Clinical & Refractive Optometry CRO
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CE Credit - Case Report

Early Detection of Hydroxychloroquine Retinopathy in a Middle-Aged Male

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CRO (Clinical & Refractive Optometry) Journal

ABSTRACT

Introduction
Toxic hydroxychloroquine retinopathy is a well-known but uncommon complication of long-term hydroxychloroquine use. Patients are typically asymptomatic and retinal fundus examination is inadequate for detecting early retinal damage. Eye care providers should rely more heavily on objective testing to detect these early structural changes.

Case Report
A 48-year-old Asian male with systemic lupus erythematosus diagnosed 20 years prior and treated with hydroxychloroquine 400mg daily presented for his annual eye exam. Best corrected visual acuity was 20/20 in each eye, and the patient had no visual complaints. Dilated fundus examination was unremarkable, however spectral domain optical coherence tomography revealed focal loss of the ellipsoid zone line temporal to the fovea and inferior to the optic nerve in the right eye. After discussions with the patient's rheumatologist and the ophthalmology retina service, the medication was discontinued.

Conclusion
Hydroxychloroquine retinopathy is a potentially vision threatening and progressive condition without any treatment. As such, the goal of every eye care provider should be to detect early structural retinal damage with objective testing preferred over subjective testing before retinopathy can progress to a bull's eye pattern.

Key words: automated visual fields, ellipsoid zone, hydroxychloroquine, optical coherence tomography

BACKGROUND

Retinal toxicity secondary to hydroxychloroquine use is an uncommon and well-known complication of long-term use. Originally used as an antimalarial drug, hydroxychloroquine is now most commonly prescribed as an antirheumatic drug for the chronic management of systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, antiphospholipid syndrome and other autoimmune conditions. More recent potential applications for hydroxychloroquine include cancer therapy.[1] Hydroxychloroquine is generally very well tolerated and without many systemic side effects.

While the mechanism of retinal toxicity is still unknown, hydroxychloroquine retinopathy is defined by outer retinal damage to the pericentral and parafoveal photoreceptors. In more advanced cases, the retinal pigment epithelium also becomes affected causing the classic bull's eye maculopathy. Patients with early hydroxychloroquine retinopathy are typically asymptomatic, and clinicians must rely on objective screening tests to diagnose these early changes.

CASE REPORT

A 48-year-old Asian American male presented to the eye clinic for his annual eye exam. The patient had no visual complaints. His previous eye exam was one year prior and was unremarkable. The patient's medical history was significant for systemic lupus erythematosus, which was diagnosed 20 years prior, and was being managed with hydroxychloroquine 200mg bid. He had been instructed by rheumatology to take one day off a week of treatment to account for the patient taking more than the recommended daily dose of 5mg/kg of weight (at the patient's current weight of 68kg, the recommended dosing is no more than 340mg daily). His medical history was also significant for anxiety which was being managed with duloxetine.

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Best corrected Snellen visual acuity was 20/20 in each eye. Pupils were round and equally reactive without a relative afferent pupillary defect. Slit lamp examination was unremarkable and without whorl-like deposits in the corneal epithelium in both eyes. Dilated fundus examination was also unremarkable in both eyes. Spectral-domain optical coherence tomography (SD-OCT) of the macula of both eyes was obtained which revealed focal loss of the ellipsoid zone line temporal to the fovea in the right eye (Figure 1). The subfoveal ellipsoid zone line remained intact. Additionally, there was focal ellipsoid zone loss inferior to the optic nerve in the right eye (Figure 2). The left eye SD-OCT scans were unremarkable. Fundus autofluorescence revealed an area of hyper-autofluorescence temporal to the fovea in the right eye and was unremarkable in the left eye (Figure 3). At this time there was concern for hydroxychloroquine toxicity in the right eye, and the patient was instructed to return to clinic in one day for Humphrey visual field testing.

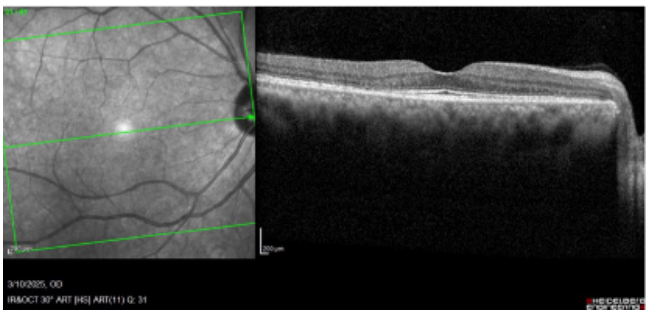

Figure 1. SD-OCT raster scan at the level of the macula in the right eye with focal ellipsoid zone loss temporally (blue arrow).

