Retinal Toxicity from chronic hydroxychloroquine use in Kenya

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Abstract

Irreversible visual loss due to retinal toxicity is one of the side effects of hydroxychloroquine (HCQ) therapy. The recent outbreak of the novel coronavirus-19 (COVID 19) has seen HCQ proposed as a possible treatment and prophylactic drug, leading to its increased use. Many are unaware of its ocular side effects. We describe a case of HCQ-induced retinopathy in a 46-year-old female who was referred by a rheumatologist for routine eye review.

Abstract in French

Résumé
La perte de vision irréversible secondaire à la toxicité rétinienne est l'un des effets indésirables du traitement à l'hydroxychloroquine (HCQ). Nous décrivons un cas d'une patiente âgée de 46 ans, présentant une rétinopathie secondaire au traitement à l'HCQ référée par un Rhumathologue pour un examen ophtalmique.
Mots-clés: Hydroxychloroquine, rétine toxicité rétinienne, rétinopathie

Keywords: Hydroxychloroquine, retina toxicity, retina, retinopathy

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Introduction

Hydroxychloroquine (HCQ) has been historically used for the treatment of various chronic inflammatory and dermatologic diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis.[1],[2] The emergence of COVID-19 led to a surge in HCQ use after it was reported to be effective in preventing severe disease and progression to death.[3] Despite inconclusive results on its effectiveness,[4] HCQ use peaked and self-prescribed use among the general public increased. Ocular toxicity as a side effect of chronic HCQ use has been well described, with the most serious adverse effect being irreversible visual loss or blindness from retinopathy.[2],[5] Early retinal damage is asymptomatic and progression of retinopathy is possible even after cessation of the drug.[2] Furthermore, medicolegal consequences of failure to detect toxicity may occur during the follow-up of the involved patients. A maximum daily dosage of less than 5.0 mg/kg real weight or <6.5 mg/kg ideal body weight is recommended. A cumulative total dose of <1000 g may also be used.[6]

Case Report

A 46-year-old female of African descent reported blurry vision for several months before being referred to an ophthalmologist for eye review. She had been on follow-up for SLE for more than 15 years. During this time, she had various dosage regimens for HCQ, which were started at HCQ 200 mg BID (Twice a day) then increased to 400 mg BID over the course of her treatment. Based on the rheumatologist, her renal and liver function tests were normal and her weight had remained stable throughout the course of treatment. Exact weight tallies were not available. Aspirin 75 mg OD was also included in the treatment during her follow-up.

On eye examination, her best-corrected visual acuity was 6/12 (distance) and N5 (near) in both eyes. No visual improvement was noted with subjective refraction. Further examination showed normal anterior segments, clear vitreous and normal optic nerves, and blood vessels on fundoscopy. Both maculae were normal with no pigmentary changes. Color vision testing done by Ishihara was normal, with 24/24 plates correct in both eyes. An optical coherence tomography (OCT) and multifocal electroretinogram (mfERG) were done in both eyes.

BE OCT macula scans: Both eyes show normal maculae on OCT scans. There are no abnormal changes in the outer retinal layers [Figure 1].

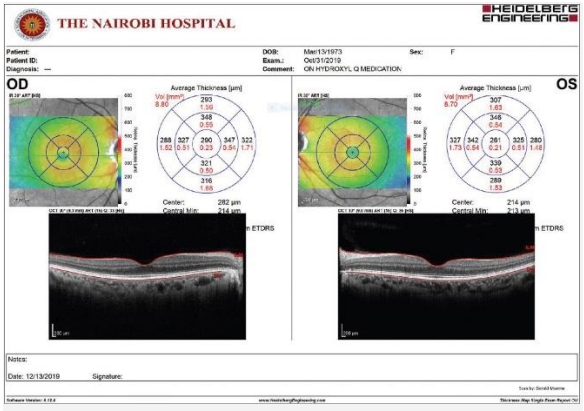

Figure 1: BE optical coherence tomography macula scans

RE mfERG on local responses map [Figure 2].

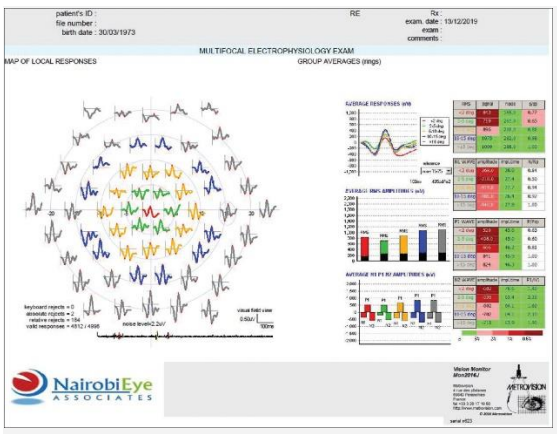

Figure 2: RE mfERG on local responses map

LE mfERG on local responses map [Figure 3].

