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A Comparison of Structural and Functional Changes in Patients Screened for Hydroxychloroquine Retinopathy

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Abstract

Purpose—The aims of this retrospective study were to compare the results of recommended screening tests for hydroxychloroquine related retinal toxicity and analyze disparities between the structural and functional findings.

Methods—Thirty four patients (31 women, 3 men) were included in the study. All were evaluated with standard automated perimetry using the 10-2 and/or 24-2 visual field program (Zeiss, Meditec), multifocal electroretinography (mfERG), spectral domain optical coherence tomography (SD-OCT), and short wavelength fundus autofluorescent imaging (SW-FAF). The results for the right eye from each patient were analyzed. Visual fields were classified as normal or abnormal based on pattern deviation plots, and mfERGs based on a comparison of R₅ ring ratios to values from 20 controls. The SW-FAF images were examined for areas/rings of abnormal hypo- and/or hyperautofluorescence, and the SD-OCT line scans were classified as abnormal based on visual inspection and thickness measurements of the outer segment plus retinal pigment epithelial layer and total receptor layers compared to mean thicknesses from 35 controls.

Results—Fifteen patients had abnormal results on at least 1 test, however only 2 patients had abnormal results on all 4 tests. Excluding SW-FAF, 7 of the 15 had abnormal visual fields, mfERG ring ratios and SD-OCTs. The remaining 8 had either abnormal mfERGs and/or visual fields and normal SD-OCTs. We found no evidence of abnormal SD-OCTs in the presence of normal mfERG and visual field results.

Conclusions—The findings suggest that functional deficits precede structural changes seen on SD-OCT in these patients.

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Keywords

visual fields; multifocal ERG; short-wavelength fundus autofluorescence; optical coherence tomography

INTRODUCTION

Hydroxychloroquine an anti-malarial drug is used in the treatment of a range of rheumatologic and dermatologic diseases. Although uncommon, long-term use can cause irreversible toxicity of the retina. Because progression of structural and functional deficits can occur even after cessation of drug therapy [1–3], screening for identification of early HCQ toxicity is critical for the prevention of vision loss.

The characteristics of clinically manifest HCQ retinopathy include maculopathy, ranging from slight disturbance of the retinal pigment epithelium to “bull’s eye maculopathy” and/or macular atrophy. However fundus changes in the early stages of the disease are subtle and the retina can appear to be normal on fundus examination. Visual field changes can also be subtle with areas at risk reported to be between 2 to 6 degrees from the center of the field [4]. Some patients may be aware of paracentral scotomas, but central visual acuity is often preserved until the later stages of the retinopathy.

Recently Marmor et al. [5] have made specific recommendations for screening for toxicity have been revised. In addition to an ophthalmologic examination and automated “white-on-white” 10-2 visual fields, the recommendations include one or more of the following objective tests if available: spectral domain optical coherence tomography (SD-OCT), autofluorescence (FAF) and multifocal electroretinography (mfERG) [5]. Currently, there is no “gold standard” for the detection of HCQ retinal toxicity and there is no agreement in the literature as to which of the recommended screening tests is the most definitive. For example in a recent study a few patients with early HCQ toxicity had ring scotomas on visual field testing but did not show an obvious SD-OCT abnormality. The other patients had clear parafoveal damage on SD-OCT accompanied by visual field abnormalities [6]. A possible explanation for this discrepancy between functional and structural measures is that if a given individual shows signs of damage only on the visual field test, they may have had retinal thickness values at the upper limit of normal but visual field sensitivities close to the lower limit of the normal range before HCQ treatment was started. An alternative explanation is that detection of early functional loss may precede structural changes. This was suggested by Dale et al., [7] and Talamini et al. [8] to explain disparities between the results of functional and structural measures in patients with cone or cone-rod dystrophies. These patients had visual field and mfERG deficits with no accompanying qualitative or quantitative SD-OCT abnormalities [7,8]. As deficits in the mfERG reflect damage at or before the level of the bipolar cells [9], the implications of these studies are that detection of functional changes can precede not only clear qualitative structural changes on SD-OCT but also any quantitative evidence of thinning of the outer retinal layers.

