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Case Report

Hydroxychloroquine-induced Maculopathy: enface Imaging as a Sign of Damage

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Abstract

Purpose: To describe the findings using optical coherence tomography (OCT) Spectralis (Heidelberg Engeneering) with *enface* transversal section a case of hydroxycloroquine-induced maculopathy.

Case: A 77-year-old woman on hydroxichloroquine for treatment of erythematous systemic lupus was referred from to screen for hydroxichloroquine-induced toxicity. The daily dosage was 50 mg for 8 years (approximated accumulate dose: 146g). Clinical examination was normal with a best-corrected visual acuity of 20/20 on both eyes (OU). Humphrey visual field 10-2 white showed significant persistent paracentral defect on right eye (OR) and a subtle superior paracentral defect on pattern deviation map on left eye (OS) without correlation on grey scale map. A multifocal electroretinogram (mERG) confirmed the diagnosis of premaculopathy. The Spectral Domain OCT (Heidelberg Engineering) showed aberration of ellipsoid layer and pigmentary epithelium defects using Retina Fast protocol but those findings where nonspecific and difficult to correlate with the HFA results in right eye and left eye appears to be unaffected. Using the *enface* protocol on right eye hiperreflectance lesions where described as well as in left eye which had been previously informed as normal OCT using sectional protocols.

Conclusions: Hydroxychloroquine maculopathy OCT findings are sutile and difficult to asses using the common OCT B-mode retinal scans. Using *enface* protocol OCT alterations could be correlated to visual field scotoma and even present lesions prior to visual field changes which could be missed using other protocols. These findings have not been reported earlier in other cases of hydroxychloroquine maculopathy could be implemented as a detector on the screening of these patients among the other commonly used tests . Nevertheless, it is need to perform larger studies to determine the diagnostic feasibility of this test.

Keywords: Optical coherence tomography, Hydroxychloroquine-induced maculopathy, *enface* protocol

Purpose

To describe the findings in a case of hydroxychloroquine-induced maculopathy using optical coherence tomography (OCT) Spectralis (Heidelberg Engeneering) with *en-face* transversal section.

Case

A 77-year-old woman on hydroxichloroquine for treatment of erythematous systemic lupus was referred from to screen for hydroxichloroquine-induced toxicity. The daily dosage was 50 mg for 8 years (approximated accumulate dose: 146g). Clinical examination was normal with a best-corrected visual acuity of 20/20 on both eyes (OU). Humphrey visual field 10-2 white showed significant persistent paracentral defect on right eye (OR) and a subtle superior paracentral defect on pattern deviation map on left eye (OS) without correlation on grey scale map (Figure 1). A multifocal electroretinogram (mERG) confirmed the diagnosis of premaculopathy showing a decrease in retinal response in OU with an abnormal R1/R2 relation being 2.62 on OD and 5.22 on OS, assuming the normal value is 2.6 according to the age of the patient [1,2] (Figure 2). The Fanswoth-Munsell test revealed a moderate decrease of sensitivity to colors on OD with a possible protanopia, being normal OI. The Spectral Domain OCT (Heidelberg Engineering) showed aberration of ellipsoid layer and retinal pigment epithelium (RPE) defects using Retina Fast protocol but those findings where

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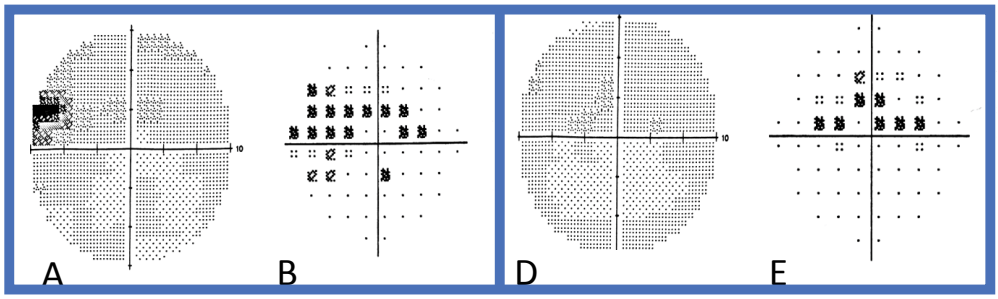

Figure 1: Visual field (10-2 Humphrey Visual Field analyzer) RE. Both grey scale map (A) and pattern map (B). LE. Grey scale map (D) without remarkable changes, pattern map deviation (D) with superior decrease of sensitivity compare to the model.

