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Highly Accelerated Onset of Hydroxychloroquine Macular Retinopathy

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Background: Hydroxychloroquine (HCQ, Plaquenil) is often prescribed in lieu of other sulfate antimalarials to treat rheumatologic diseases because of its pharmacologic efficacy and few reported side effects. However, a known potential side effect of HCQ is retinal toxicity.

Case Report: A 61-year-old black female presented for screening of ophthalmic disease 2 months after initiation of HCQ for the treatment of polyarthralgia with a positive rheumatoid factor. At the time of the examination, she had taken a cumulative total of 19.8 g of HCQ and was found to have bilateral bull's-eye retinopathy. The patient had no known risk factors for HCQ toxicity. HCQ was discontinued, and the patient was prescribed ibuprofen for her polyarthralgia symptoms. The ophthalmic effects of HCQ toxicity were permanent.

Conclusion: Known major risk factors for HCQ retinal toxicity include drug loads >300 mg/day (5 mg/kg/day), use for >5 years, a cumulative dose >1,000 g, underlying retinal disease or retinopathy, tamoxifen use, and renal disease. Despite not having any of these risk factors and having a reduced drug load during the treatment period, our patient developed the signs and symptoms of HCQ toxicity. This case suggests underlying mechanisms for HCQ toxicity other than those previously reported and a need for additional screening tests to prevent HCQ toxicity.

Keywords: *Hydroxychloroquine, retinal diseases, scotoma*

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INTRODUCTION

Patients with rheumatologic diseases, especially rheumatoid arthritis and Sjögren syndrome, are often treated with antimalarial drugs that have been shown to reduce autoimmune-induced inflammation.[1] Hydroxychloroquine (HCQ, Plaquenil) is often prescribed in lieu of other sulfate antimalarials because of its pharmacologic efficacy and few reported side effects.[2] However, a known potential side effect of HCQ is retinal toxicity.

Although the mechanism of HCQ toxicity in the retina has not been fully explained, clinical signs and symptoms are well described in the literature. Loss of visual acuity and bull's eye retinopathy are consistently seen in patients with developing HCQ toxicity, although neither symptom is exclusive to the condition.[3] In addition to HCQ toxicity, the differential diagnoses for bull's eye retinopathy include congenital and acquired conditions such as cone and rod dystrophies, central areolar dystrophy, Stargardt disease, and macular degeneration.[4]

The American Academy of Ophthalmology (AAO) defined a set of criteria to determine the presence of HCQ-induced retinal toxicity.[5] The AAO guidelines recommend a baseline examination to rule out existing maculopathy as well as annual examinations after 5 years of HCQ dosing and additional examinations upon suspicion of toxicity. In addition to an ocular examination to assess for any underlying causes of toxicity or preexisting conditions, ophthalmologists must perform a Humphrey visual field (HVF) central 10-2 white-on-white pattern test and spectral domain optical coherence tomography (SD-OCT) to make a clinical diagnosis.[5,6]

Certain preexisting conditions and drug dosing factors establish risks for retinal HCQ toxicity. HCQ is metabolized in the liver and excreted in the kidney, and, thus, renal disease is a prominent risk factor for HCQ toxicity.[2] Hepatic failure has been shown to be only a minor risk factor for toxicity.[2,5] Additionally, the AAO has stated that a dose of HCQ >5 mg/kg/day increases the risk for HCQ toxicity.[5] Previous guidelines presumed that HCQ was not retained in fat, and, therefore, dosing was calculated based on ideal weight. This practice led to increased HCQ loads in patients, especially in thin patients for whom calculations using ideal weight led to overdosage.[5] The calculation of a patient's HCQ dose, therefore, should be based on real weight and not ideal weight as mentioned in the AAO guidelines.[5] A cumulative dose >1,000 g and duration of use >5 years have also been shown to be significant risk factors for