The aims of this retrospective chart review of patients referred for screening for HCQ toxicity were to compare the results of the recommended functional and structural screening tests for HCQ related retinal toxicity and to evaluate any disparities that may be found.

METHODS

Subjects

The medical records of all 39 patients referred to one of the authors (SHT) by rheumatologists and ophthalmologists for evaluation of possible HCQ or chloroquine toxicity from 2012 to 2013 were reviewed with the approval of the Institutional Review Board of Columbia University Medical Center and in compliance with the Declaration of Helsinki. Patients were excluded if they had a refractive error greater than ± 6.0 diopters spherical or ± 2.0 diopters cylindrical, an epiretinal membrane, a significant cataract, and evidence or a history of other ocular diseases (e.g. glaucoma, diabetes, age-related macular degeneration, inherited retinal degeneration). Thirty four patients fit the inclusion criteria. The 34 included 31 women and 3 men who ranged in age from 15–79 years, mean 47 years, had corrected visual acuity of 20/30 or better, and had no signs of ocular disease aside from HCQ retinal toxicity. All had undergone a comprehensive ophthalmologic examination by one of the authors (ST) in the retina clinic. This included a full medical history, best corrected visual acuity, slit lamp biomicroscopy, dilated funduscopic examination, standard automated perimetry 10-2 and/or 24-2 visual field program, SD-OCT, short wavelength fundus autofluorescent imaging (SW-FAF) and mfERG testing. The results for one eye, the right eye, from each patient were included for analysis in the study.

Procedures

Visual Fields—As part of the screening for retinal toxicity 10-2 and/or 24-2 automated Humphrey visual field tests (Humphrey Visual Field Analyzer, Carl Zeiss Meditec Inc, Dublin, CA) were performed on each patient using the SITA standard technique. All patients included in the study had reliable visual fields (global indices $<33\%$). The total deviation and pattern deviation plots were reviewed for abnormalities by two of the authors (LA and VCG) masked to the patients' clinical data, mfERG, and SD-OCT results. The following were defined as abnormalities on the 10-2 visual field: paracentral (2–6 degrees from fixation) partial and complete ring scotomas (sparing the central 2°), and 2 or more parafoveal points with $P < 1\%$ probability. In the case of 3 patients with only 24-2 visual fields, an abnormal visual field was defined as one with a small central defect on the pattern deviation plot where one or more of the 4 central points surrounding fixation had a probability of $<1\%$.

mfERG recording and analysis—Responses were recorded monocularly using the VERIS system (VERIS EDI, California, USA). The protocol followed International Society for Clinical Electrophysiology of Vision guidelines [10]. Pupils were dilated with topical 1.0% tropicamide and 2.5% phenylephrine, and the cornea was anesthetized with 0.5% proparacaine. Subjects were instructed to fixate a small "x" at the center of a 45° array of 103 scaled black and white hexagons. The mean stimulus luminance was 100 cd/m^2 with dark hexagons $< 3 \text{ cd/m}^2$ and bright hexagons 200 cd/m^2 . The stimulus was viewed through

a refractor system that provides spherical correction of the subject's refractive error and an IR camera allowed the examiner to monitor the position of the pupil during the recording. First-order mfERG responses were acquired using a bipolar contact lens electrode (Burian-Allen; Hansen Ophthalmic, Solon City, IA), and a forehead ground electrode. The first order kernel mfERGs were analyzed using VERIS software (version 5.1) by grouping the 103 responses into 6 concentric rings (see Figure 1). R₅ ring ratios were calculated using the R₅ ring response as the “reference” and dividing by all other ring response amplitudes (R₁–R₆) [11,12]. The ratios of R₅ to each of the other rings were compared to 95% CIs from 20 control eyes of 20 healthy subjects who ranged in age from 18–71 yrs., mean age 42+/-18 yrs.

