Multimodal imaging characteristics of hydroxychloroquine retinopathy

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Hydroxychloroquine (HCQ) is known to cause retinal toxicity. Early detection of the toxicity is necessary to stop the drug in time. Multicolor imaging (MC) is a new noninvasive retinal imaging modality that simultaneously acquires three reflectance images of the retina using three individual lasers producing a composite image, thereby allowing analysis of changes at various levels within the retina. It is a new and promising addition to the retinal imaging armory. MC characteristics of HCQ toxicity are hitherto unreported. A 61-year-old female presented with history of HCQ intake (400 mg/day) for the last 6 years. She had retinopathy in both eyes. Multicolor composite image showed circumscribed perifoveal arcuate area of darkening, and infrared reflectance showed speckled hyperreflecetance in both eyes. MC

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imaging shows definite changes in HCQ toxicity, and it might emerge as a possible screening tool in future.

Key words: Hydroxychloroquine, multicolour imaging, multimodal imaging, retinal toxicity

Hydroxychloroquine (HCQ) retinal toxicity is known to cause irreversible vision loss.[1-4] It is a progressive condition which progresses even after stopping the drug. Therefore, the detection of toxicity at earliest possible time is of utmost importance to prevent visual morbidity. The American Academy of Ophthalmology has provided screening guidelines for HCQ retinopathy. It includes visual fields (VF), spectral domain optical coherence tomography (SDOCT), fundus autofluorescence (FAF), and multifocal electroretinogram (mfERG).[4] Multicolor imaging (MC) is a new noninvasive retinal imaging modality that simultaneously acquires three reflectance images of the retina using three individual lasers producing a composite image, thereby allowing the analysis of changes at various levels within the retina. It is a new and promising addition to the retinal imaging armoury. Its utility has already been described in conditions such as age-related macular degeneration, dominant cystoid macular edema, and epiretinal membranes.[5-7] We present the hitherto unreported multicolor imaging signature of HCQ retinal toxicity.

Case Report

A 61-year-old female, known to be using HCQ (400 mg/day) for 6 years for antiphospholipid syndrome, presented with dimness of vision for both distant and near objects in both eyes for the last 8 months. She did not have any history of renal or liver disease and was not taking any other drug known to cause retinal toxicity. Her body weight was 61 kg. The best-corrected visual acuity was 20/30, N8 in both eyes. The anterior segment was unremarkable in both eyes. Fundus of both eyes showed attached retina with normal optic disc. Both eyes showed an area of arcuate hypopigmentation around fovea [Fig. 1a and b]. Line scan using Spectralis SDOCT (Heidelberg Engineering, Germany) revealed the loss of ellipsoid zone and thinning of outer nuclear layer, temporal, and nasal to fovea in both eyes. Relative preservation of these layers underneath fovea created an ovoid appearance of fovea in both eyes [Fig. 2a and b]. Central foveal thickness was 151 μ in the right and 158 μ in the left eye. mfERG of both eyes showed reduced central and paracentral amplitudes more predominantly affecting rings 1, 2, 3, and 4 [Fig. 2d-g]. There was no history of prolonged use of any other drug neither there were any drusen flecks nor pigmentary changes anywhere else in fundus which would suggest age-related macular degeneration or retinal dystrophy.

Composite multicolor image (MC) of both eyes showed a circumscribed perifoveal arcuate area of darker hue sparing the fovea; which corresponded to the zone of retinal thinning seen on SDOCT [Fig. 1c and d]. Infrared reflectance (IR) image of the right eye showed speckled hyperreflectance at the center of macula with an arcuate zone of hyporeflectance surrounding it [Fig. 3a and b]. The hyporeflectance in these eyes coincided with the zone of outer retinal thinning seen