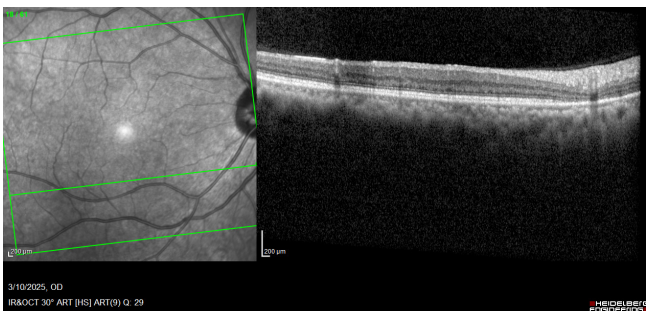

Figure 2. SD-OCT at the level of the inferior temporal arcades in the right eye with focal ellipsoid zone loss inferior to the optic nerve (blue arrow).

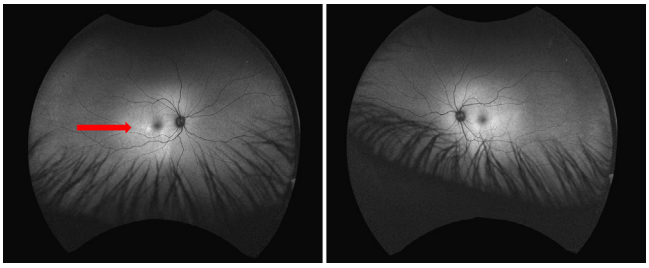

Figure 3. OPTOS Fundus auto-fluorescence images of the right and left eyes showing subtle hyper-autofluorescence inferior temporal to the fovea (red arrow).

The following day the patient returned for visual field testing. A 24-2C test strategy (which tests selected points from the 10-2 within the 24-2 strategy) was selected based on the 2016 American Academy of Ophthalmology recommendations for screening of patients with Asian ethnicity.[2] The test was reliable in both eyes and showed some shallow superior losses in both eyes that were not consistent with the macular SD-OCT scans in the right eye, or with hydroxychloroquine retinopathy. Due to high clinical suspicion for toxic retinopathy in the right eye, a 10-2 visual field test was subsequently performed on the right eye on the same day. The 10-2 visual field was reliable and revealed 2 shallow losses at 6 degrees temporal to fixation that possibly correlated with the peripapillary ellipsoid zone thinning noted on the SD-OCT scans (Figure 4).

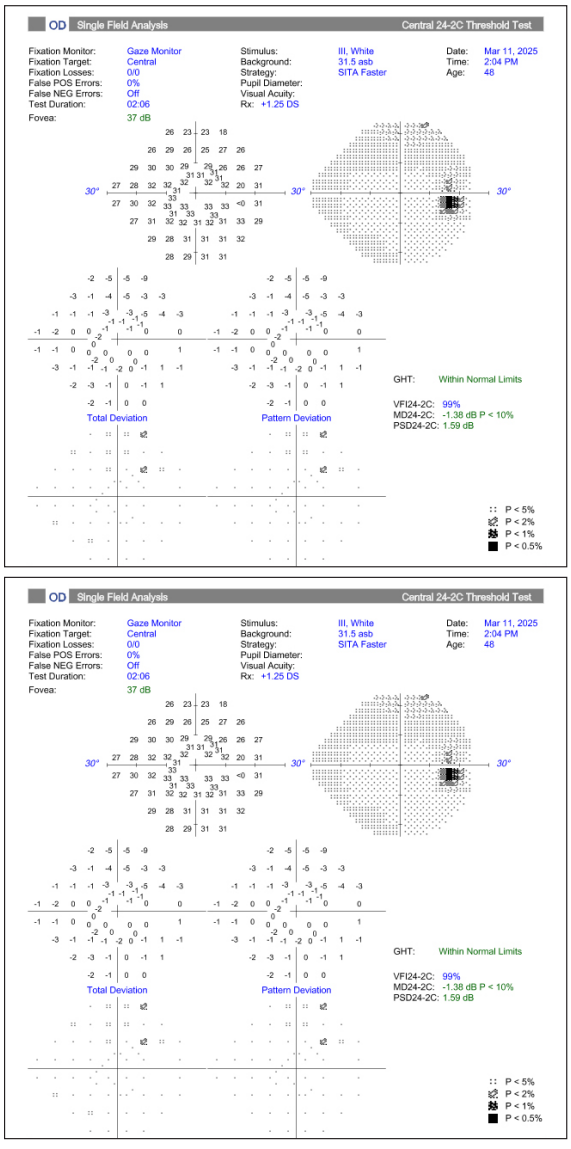

Figure 4. HVF-24-2C Sita Faster and HVF-10-2 Sita Fast printouts of the right eye, 2 shallow depth defects on 10-2 corresponding with structural damage seen at the fovea.