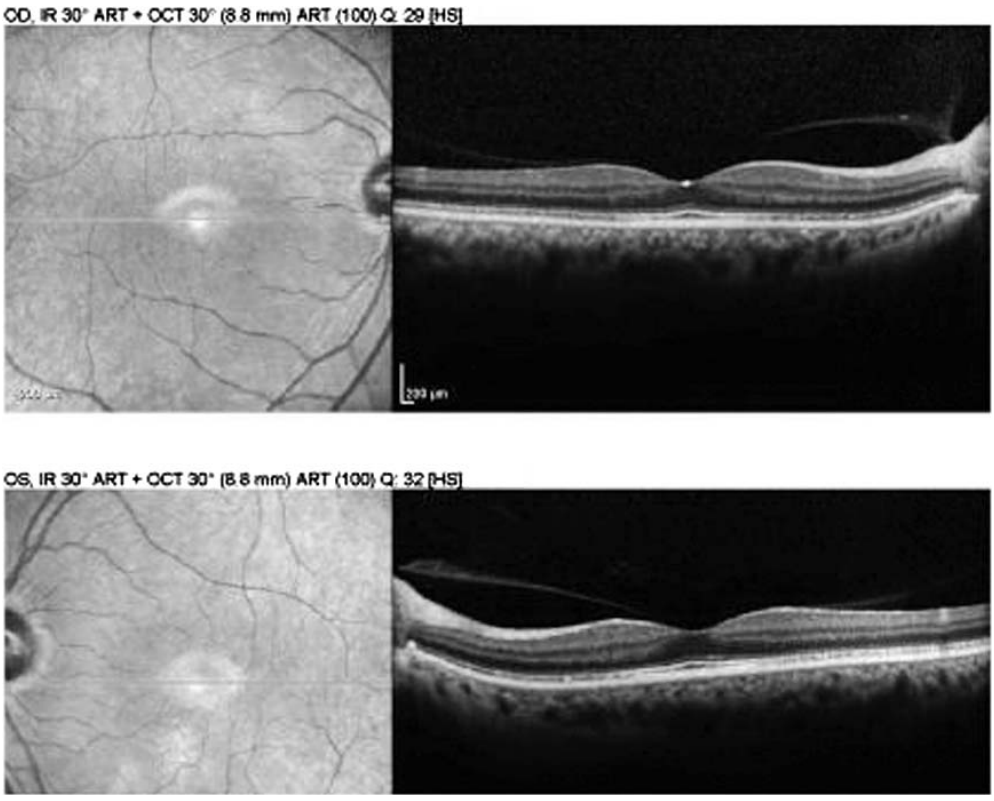

Figure 1. Spectral domain optical coherence tomography (OCT) reveals early parafoveal inner segment/outer segment junction and retinal pigment epithelium disruption in both eyes. OD, right eye; OS, left eye.

developing bull's eye retinopathy.[5] Finally, previous ocular disease can put patients at risk for retinal HCQ toxicity.[2]

We present an unusual and early presentation of HCQ toxicity in a patient who did not follow the expected progression of retinal disease during treatment with this drug.

CASE REPORT

A 61-year-old black female with no family or personal ocular history presented in March 2015 with intermittent blurred vision and for assessment of HCQ toxicity 2 months after a normal baseline assessment. The patient had been started on 400 mg/day of HCQ in January 2015 for polyarthralgia with a positive rheumatoid factor. After 1 week, she decreased the dose to 200 mg/day after developing dizziness. Prior to treatment, the patient had been taking ibuprofen as needed and continued to take ibuprofen throughout her HCQ therapy for arthralgia. Her best corrected visual acuity at her presentation in January was 20/20 in both eyes. Her intraocular pressures, confrontational visual fields, and extraocular movements were normal. Her anterior segment examinations were within normal limits in both eyes, and her dilated fundus examination in January 2015 was normal.

At her presentation in March 2015, 2 months after she initiated treatment, SD-OCT (Figure 1) showed parafoveal retinal pigmented epithelium (RPE)/photoreceptor disruption consistent with bull's eye retinopathy. HVF 10-2 tests (Figure 2) showed central scotomas of both eyes. The patient discontinued HCQ use at the beginning of April and continued ibuprofen for her arthralgia. She returned 3 months later in June with an essentially unchanged examination with the exception of macular RPE mottling. Repeat SD-OCT again showed parafoveal RPE/photoreceptor disruption, and repeat HVF showed consistent central scotomas in both eyes, indicating that the effects of HCQ toxicity were permanent. We continued to monitor the patient after she discontinued HCQ and found no resolution or progression of her symptoms. A full-field electroretinogram (Figure 3), normal in both scotopic and photopic settings, ruled out a possible cone dystrophy. The patient's cumulative HCQ dose was calculated to be 19.8 g.

DISCUSSION

Barring significant risk factors, patients with toxicity typically present with bull's eye retinopathy several years into treatment with HCQ. Published case studies and reports show HCQ has $<$1% risk of toxicity in the first 5 years of therapy and $<$2% up to 10 years.[5] Yam et al report only 2 published case reports of patients who exhibited HCQ toxicity from treatment with tolerable doses in $<$1 year.[2]

Furthermore, a review of HCQ toxicity by Geamănu Pancă et al shows that the best predictors of HCQ-induced retinal damage are duration of treatment, previous retinal disease, increased age, and kidney or liver dysfunction.[4] The drug's poor distribution in adipose tissue underlies the 5 mg/kg maximum daily dosage recommended by the AAO.[5] Our patient was taking a highly minimized dose well within the limits of AAO recommendations. Most of these predictors are based on the current understanding of the metabolism of HCQ and the drug interactions that are observed with