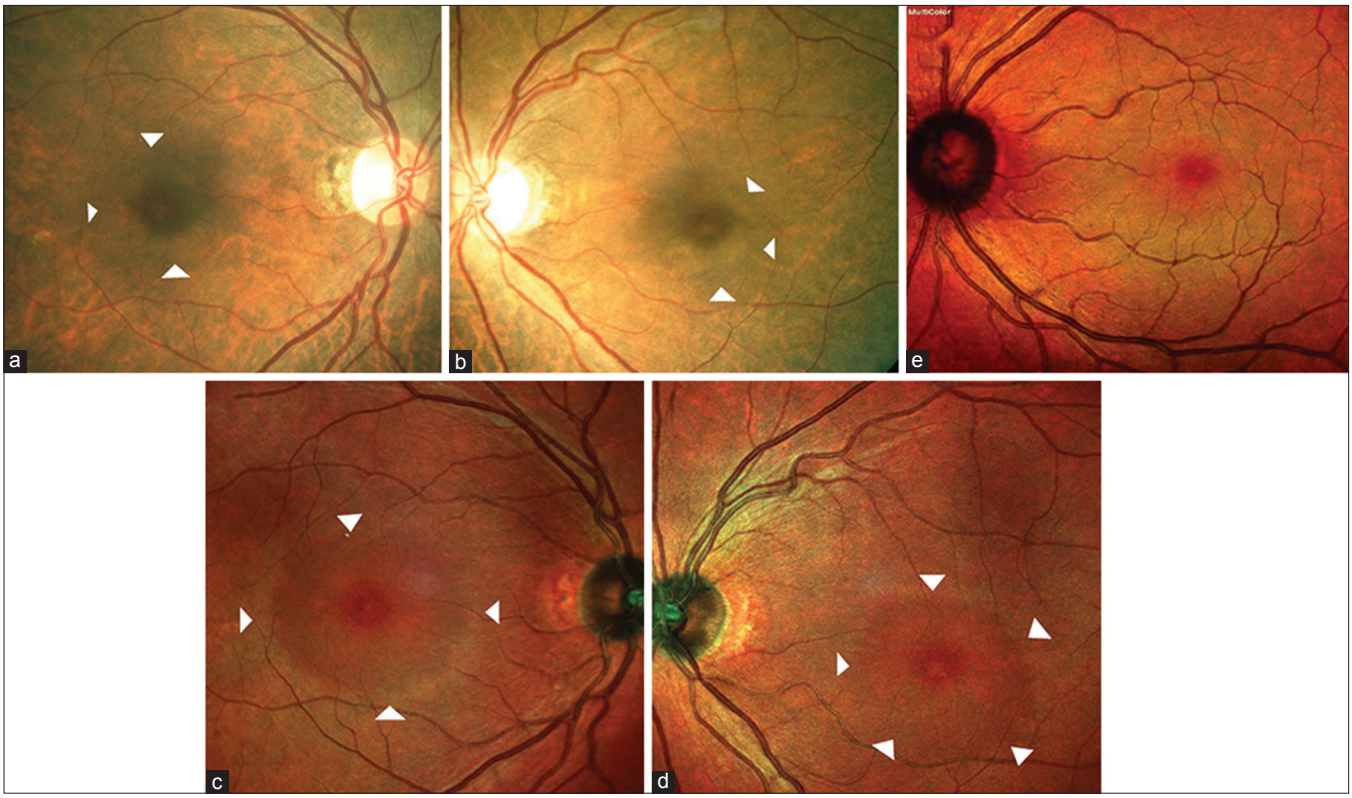

Figure 1: (a and b) Color fundus photography of the right and left eyes show arcuate zone of hypopigmentation (white arrow heads) superior, temporal, and inferior to fovea. (c and d) Multicolor imaging of the right and left eyes shows ring of darker hue around fovea (white arrow heads) corresponding to the arcuate hypopigmentation seen on color fundus photography and extending beyond. (e) Multicolor imaging image of the left eye of a normal individual shows deep pink center of the fovea surrounded by a greenish hue corresponding which is missing in the eye with hydroxychloroquine retinal toxicity