The case was discussed with the retina service who also agreed that the patient was likely to have hydroxychloroquine toxicity. The patient's rheumatologist was notified on the same day. The rheumatologist deferred the decision of whether to discontinue hydroxychloroquine to ophthalmology, while noting that from a rheumatological perspective, there are currently no other medications that offer the same mortality benefit as hydroxychloroquine. Given the patient's young age and his already long-term use of hydroxychloroquine of 20 years, the irreversible nature of toxic hydroxychloroquine retinopathy, and the risk of progressive vision loss, ophthalmology recommended that the patient discontinue hydroxychloroquine. The patient was instructed to follow up with the retina clinic in one month.

DISCUSSION

There are several risk factors for developing hydroxychloroquine retinopathy, with the most significant risks being daily dose and cumulative dose. The current recommended daily dose from the revised 2016 American Academy of Ophthalmology is less than 5.0 mg/kg of real body weight.[2] Dosages higher than the recommended dose, as well as long term use, significantly increase the risk of toxicity. However, it should be noted that dosages less than the recommended amount do not preclude a patient from developing toxic retinopathy. The risk of developing retinopathy with proper dosing is under 1% for the first 5 years. The risk doubles to 2% at 10 years and dramatically increases to 20% at 20 years.[2] These calculated risk percentages are isolated however, as systemic and genetic factors may increase the risk of developing toxicity. Decreased renal function adds to the risk for toxicity since the main excretory pathway for hydroxychloroquine is through the kidneys.[3,4] Melles and Marmour report that a 50% drop in kidney function results in an approximate double the risk of developing hydroxychloroquine retinopathy.[3] Concurrent tamoxifen use for the long-term treatment of breast cancer has been associated with a 5 times risk for developing hydroxychloroquine retinopathy.[2,3] A less significant risk factor is certain polymorphisms of cytochrome P450 that are common in Asian populations which interfere with metabolism leading to increased serum concentrations of hydroxychloroquine and increased susceptibility to toxicity.[5]

Recommended screening tests for HCQ retinopathy include SD-OCT, visual field testing, fundus autofluorescence and multifocal electroretinography. SD-OCT is an objective, highly sensitive test that can detect early structural damage to the retina prior to visual field loss and fundoscopic changes. Parafoveal thinning or disruption of the ellipsoid zone and outer nuclear layer are characteristic of early hydroxychloroquine retinopathy.[6,7] In more severe retinopathy, the retinal pigment epithelium is also disrupted or completely lost. The inner retina is not affected by hydroxychloroquine.8 Patient ethnicity should be considered when performing SD-OCT as the location of retina affected by hydroxychloroquine toxicity varies. Caucasian patients are susceptible to parafoveal damage, while Asian patients are susceptible to pericentral damage.[9] African American and Hispanic patients are most likely to exhibit paracentral retinal damage but are also more likely to exhibit paracentral or mixed pattern retinal damage than Caucasian patients.[9] Early parafoveal retinal damage is reported to occur more frequently inferior and temporal to the fovea while pericentral damage occurs more frequently nasal to the fovea and in the peripapillary area.[10]

Automated visual field-testing strategies should reflect the pathophysiological differences among different ethnicities. A central 10-2 visual field strategy is recommended for Caucasian patients, while wider test strategies such as 24-2 or 30-2 are recommended for Asian patients. It is important for clinicians to be mindful that visual field testing is subjective, and as such, defects should be confirmed with an objective test.[11]

Fundus autofluorescence imaging can be a useful adjunct screening tool for the detection of retinal damage. Early structural damage to the ellipsoid zone manifests as areas of hyper-autofluorescence near the macula, while more severe disease manifests as hypo-autofluorescence secondary to retinal pigment epithelium loss. Changes in autofluorescence may be subtle and difficult to detect with early toxic retinopathy. Tsang et al suggest that fundus autofluorescence may be useful for monitoring progression rather than as a screening tool in early toxicity.[12]

Multifocal electroretinography has also been investigated as a screening tool. Multifocal electroretinography is highly sensitive at detecting morphological changes in the retina; however, its specificity is variable when compared to SD-OCT and automated visual field testing. Multifocal electroretinography tends to produce high false positives rates which may suggest that electrophysical changes precede clinically visible morphological changes, or that multifocal electroretinography is able to detect subclinical cases of hydroxychloroquine toxicity.[12] However, given that multifocal electroretinography is largely unavailable, its use as a screening tool for the average eye care provider is very limited.