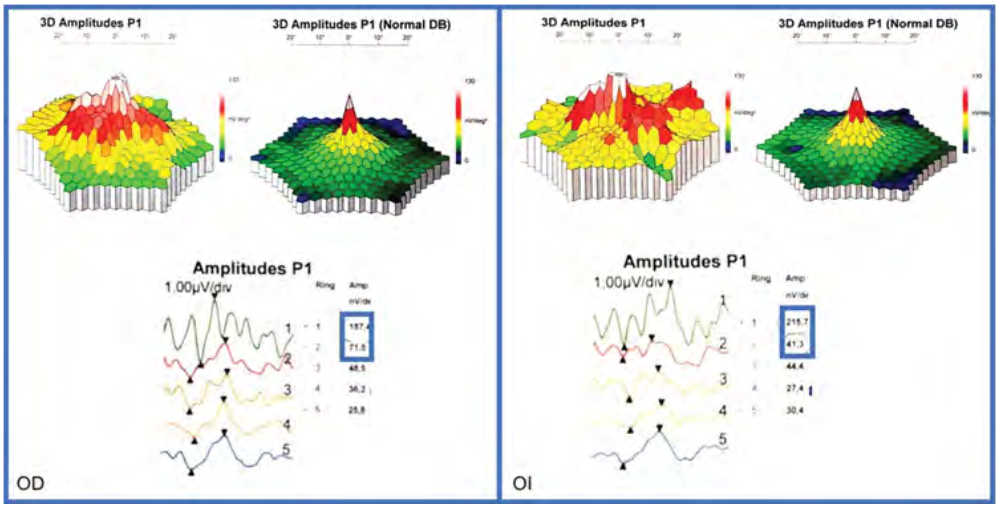

Figure 2: mERG. (RETIScan) Right eye. Global decrease of potential. R1/R2= 2,621 (normal value <2.6) Left eye. Global decrease of potential. R1/R2 = 5,22 (normal value <2.6)

nonspecific and difficult to correlate with the HFA results on OD, although OS appears to be unaffected (Figures 3 and 4). Using the *enface* protocol on OD hypo/hyperreflective lesions where described as well as in OS which had been previously informed as normal OCT using sectional protocols (Figures 3 and 4).

Discussion

Hydroxychloroquine is a wide range used drug for rheumatologic or dermatological disorders. It may induce retinal toxicity due to the deposit of the drug at the RPE causing alterations at that level that induce cellular death and secondary to the metabolically disturbance, photoreceptor loss.

Since 2011, the recommendations for surveillance of these patients include spectral domain OCT (SD-OCT), ophthalmological exploration and 10-2 perimeter. If available, it is recommended to perform an auto fluorescence and mERG among others tests [3]. There is not a gold standard method, so the use of a combination of tests is recommended [4].

SD-OCT examination interpretation can be done in either a qualitative or quantitative method. The qualitative methods take into consideration the alterations on RPE or the disruption of the inner segment (IS) layer due to cellular loss [5-7]. On the other hand, the quantitative analysis uses the thinning of inner layers to measure the thickness from inner limiting membrane (ILM) to RPE [8]. Johson, et al. found a significant relationship between the thinning of inner nasal and temporal quadrants related to the accumulated dose and, according to its reproducibility, it could be used as an early detector. However, it presents a low sensitivity, being very specific (97%), so in case of presenting a pathological exploration, the thinning of the ILM – RPE measurement would be pathognomic for toxicity [9], but being useless as an screening method due to the low sensitivity. The qualitative analysis showed even lower sensibility than the quantitative, and also less reproducibility because of the difficulty for surveillance, so it won't be recommended as a screening method [10].

As Browning, et al. suggests, mERG may be affected on an early stage being very sensible, nevertheless, associating a high rate of false positives so its role as an screening method is also questioned [11].

In our case, the right eye is affected with a subtle scotoma that maintained persistent on nasal inferior quadrant, using autofluorescence (HFA-AF) a hypoautofluorescent lesion could be observed at temporal superior quadrant. The topographical correspondence of the lesion correlates with the lesions