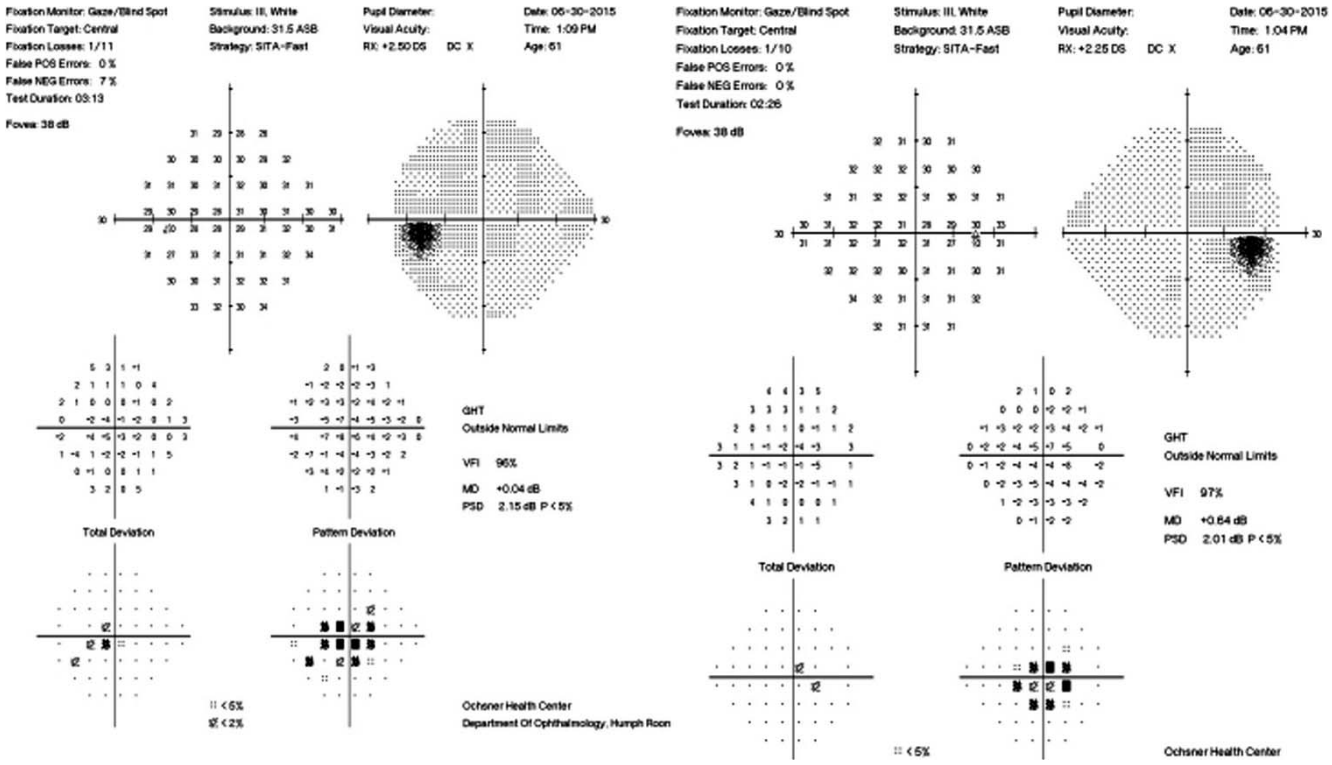

Figure 2. Humphrey visual field 10-2 tests reveal central scotomas of both eyes.