The revised 2016 American Academy of Ophthalmology guidelines for screening suggest that the initial examination can be deferred until five years after initiation of hydroxychloroquine treatment based on the low risk for developing retinopathy in the first 5 years. However, the interval of screening should be based on the aforementioned risk factors, and patients with more risk factors should be monitored more frequently.[13]

The detection of early structural damage to the retina and subsequent cessation of hydroxychloroquine leads to improved visual acuity and visual function outcomes.

While it is well established that retinal toxicity can progress despite drug discontinuation, the duration of progression is thought to be correlated to the severity of retinopathy. In cases of early or moderate retinopathy, progression is expected for only about one year while in severe cases progression is expected to be chronic and permanent.[8,14] As there are currently no treatments available to patients with hydroxychloroquine retinopathy, it is imperative that clinicians detect hydroxychloroquine retinopathy in its early stages. Bull's eye maculopathy is a severe ocular presentation of hydroxychloroquine retinopathy that should no longer be observed today given the sensitivity of objective testing currently available. Once hydroxychloroquine retinopathy is detected it is essential to communicate the findings with both the patient and their managing rheumatologist.

CONCLUSION

Hydroxychloroquine retinopathy is an uncommon but potentially sight threatening complication that eye care and medical professionals should be aware of. Duration of treatment and daily dosing are the main risks factors for development of retinopathy. At a minimum, the managing eye care provider should have access to a SD-OCT and automated visual fields to be able to detect retinopathy, as funduscopic evaluation is neither sensitive nor adequate in detecting early structural damage. Inter-disciplinary communication with the patient's rheumatologist is key to preventing irreversible vision loss.

REFERENCES:

1. Al Adel F, Shoughy SS, Tabbara KF. Hydroxychloroquine dosing and toxicity: A real-world experience in Saudi Arabia of 63 patients. Saudi J Ophthalmol 2021;34(3):151-155.
2. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF; American Academy of Ophthalmology recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 Revision). Ophthalmology2016;123(6):1386-1394
3. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol. 2014;132(12):1453-1460
4. Costedoat-Chalumeau N, Dunogue B et al. A Critical Review of the effects of hydroxychloroquine and chloroquine on the Eye. Clinic Rev Allerg Immunol 2015; 49:317-326
5. Lee JY, Vinayagamoorthy N, Han K, et al. Association of polymorphisms of cytochrome P450 2D6 with blood hydroxychloroquine levels in patients with systemic lupus erythematosus. Arthritis Rheumatol 2016;68(1):184-190
6. Chen E, Brown DM, Benz MS, et al. Spectral domain optical coherence tomography as an effective screening test for hydroxychloroquine retinopathy (the "flying saucer" sign). Clin Ophthalmol 2010;4:1151-1158
7. Pandaya H, Robinson M et al. Hydroxychloroquine retinopathy: A review of imaging. Indian J Ophthalmol 2015;63:570-574
8. De Sisternes L, Hu J, Rubin D, Marmor M. Localization of damage in progressive hydroxychloroquine retinopathy on and off the drug: inner versus outer retina, parafovea versus peripheral fovea. IOVS 2015;56(5): 3415-3426
9. Melles RB, Marmor MF. Pericentral retinopathy and racial differences in hydroxychloroquine toxicity. Ophthalmology 2015;122(1):110-116
10. Kim K, Kim J, Kim Y, Ahn S. Clock-hour topography and extent of outer retinal damage in hydroxychloroquine retinopathy. Sci Rep 2022; 12(1):11809
11. Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. Eye 2017;31: 828-845
12. Tsang AC, Ahmadi Pirshahid S, Virgili G, Gottlieb CC, Hamilton J, Coupland SG. Hydroxychloroquine and chloroquine retinopathy: a systematic review evaluating the multifocal electroretinogram as a screening test. Ophthalmology. 2015;122(6):1239-1251.
13. Marmor MF. Comparison of screening procedures in hydroxychloroquine toxicity. Arch Ophthalmol 2012;130(4):461-469.
14. Mittelu M, Wong B, Brenner M et al. Progression of hydroxychloroquine toxic effects after drug therapy cessation. JAMA Ophthalmol 2013;131(9):1187-1197