SD-OCT scan acquisition and analysis—SD-OCT imaging (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) was performed on each patient. A 9 mm line scan along the horizontal meridian centered at the fovea was obtained using high-resolution settings and automated tracking (ART). The line scan was obtained as an average of 100 scans to give the highest signal to noise ratio (>25 dB). The foveal line scans were examined for local abnormalities such as perifoveal loss or disruption of the ellipsoid zone (EZ) band and apparent thinning of the outer retinal layers by three experienced observers including two of the authors (ST and VCG). The results were categorized as normal/inconclusive or abnormal. The scans were then analyzed using a computer-aided, manual segmentation technique [13,14]. The following borders/boundaries were segmented: the border between the inner nuclear layer (INL) and the outer plexiform layer (OPL); the EZ band (also known as the inner segment/outer segment junction); the border between the outer segment (OS) and retinal pigment epithelium (RPE); and the border between Bruch’s membrane (BM) and the choroid (see Fig. 2). Segmentation was performed by a trained observer (RR). The thickness of the total receptor (REC+: BM/choroid to the OPL-INL border) layer and the outer segment plus retinal pigment epithelium layer (OS+: BM/choroid border to the EZ band aka IS/OS junction) were measured. The values were compared to mean thicknesses from 35 age-similar control eyes from 35 subjects with a mean age 45 +/-15 yrs.

Short-wavelength fundus autofluorescence (SW-FAF)—30° images (Heidelberg Spectralis HRA+OCT; Heidelberg, Germany) were obtained after pupil dilation. Standard procedure was followed for the acquisition of the SW-FAF images [15]. This included focusing of the retinal image and adjusting the sensitivity at 488 nm before acquiring 9 consecutive 30°×30°(768×768 pixels) SW-FAF images encompassing the entire macular area with at least a portion of the optic disc. The 9 single images were automatically averaged to compute a single frame with improved signal-to-noise ratio. The images were examined by three experienced observers for pericentral areas/rings of abnormal hypo- and/or hyperautofluorescence.

RESULTS

Of the 34 patients, 20 were treated with HCQ for ≥5 years, 11 of the 20 had been treated for ≥10 years with a cumulative dose >1000g; 1 patient was treated with chloroquine for 25 yrs with a cumulative dose of 912g (see Table 1 for details).

Visual Fields

The visual fields for 24 eyes of 24 patients were classified as normal and 10 were classified as abnormal. Of the 10 fields classified as abnormal, 7 showed parafoveal sensitivity losses with partial or complete paracentral ring scotomas on the 10-2 Humphrey visual field test, 2 had central scotomas on the 24-2, and 1 was classified as abnormal based on 4 parafoveal points with $P < 1\%$ on the 10-2. Eight of the 10 patients with abnormal visual fields had been treated for ≥ 10 years. Figure 3 shows representative examples of abnormal 24-2 and 10-2 visual fields together with the corresponding mfERG trace arrays. For P22, the 24-2 PD plot shows a central scotoma with loss extending inferiorly and for P6, the 10-2 plot shows a paracentral ring scotoma.

mfERG

Thirteen of the 34 patients had abnormal mfERG R_5 ring ratio results. Of the 13, 10 had significantly increased ratio values including P6 and P22 in Fig. 3, and 3 had decreased values compared to controls. Ratio values that were higher than the 95th percentile were defined as being significantly increased and values lower than the 5th percentile were defined as being significantly decreased. This is illustrated in Figure 4 where the symbols represent R_5 ring ratio values for all 34 patients; the horizontal lines indicate the 5th and 95th percentiles of the normal control values and the filled red circles are the individual values for 20 control eyes. The greatest differences occurred for the $R_5:R_3$ and $R_5:R_2$ ratios. Nine of 13 patients had been treated for ≥ 10 years and 3 for at least 5 years. A comparison between the mfERG and visual field results showed that of the 13 patients with abnormal mfERG ring ratios 8 had visual field defects, including P6 and P22, and 5 patients had normal visual field results (see Table 2).

SW-FAF

Only 2 patients (P22, P10) showed signs of abnormal FAF (see SW-FAF images Fig. 5). For P22 the central hypoautofluorescent area is increased and for P10 a pericentral ring of increased FAF surrounded by an incomplete ring of hypoautofluorescence can be seen. Both P22 and P10 had paracentral ring scotoma on visual field testing, increased R_5 ring ratio results, and parafoveal disruption of the EZ band on SD-OCT (indicated by vertical arrows in Fig. 5). They had used HCQ for 10 and 17 years respectively. In addition the SD-OCT scan for P10 shows parafoveal thinning of the RPE.