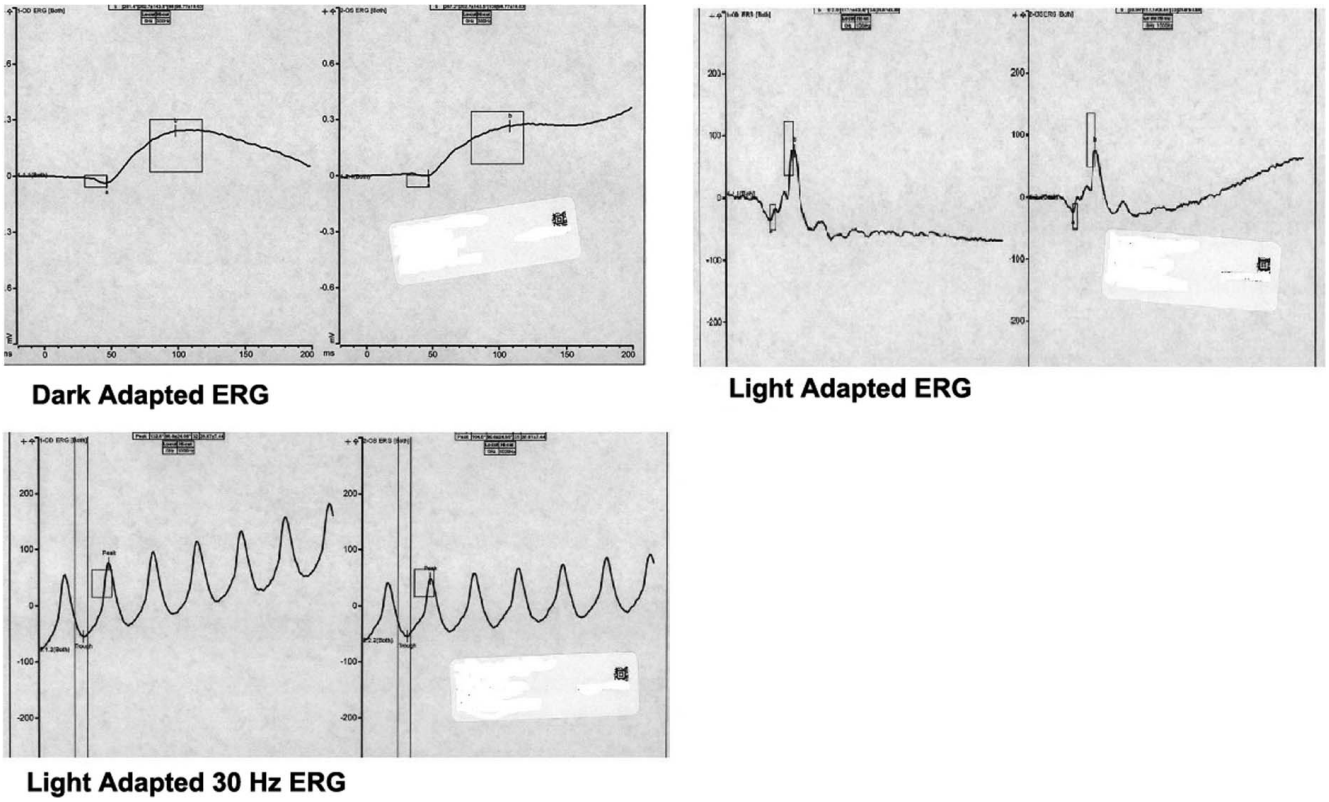

Figure 3. Dark adapted, light adapted, and light adapted 30 Hz flicker full field electroretinographs (ERGs) with normal amplitude and implicit times of the a and b waves.

HCQ. Melles et al[6] showed that the only major drug interaction is the anti–breast cancer drug tamoxifen citrate and that kidney disease highly predisposes patients to toxicity because HCQ is excreted via the kidney.[7,8]

Despite the fact that many patients present with central field defects earlier than fundoscopic evidence on the retina,[9] our patient exhibited both the central scotomas and maculopathy that classically present in HCQ toxicity. As seen in Figures 1 and 2, she had clear and demarcated lesions on fundoscopy, distinct parafoveal RPE disruption, and photoreceptor disruption on SD-OCT; the HVF 10-2 showed central scotomas bilaterally. Our patient's signs of HCQ toxicity were clear, and other bull's eye retinopathies were ruled out. Her age, lack of dark choroid, and lack of OCT flickering ruled out Stargardt disease, cone dystrophy, and central areolar choroid dystrophy. We ruled out age-related macular degeneration because the patient lacked clinically significant drusen and did not report line distortion.

Although the mechanism of HCQ toxicity is not understood, Sundelin and Terman proposed in a major theory that an inexplicable relationship between the accumulation of HCQ (or the more retinotoxic chloroquine) in the lysosomes of RPE and hypoxia lead to the changes seen in HCQ bull's eye retinopathy.[10] This relationship may explain why chloroquine, which accumulates more readily in lysosomes, exhibits more potent retinal toxicity than HCQ and potentially explains why our patient presented with retinopathy so early.

Our patient did not have any of the expected risks for HCQ toxicity according to current understanding of HCQ and ocular disease. She could have had an unknown genetic predisposition or acquired susceptibility to this potential mechanism of retinal toxicity, possibly resulting from subclinical hypoxia. Phillips and Chun reported retinopathy in a patient after 4 years of taking HCQ and investigated the various reasons that their patient showed early toxicity.[11] The authors postulated that the patient's combination of nonsteroidal antiinflammatory drugs (NSAIDs) progressed the development of HCQ toxicity because many NSAIDs are limited inhibitors of cytochrome p450 enzymes, leading to increased levels of bioavailable HCQ and yielding a lower toxic dose of HCQ. Although highly unlikely to be the only cause of this highly unusual early presentation of retinal toxicity, our patient's history of ibuprofen therapy may be a contributing factor to her bull's eye retinopathy.

CONCLUSION

The drastically shortened development of HCQ toxicity in our patient indicates that other factors promote HCQ retinopathy, and these risks must be explored further to prevent this permanent drug toxicity. These factors, once elicited, should reduce the number of patients who experience HCQ-induced retinal toxicity.

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