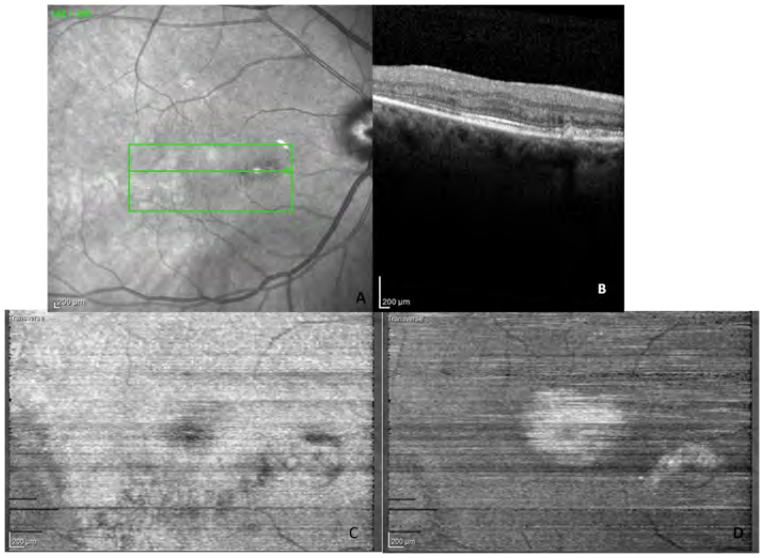

Figure 3: OCT Spectralis (Heidelberg Engineering) Right eye: A. HFA mode showing a hypoautofluorescent parafoveal lesion. B. B-mode OCT scan with non-specific alteration of IS/OS layer C. Hyporreflective lesion affecting parafoveal area at elipsoid layers D. Hyperreflective lesion affecting parafoveal area at inner layers.

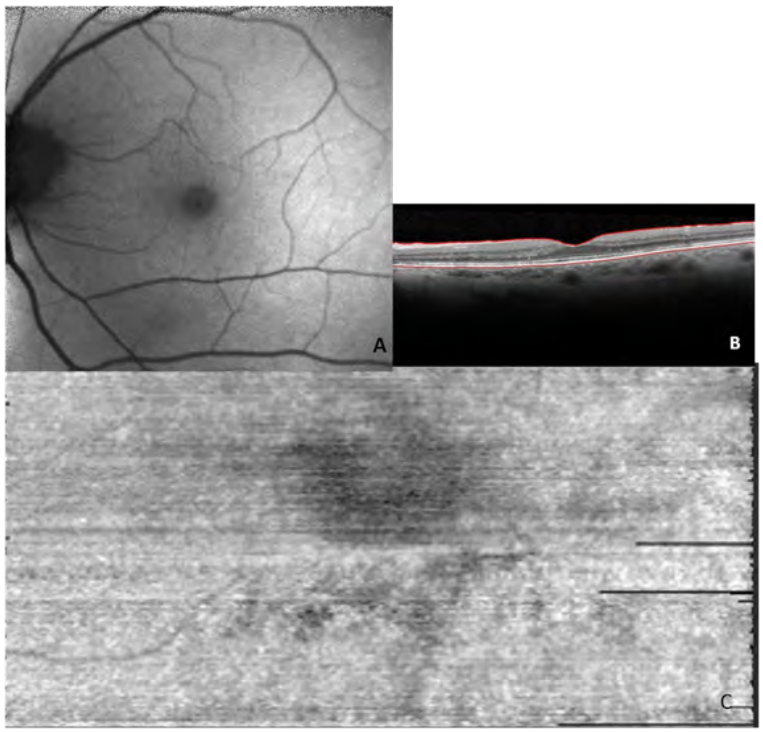

Figure 4: Left eye: A. HFA mode, non hypo/hyperautofluoresce lesions. B. B-mode OCT scan C. Hyporreflective lesion affecting parafoveal area at the ellipsoid layer.

showed with transversal reconstruction *en-face* presenting an hyperreflective patron at inner layers and hyporreflective at outter layers, corresponding to the region affected among other tests such as HFA-AF or 10-2 visual field. Nevertheless, on the left eye, it was noticed a subtle decrease of sensibility using the 10-2 perimetry pattern map with at superior and paracentral area. The OCT B-Scan sectional protocol appears unaffected as well as the autoflourescence, however, using *en-face* protocol, hyporreflective lesions were shown at the inferior and paracentral area of ellipsoid layer.

Recently, Itoth Y, et al. [12] obtained using ellipsoid mapping with *en-face* OCT a volumetric scale of this layer showing a decrease in volume of those patients with hydroxicloroquine intake among other maculopathies such as geographical atrophy and after

ocriplasmin inyection. Also there are described morphologic changes that could be associated, in pattern-based analysis, with bull-eye maculopathy in advanced cases and with the disruption of ellipsoid layer in cases of moderate affection. Using *en-face* protocol, other cases of paramaculopathies have been studied, such as retinal artery obstruction. On those patients, were found hyperreflective lesions at ischemic areas which coincide with the areas of hypoperfusion using angioOCT. In addition, *en-face* protocol produce images with enough reproducibility to perform an accurate follow-up [13]. In the case of diabetic patients, the reconstruction showed the decrease of photoreceptors at IS layer, being unremarkable at the B mode imaging [14]. Similar findings are described affecting outter retina using different methoths such as adaptive optics, microperimetry, HFA... with good topographical correlation with the images produced by *en-face* OCT scans [15-17].