SD-OCT

Of the 34 patients in the study, visual inspection of the SD-OCT images showed loss or disruption of the EZ band in only 3 patients, P22, P10, and P33 (see Fig 5). All 3 show parafoveal discontinuity or disruption of the EZ band, and the "flying saucer" sign of HCQ retinopathy is evident for P22 [16]. The 3 patients had been on HCQ for ≥ 10 years, 2 had abnormal visual fields typical of HCQ toxicity, and all 3 had significantly increased R_5 ring ratio values (see Fig. 4). Quantitative analysis with segmentation showed significant thinning of their REC+ and OS+ layers (see Figs 6A and B). A layer was classified as being significantly thinned if the thickness values fell below the mean for controls minus two standard deviations represented by the lower black continuous line in Figs 6A and B). Of the

remaining 31 patients with normal appearing SD-OCT scans, 4 (P4, P6, P24, P30) had significant thinning of the REC+ and OS+ layers in the parafoveal region. These patients had also been treated for ≥ 10 years. They had abnormal visual fields and mfERG ring ratio values (see Fig. 4).

Comparison of Results of Structural and Functional Tests

We compared the results of the structural and functional tests, excluding SW-FAF as only 2 patients showed signs of abnormal FAF, and found agreement among the 3 tests (i.e. visual field, mfERG and SD-OCT) in 26 patients (see Table 2). Nineteen showed no evidence of structural and functional deficits, and 7 had mfERG and visual field abnormalities with accompanying changes on SD-OCT. We found discrepancies between the test results in 8 patients. They had functional deficits, either abnormal mfERG results and/or visual field results but the SD-OCT scans were normal not only on visual inspection but also on quantitative analysis. Six of these patients had been treated for ≥ 5 years.

DISCUSSION

A comparison of the results of the screening tests showed that more abnormalities were detected for the two functional tests, the mfERG and visual field, than for the two tests of retinal structure, the SD-OCT and SW-FAF. Ten patients had abnormal visual fields, and 13 had abnormal mfERG ring ratio values. The visual field findings were similar to those previously reported; inspection of the PD plots for the 10-2 white-on-white visual field test showed that the majority of patients classified as abnormal had partial or complete paracentral ring defects with foveal sparing, and the 2 patients who had 24-2 visual fields had central scotomas [6,17,18]. The mfERG ring ratio values were used to analyse the data as they are reported to provide a sensitive measure of dysfunction in patients with HCQ retinal toxicity [11,12]. We chose the R₅ ring response as the internal reference ring rather than R₁, as R₁ is the most variable in normal control eyes [10,12]. A comparison between the two functional tests, showed that not only were the results abnormal for both tests for 8 patients, but there was also topographical agreement in terms of the regions that showed damage (see P6 and P22, Fig. 3). However, when we compared these results to the two structural tests only 3 of the 8 patients, P22, P10, and P33 (see Fig 5) showed clearcut structural deficits in the form of discontinuities of the EZ band in the parafoveal region on SD-OCT, and only P22 and P10 showed accompanying morphological abnormalities on SW-FAF indicative of alterations in the RPE. It should also be noted that in our group of 34 patients we could not find a single example of an abnormal SD-OCT or SW-FAF in the presence of normal mfERG and visual field results.

The question arises as to why we found discrepancies between the results of the functional and structural tests. We do not have a simple explanation. We are not the first to describe this in patients treated with HCQ. For example our finding of normal SD-OCT scans on visual inspection in the presence of abnormal mfERG and/or visual fields is in agreement with Marmor and Melles [6]. They documented a subset of patients with early HCQ toxicity who had ring scotomas on visual field testing but no obvious SD-OCT abnormalities. The absence of visible abnormalities on SW-FAF in patients with abnormal mfERGs is also in

agreement with Kellner et al [19] who found that more retinal abnormalities were detected with the mfERG than with SW-FAF. With regard to a possible explanation, we were able to resolve some of the discrepancies we found between the SD-OCT and two functional tests by measuring the thickness of the REC+ and OS+ layers. Quantitative analysis with segmentation showed significant thinning of the REC+ and OS+ layers in 7 of the patients with abnormal visual fields and mfERGs (see Fig.6A and B), demonstrating the importance of measuring the thickness of the outer retina even when the anatomy appears to be normal. However we still have to account for the absence of significant thinning in 8 patients with either abnormal mfERGs and/or visual fields (see Table 2).