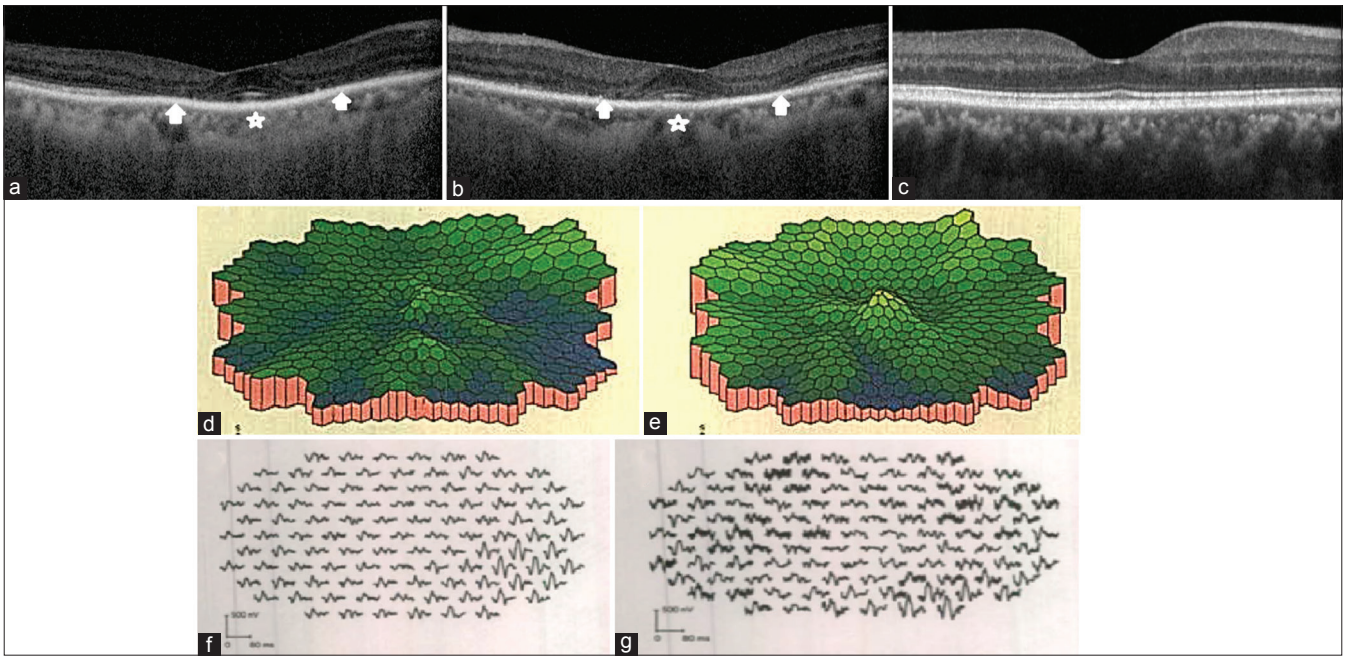

Figure 2: (a) (right) and (b) (left): Spectral domain optical coherence tomography line scan shows loss of external limiting membrane and ellipsoid zone along with thinning of the outer nuclear layer on both sides of fovea (white solid arrows). Outer nuclear layer, external limiting membrane, and ellipsoid zone are spared underneath the fovea creating an ovoid appearance characteristically termed as "flying saucer sign" (white star). (c) Spectral domain optical coherence tomography image of the left eye of a normal individual shows the normal foveal contour for comparison. (d) (right) and (e) (left): Multifocal electroretinogram images show depressed central and paracentral responses. Foveal responses are also shows some depression. (f) (right) and (g) (left): Multifocal electroretinogram trace array show depressed responses

on SDOCT. Blue autofluorescence (BAF) of both eyes showed normal hypoautofluorescence of fovea and a demarcated arcuate zone of hyperautofluorescence corresponding to the hyporeflectance seen on IR image [Fig. 3d and e]. The normal hyperautofluorescence at the center of macula seen in near-infrared autofluorescence (NIR-AF) imaging was limited to the center of the fovea in both eyes. The hyperautofluorescence was interspersed by a circular ring of hypoautofluorescence followed by another zone of hyperautofluorescence and finally by arcuate zone of hypoautofluorescence [Fig. 3g and h]. Automated VF (10-2) showed depressed paracentral responses with relatively preserved responses at fovea [Fig. 4a and b]. A diagnosis of HCQ retinal toxicity was made, and the patient was advised to consult treating physician to stop using HCQ.