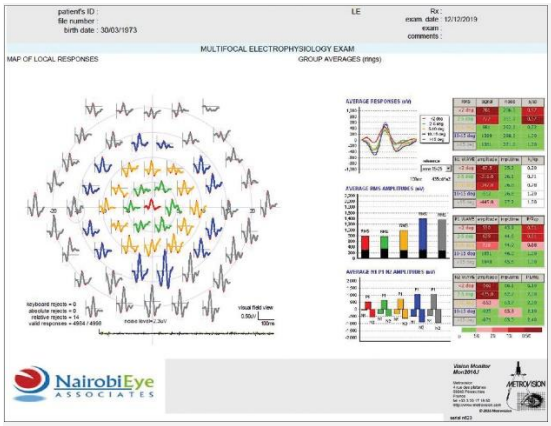

Figure 3: LE mfERG on local responses map

Both eyes mfERG on local responses map show good reliability indices and acceptable noise levels with good fixation. Note the reduced amplitudes on the N1, P1 and N2 amplitudes in the foveal and parafoveal zones of both eyes, indicating macula damage.

Findings

Good reliability indices, acceptable noise levels with good fixation. Note the reduced amplitudes on the N1, P1, and N2 amplitudes in the foveal and parafoveal zones of both eyes, indicating macula damage.

Discussion

The mechanism of HCQ retinal toxicity is not well understood.[6],[7] It is postulated that the drug causes photoreceptor damage with secondary disruption of the retinal pigment epithelium (RPE).[6] Moreover, HCQ binds to the melanin in the RPE where it may contribute to or prolong the drug's toxic effects. The macular localization of the disease suggests that light absorption or possibly cone metabolism may also play a role.[2],[6] Choroidal thinning has also been reported as a possible mechanism of HCQ toxicity.[5]

HCQ-induced retinopathy progresses from a premaculopathy stage to the classic bull's-eye maculopathy. Patients usually remain asymptomatic in the initial stages of toxicity. As the disease progresses, a gradual reduction in visual acuity and paracentral scotomata may be seen. Irreversible loss of central and peripheral vision develops in the later stages of the disease.[1],[8]

Several studies have shown varying rates in the incidence of retinal toxicity ranging from <1% to as high as 20%.[7],[9] These rates depend on various risk factors which have been broadly categorized as major and minor risk factors.[6] Studies differ as to whether there is any association between the minor risk factors and the occurrence of HCQ-induced retinopathy.[6],[7]

Major risk factors include:

- Dosage and duration of use (dosages above 5 mg/kg real weight and more than 5 years)
- Renal disease
- Concomitant tamoxifen use
- Preexisting retinal and macular disease.

Minor risk factors include:

- Age. Patients above 60 years of age seem to be at higher risk
- Liver disease

- Obesity
- Short stature
- Genetic factors including ABCA4 and cytochrome p450 mutations. These may underlie the difference in disease presentation between races.

Effective screening is key in the management of HCQ-induced retinal toxicity. Depending on the availability of resources and expertise, screening may involve visual acuity assessment, color vision assessment, fundoscopy, perimetry, OCT, fluorescein angiography, autofluorescence imaging, and mfERG.[6]

Multifocal electroretinography (mfERG) enables the stimulation of multiple retinal areas simultaneously and recording of each response independently. A topographic measure of retinal electrophysiological activity in the central 40°–50° of the retina can therefore be determined. It has in some series been considered the gold standard test for the detection of suspected toxicity, particularly in early retinopathy. If available, mfERG may be used as a primary screening and follow-up tool for HCQ retinopathy.[8] However, mfERG requires expensive equipment and experienced personnel to perform and interpret and is not readily available in most centers.

mfERG can objectively document parafoveal or extramacular electroretinogram depression of signals.[8] More specifically, Lai *et al*. recorded reductions in N1 and P1 response amplitudes in patients receiving HCQ, with increases in P1 peak latencies compared with controls.[10] Several studies have shown that patients who stop HCQ therapy may recover from retinopathy, with significant increases in response amplitudes at follow-up visits for both central and peripheral retinal zones.[8],[10] This suggests that early toxicity is probably reversible, and the detection of HCQ retinopathy at the subclinical stage is necessary to prevent permanent toxicity.

With regard to our patient, her major risk factor was the duration of use. According to the rheumatologist, her renal and liver functions remained within normal range throughout her period of treatment. She was not on tamoxifen during the period of treatment. On fundoscopy, she did not have any retinal lesions at the time of diagnosis of the retinopathy and it was assumed that there were no preexisting lesions. However, both a baseline evaluation and subsequent screening were not done. Weight charts were also not recorded, thus making it difficult to calculate her daily dosage. In our case, the diagnosis of HCQ-induced toxicity could not be made clinically but was picked by the mfERG responses. The mfERG findings for our patient match those seen by Lai *et al*.[10] HCQ was thereafter stopped with the intent to halt or reverse the effects of the possible drug-induced retinopathy.

Conclusion

It is recommended that all patients beginning long-term HCQ therapy should have a baseline ophthalmologic examination within the 1st year of starting the drug to document any preexisting ocular conditions and to establish a record of the fundus appearance and functional status. Baseline evaluation should also involve weight assessment, renal and liver function tests.

Following baseline evaluation, annual screening may be done in subsequent follow-up visits. Screening should begin sooner and should be done more frequently if the risk of retinopathy is high (see risk factors above). It is important to check the dosage relative to weight at every visit and repeat renal and liver function tests as needed.

The occurrence of HCQ retinopathy in this patient should raise our concern regarding the long-term usage of HCQ. As the pandemic enters its 2nd year, self-prescription should be discouraged in the general public. Due to the risk of HCQ retinal toxicity, modern screening methods should be made available and implemented. Guidelines regarding optimal dosing and screening should be available to both the patients and health-care workers.

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Conflicts of interest

There are no conflicts of interest.

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