A similar discrepancy between structural and functional tests was observed in a group of patients with retinal disease [7, 8]. Dale et al. [7] described patients with abnormal mfERGs and visual fields but with normal appearing SD-OCT scans. They hypothesized that some of the SD-OCT scans would be abnormal if a quantitative analysis of outer retinal layers was performed. Talamini et al.[8] performed this analysis on some of these patients and demonstrated that while the outer retinal thicknesses were abnormal in some eyes, they were in the normal range in other eyes. They concluded that in certain retinal diseases the changes affecting the outer retina at the cellular level might not be measureable with current SD-OCT technology.

Before concluding that functional changes can precede structural changes in our study, we need to consider the possibility that the eyes that were abnormal on functional, but not on structural, tests were false positives, i.e., really were normal. Ideally testing should be repeated and results compared to baseline measurements to determine if losses are consistent and reliable. Of the 8 patients with normal SD-OCT but abnormal visual field and/or mfERG, 6 of the 8 had abnormal mfERGs, 3 had abnormal visual fields, and only 1 had abnormalities on both mfERG and visual field tests (see Table 2). After careful inspection of our results, including quantitative analysis of the thickness of the outer retinal layers and a review of the medical charts, we can rule out HCQ toxicity in 2 of these 8 cases, P8 (visual field abnormal) and P31 (visual field and mfERG abnormal). Based on the history of a cumulative dose of less than 250 grams, and that neither of the two patients had any of the following risk factors that may have increased the likelihood of retinal toxicity: age >60 years (P8 was 30 yrs of age and P31 was 18 yrs of age); a pre-existing retinal disease; and renal or liver failure; it is unlikely that these patients have HCQ toxicity. Follow-up data would also help determine whether the results for these patients are false positives, or signs of early toxicity. We are left with 6 patients with a history of ≥ 5 years of treatment and discrepant structural and functional results. Only one patient, P25, had an abnormal visual field and normal mfERG ring ratio values. She had been on CQ for 25 years, had a partial ring scotoma and mfERG ring ratio values within 95% CIs (see inverted green triangles Fig. 7A). The trace array does show slightly decreased response amplitudes in the central 5–10 degrees as well as scattered decreased responses in the periphery, and the $R_5:R_3$ value is at the upper limit of the 95% CI. If we modified our definition of an abnormal mfERG or if we added more normal controls then this case may fit the explanation by Talamini et al. [8] that functional loss measured by mfERG and visual fields precedes structural changes on SD-OCT. The remaining 5 had abnormal mfERG ring ratio values and normal 10-2 visual fields. For example, in Fig. 7B the trace array (field view) for P13 shows decreased response

amplitudes in the central 5–10 degrees and increased ring ratio values (see blue filled circles) for $R_5:R_1$ and $R_5:R_3$. The mfERG is clearly abnormal in this eye, while the SD-OCT and visual field are not. Although the results are consistent with reports that the mfERG is a sensitive method for detecting early loss of retinal function in HCQ retinopathy [20, 21], a longitudinal study is needed to verify whether the maculopathy in this patient can be attributable to HCQ toxicity. Regardless of the interpretation of the origin of this patient's functional deficit, this case provides another example of functional loss preceding structural changes seen on SD-OCT. The presence of mfERG abnormalities in these patients indicates outer retinal damage, and given the SD-OCT results of an intact EZ band and OS+ and REC+ thicknesses within the normal range we suggest that mfERG deficits can be detected earlier than structural changes seen on SD-OCT.

This study of patients taking HCQ not only shows the importance of including functional tests, visual fields and mfERGs, but also the need for careful analysis of functional and structural findings using quantitative techniques.