This evidence suggests that there is a good feasibility between the OCT *en-face* imaging and the demonstration of cellular lost. The findings of the *en-face* OCT scan in this case would correlate the lesions attributed to cellular lost with the evidence of a subtle sensibility decrease by the 10-2 perimetry pattern deviation map. The early detection of this lesions using *enface* instead of B-scan sectional protocol may be due to a more precise scanning avoiding the loss of defects in non-obtained cuts and, on the other hand, due to the layer reconstruction, making more evident the defects that affect a specific region or cellular population [12,18].

These findings have not been reported earlier in other cases of hydroxychloroquine maculopathy could be implemented as an early detector on the screening of these patients. Nevertheless, it is need to perform larger studies to determine the diagnostic feasibility of this test.

References

1. Lyons JS, Severns ML. Detection of early hydroxychloroquine retinal toxicity enhanced by ring ratio analysis of multifocal electroretinography. *American journal of ophthalmology*. 2017;143(5):801-809.
2. Lyons JS, Severns ML. Using multifocal ERG ring ratios to detect and follow Plaquenil retinal toxicity: a review. *Doc Ophthalmol.* 2009;118(1):29-36.
3. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology*. 2016;123(6):1386-1394.
4. Marmor MF. Comparison of screening procedures in hydroxychloroquine toxicity. *Arch Ophthalmol.* 2012;130(4):461-469.
5. Rodriguez-Padilla JA, Hedges TR, Monson B, et al. High-speed ultra-high-resolution optical coherence tomography findings in hydroxychloroquine retinopathy. *Arch Ophthalmol.* 2007;125(6):775-780.
6. Brandao LM, Palmowski-Wolfe AM. A possible early sign of hydroxychloroquine macular toxicity. *Doc Ophthalmol.* 2016;132(1):75-81.
7. Asensio-Sánchez VM. SD-OCT as screening test for hydroxychloroquine retinopathy: The "flying saucer" sign. *Arch Soc Esp Oftalmol.* 2015;90(7):338-340.
8. Lee MG, Kim SJ, Ham DI, et al. Macular Retinal Ganglion Cell–Inner Plexiform Layer Thickness in Patients on Hydroxychloroquine TherapyGC-IPL Thickness in Patients Taking Hydroxychloroquine. *Invest Ophthalmol Vis Sci.* 2014;*56*(1):396-402.
9. Marmor MF, Chien FY, Johnson MW. Value of red targets and pattern deviation plots in visual field screening for hydroxychloroquine retinopathy. *JAMA ophthalmol.* 2013;131(4):476-480.
10. Marmor MF. Comparison of screening procedures in hydroxychloroquine toxicity. *Arch Ophthalmol.* 2012;130(4):461-469.
11. Teoh SC, Lim J, Koh A, Lim T, Fu E. Abnormalities on the multifocal electroretingram may precede clinical signs of hydroxychloroquine retinotoxicity. *Eye*. 2006;*20*(1):129-132.
12. Itoh Y, Vasanji A, Ehlers JP. Volumetric ellipsoid zone mapping for enhanced visualisation of outer retinal integrity with optical coherence tomography. *Br J Ophthalmol.* 2016;*100*(3):295-299.
13. Sridhar J, Shahlaee A, Rahimy E. Optical Coherence Tomography Angiography and En Face Optical Coherence Tomography Features of Paracentral Acute Middle Maculopathy. *Am J Ophthalmol.* 2015;160(6):1258-1268.
14. Francis AW, Wanek J, Lim JI, Shahidi M. Enface Thickness Mapping and Reflectance Imaging of Retinal Layers in Diabetic Retinopathy. *PloS one*. 2015;10(12):0145628.
15. Sampson DM, Alonso-Caneiro D, Chew AL, et al. Enhanced Visualization of Subtle Outer Retinal Pathology by *En Face* Optical Coherence Tomography and Correlation with Multi-Modal Imaging. *PLoS ONE*. 2016;*11*(12):168275.
16. Flores M, Debellemanière G, Bully A, et al. Reflectivity of the Outer Retina on Spectral-Domain Optical Coherence Tomography as a Predictor of Photoreceptor Cone Density. *Am J Ophthalmol.* 2015;160(3):588-595.
17. Wanek J, Zelkha R, Lim JI, Shahidi M. Feasibility of a method for en face imaging of photoreceptor cell integrity. *Am J Ophthalmol.*. 2011;152(5):807-814.
18. Sodi A, Mucciolo DP, Cipollini F, et al. En face OCT in Stargardt disease. *Graefes Arch Clin Exp Ophthalmol.* 2016;254(9):1669-1679.