Discussion

HCQ toxicity leads to irreversible damage to retina.[1] Established modalities to screen for HCQ toxicity includes VF, FAF, mfERG, and SD OCT. Detection in the early stage is needed to prevent visual morbidity. Multicolor scanning laser imaging is a recently introduced innovative technology developed for Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany). It uses three laser colors, blue (488 nm), green (515 nm) and infrared (820 nm) that penetrate the tissue to different depths, simultaneously capturing and depicting information originating from different retinal structures.[5] The IR image visualizes structures at the level of the outer retina and choroid. The green reflectance image allows imaging of retinal blood vessels, hemorrhages, and exudates. The blue reflectance particularly provides details of the inner retina and the vitreoretinal interface such as epiretinal membranes, retinal nerve fiber layer thinning, and macular pigment changes. The information from these three images are integrated to form a composite multicolor image. Multicolor imaging has unique advantages. It is noninvasive and has higher image resolution as it uses confocal technology. MC images can be acquired in small pupil. In contrast to conventional white light color fundus photography, it is patient friendly. However, the most important advantage of this modality lies in the fact that as compared to color fundus photography (CFP); it provides topographical information such as localized retinal thickening or thinning, which is difficult to appreciate in CFP. Thus, it has emerged as a promising noninavsive imaging tool.[5,6] To the best of our knowledge, MC imaging characteristics in HCQ is yet unreported in published literature. In this report, we describe MC and IR characteristics of HCQ toxicity. Although IR images are routinely acquired along with SDOCT imaging; changes in IR in HCQ retinal toxicity have not been described in literature. While MC image showed a darker hue, IR image showed an arcuate zone of hyporeflectance; both of which corroborated with the zone of outer retinal layer loss on SDOCT. Subtle parafoveal greenish hue seen in normal eyes on multicolor imaging caused by increased thickening in that region as compared to fovea was absent in our case owing to parafoveal retinal thinning. Interestingly, compared to CFP a larger area of retinal involvement could be appreciated in MC image.

We report two rings of hypo- and hyperautofluorescence surrounding the central hyperautofluorescence at fovea on NIR-AF imaging. The third outermost arcuate zone of hypoautofluorescence corresponded with the hyperautofluorescence on BAF. Hypoautofuorescence on

