomography (SD-OCT) cross-section. OD = right eye; OS = left eye.
predominantly a parafoveal pattern of damage, but we hesitate to draw any firm conclusions about their risk for the pericentral pattern of damage; it may be slightly higher than in whites, but certainly does not approach the prevalence that we see among Asians.

A number of the patients that we identified with pericentral retinal damage were referred because of questions about other diseases that might account for their findings. Some were initially suspected of glaucoma or central nervous system disease because of bitemporal field loss, a cause of confusion also noted long ago in cases of chloroquine toxicity.\textsuperscript{5} An individual case might spur discussion of pericentral retinitis pigmentosa, early maternally inherited diabetes and deafness, unusual acute zonal occult retinopathy, autoimmune retinopathy, and so forth. These are rare conditions that might account for an isolated case but would not account for 24 cases within a select group of patients at high risk for hydroxychloroquine toxicity. Moreover, the presence of a distinct zone of pericentral retinopathy in an additional 24 patients who also had typical parafoveal changes would seem to argue that pericentral damage can result from hydroxychloroquine toxicity. Pericentral damage also may blend into the diffuse degeneration of end-stage retinopathy, but we excluded patients with diffuse disease.

Why hydroxychloroquine preferentially affects the pericentral or parafoveal areas of the retina is unknown. Pericentral damage, like parafoveal damage,\textsuperscript{1} often begins inferiorly (Fig 1B, D). The reason for a different presentation among Asians also is unclear. The effect is not solely a matter of ocular pigmentation, because pericentral retinopathy is less prevalent among blacks and Hispanics, but racial differences in pigment distribution or drug binding could be relevant.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Top: Fundus photography of the right eye was normal after 4 years of hydroxychloroquine therapy (1993, left) but showed pericentral degeneration after 13 years of treatment (2002, right). Middle: Corresponding 30-2 visual fields. Bottom: Optical coherence tomography (30° radial line scan) from 2013, 10 years after discontinuing the medication. There is broad outer retinal and retinal pigment epithelial disruption with preservation of the fovea and a partial bull’s eye appearance on the infrared view. The color thickness map shows marked thinning (blue) in a pericentral ring.}
\end{figure}
There are other diseases, such as Vogt-Koyanagi-Harada disease, that are especially prevalent in Asians, and we suspect genetics influence the manifestation of hydroxychloroquine retinopathy.

The patients with a pericentral pattern of damage had on average a longer duration of hydroxychloroquine use and a greater cumulative drug exposure (Table 3), but we suspect this largely reflects the fact that these patients were recognized to have toxicity later than those with parafoveal changes. The late diagnosis of pericentral damage is an issue of concern to ophthalmologists who screen for hydroxychloroquine toxicity. Present screening techniques focus on the central macula with 10-2 fields and imaging techniques that typically do not go beyond 10 to 15 degrees of eccentricity from the fovea. Thus, unless an examiner is looking for damage at the periphery of these examination fields, changes can be missed or dismissed as irrelevant. Some of our pericentral cases continued on the drug long beyond the time when damage would have been clearly recognizable, because the peripheral areas were not examined or the examiners interpreted test results as being due to retinitis pigmentosa, glaucoma, or chiasmal pathology and were not attuned to thinking that they might result from

Table 1. Racial Distribution of Patients versus Patterns of Hydroxychloroquine Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Asian*</th>
<th>Black</th>
<th>Hispanic</th>
<th>White</th>
<th>Other†</th>
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<td>37</td>
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<td>1</td>
<td>2</td>
<td>1</td>
<td>22</td>
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<tr>
<td>Total</td>
<td>29</td>
<td>14</td>
<td>19</td>
<td>111</td>
<td>1</td>
<td>174</td>
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<tr>
<td><strong>Stanford</strong></td>
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<tr>
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<td>3</td>
<td>16</td>
<td>1</td>
<td>22</td>
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<tr>
<td>Total</td>
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<td>0</td>
<td>3</td>
<td>16</td>
<td>1</td>
<td>27</td>
</tr>
</tbody>
</table>

*East Asian, Southeast Asian, and Filipino race. †East Indian race.

Table 2. Pattern versus Severity of Toxicity (Kaiser and Stanford Patients)

<table>
<thead>
<tr>
<th>Severity</th>
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<th>Pericentral</th>
<th>Total</th>
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<td>Mild</td>
<td>49</td>
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<td>53</td>
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<tr>
<td>Moderate</td>
<td>62</td>
<td>4</td>
<td>8</td>
<td>74</td>
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<tr>
<td>Severe</td>
<td>42</td>
<td>17</td>
<td>15</td>
<td>75</td>
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<tr>
<td>Total</td>
<td>153</td>
<td>24</td>
<td>24</td>
<td>201</td>
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</table>
Recognition of this pattern is especially important for patients of Asian ancestry. Examiners should look critically at the edge of 10-2 fields, 30/C14 SD-OCT scans, and standard FAF images for hints of more peripheral damage. When possible, widefield FAF should be obtained, and 30-2 fields may be indicated in addition to 10-2 fields. The mfERG extends in most laboratories to 20 degrees of eccentricity or more and may show a pattern of peripheral rather than parafoveal loss.

In conclusion, parafoveal (bull’s eye pattern) retinopathy is not the only distinctive sign of early hydroxychloroquine toxicity. There is also a population of patients with damage exclusively in a pericentral pattern (arcade region) and others who show a mix of parafoveal and pericentral damage. The pericentral and mixed patterns of damage are especially prevalent in Asians, but may occur in all races. Awareness of this pericentral variant of hydroxychloroquine retinopathy is important if screening is to be effective in catching toxicity early.

References


Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
FAF = fundus autofluorescence; mfERG = multifocal electroretinography; RPE = retinal pigment epithelium; SD-OCT = spectral-domain optical coherence tomography.

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