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Figure 1. Ring averaged waveforms R_1 – R_6 for a normal observer obtained after grouping the 103 mfERG responses in the trace array (shown in field view) in the form of 6 rings. The locations of the first negative peak N1 and first positive peak P1 for the average waveforms are shown. Response densities are calculated as P1-N1 expressed in nV/deg². The R_5 ring ratio values are presented in the column on the left hand side.

Figure 2.

Image of a SD-OCT scan through the horizontal meridian for a normal observer. The colored lines indicate the borders that were segmented. The thicknesses of the OS+ and REC+ layers were measured.

P22

P6

Figure 3.

HVF 24-2 and 10-2 pattern deviation plots and multifocal ERG trace arrays (field view) for P22 and P6.

Figure 4.

R₅ ring ratio values for 34 eyes of 34 patients. Horizontal lines indicate the 5th and 95th percentiles of the values for the group of normals. The filled red circles are the values for 20 eyes of 20 controls.

Figure 5. SW-FAF and corresponding SD-OCT images of P22, P10 and P33. The vertical arrows indicate the location of discontinuity of the EZ band.

Figure 6.

Thickness values along the horizontal meridian of the REC+ (A) and OS+ (B) layers for 34 eyes of patients on HCQ. The dashed and continuous black lines represent the mean $\pm$ 2SDs thickness values for 35 normal control eyes.

A

P25

HVF 10-2

mfERG trace array

P13

B

Figure 7.

HVF 10-2 gray scale, total deviation and pattern deviation plots, multifocal ERG trace arrays (field view) and R₅ ring ratio values for P25 (represented by inverted green triangles in A) and P13 (represented by filled blue circles in B).

Table 1

Selected Demographics and Clinical Characteristics

Patient #	Age (yrs)	HCQ (mg/d)	Rx (yrs)	HCQ Cum. (g)	VA logMAR
1	23	400	2	292	0
2	53	400	5	730	0
3	24	400	2	292	0
4	74	400	12	1752	0.1
5	43	400	3	438	0.1
6	68	400	16	1556	0.2
7	53	200	4	292	0
8	30	400	1	146	0
9	57	400	6	876	0.2
10	73	400	10	1460	0.1
11	35	100	0.2	12	0
12	49	300	5	548	0
13	43	300	10	1095	0
14*	15	200	4	292	0
15	53	400	10	1460	0
16	73	400	12	1752	0.3
17	65	400	2 wks	5.6	0
18	68	400	0.5	73	0.1
19	21	400	0.4	58.4	0
20	51	400	1.5	219	0.1
21*	37	400	10	1460	0
22*	48	400	17	2482	0.1
23	25	400	0.2	24	0.1
24	66	400	14	2044	0.2
25**	79	100	25	912	0.1

Patient #	Age (yrs)	HCQ (mg/d)	Rx (yrs)	HCQ Cum. (g)	VA logMAR
26	54	400	5	730	0.2
27	54	200	3	219	0.2
28	57	400	5.5	803	0
29	21	200	8	584	0
30	72	400	12	1752	0.2
31	18	200	1	73	0
32	21	340	5	620.5	0
33	49	400	12.5	1825	0.1
34	18	200	5	365	0

* Male;

** patient treated with chloroquine

Table 2

Summary of Test Results

Patient #	Rx (yrs)	VF	mfERG	SD-OCT	SW-AF
1	2				
2	5		<<		
3	2				
4	12		>>		
5	3				
6	16		>>		
7	4				
8	1				
9	6				
10	10		>>		
11	0.2				
12	5				
13	10		>>		
14	4				
15	10				
16	12		>>		
17	2 wks				
18	0.5				
19	0.4				
20	1.5				
21	10				
22	17		>>		
23	0.2				
24	14		>>		
25	25				
26	5		>>		
27	3				

Patient #	Rx (yrs)	VF	mERG	SD-OCT	SW-AF
28	5.5				
29	8				
30	12		<<		
31	1		<<		
32	5		>>		
33	12.5		>>		
34	5				

Filled cells indicate abnormal results
>> = Increased ring ratio values
<< = decreased ring ratio values