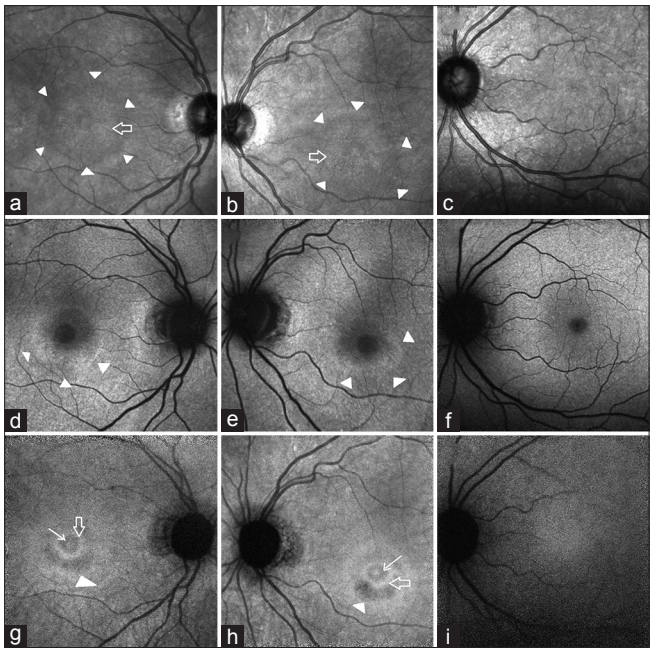

Figure 3: (a and b) Infrared reflectance images of the right and left eyes shows speckled hyperreflectance at the center of macula (blank white arrow). This area is surrounded by an arcuate zone of hyporeflectance (white arrow heads). (c) Infrared reflectance image of the left eye of a normal individual for comparison shows nondescript pattern of hypo- and hyperreflectance at the macula; devoid of any arcuate zone as seen in hydroxychloroquine retinal toxicity eyes. (d and e) Blue autofluorescence images show normal foveal hypoautofluorescence. The zone of hyperautofluorescence around fovea (white arrowheads) on blue autofluorescence corresponded with the hyporeflectance seen on infrared reflectance images in the upper panel. (f) Blue autofluorescence image of the left eye of a normal individual for comparison shows normal foveal hypoautofluorescence with gradually increasing hyperautofluorescence in all directions from fovea. The maximum hyperautofluorescence is attained near the arcades whereas in eyes with hydroxychloroquine retinal toxicity there was a ring of discrete arcuate zone of hyperautofluorescence around fovea. (g and h) Center of the macula showed normal hyperautofluorescence on near infrared autofluorescence. There were two rings; first of hypoautofluorescence (white arrow) and second of hyperautofluorescence (blank white arrow) around fovea creating a bull's eye pattern. Outermost arcuate zone of hypoautofluorescence (white arrowhead) was present mainly inferiorly and temporally and corresponding to the loss of outer retinal layers. (i) Near-infrared autofluorescence image of the left eye of a normal individual for comparison shows hyperautofluorescence at the center of the fovea with gradual diminution of autofluorescence in all directions without any ring like zones seen in hydroxychloroquine retinal toxicity

NIR-AF points toward melanin depletion due to HCQ retinal toxicity. Moreover, this arcuate zone of NIR-AF hypoautofluorescence was prominent inferiorly; the site where NIR-AF is known to be weak.[3]

Conclusion

The changes in MC and IR images noted in our case would need to be validated in a larger case series. However, our single case report does show their utility in obviating the retinal changes better than conventional CFP. MC imaging shows definite changes in HCQ toxicity and it might emerge as a possible screening tool in the future.

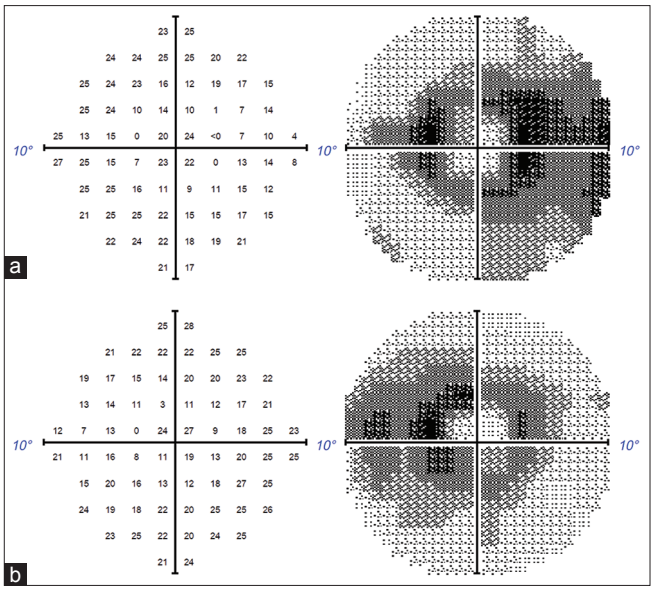

Figure 4: (a) (right) and (b) (left): Humphrey visual field analysis (10-2) shows depressed paracentral responses while the foveal responses are relatively preserved in both eyes

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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