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Microperimetry as a screening test for hydroxychloroquine retinopathy: The HARD-RISK-1 Study

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SUMMARY

Microperimetry can detect Hydroxychloroquine Retinopathy with 73% sensitivity and 93% specificity compared to multifocal electroretinography. Therefore, while it may not be useful for routine primary screening, it may be useful as an ancillary test to exclude retinopathy in high-risk patients.

Abstract

Purpose: To assess the sensitivity and specificity of microperimetry (MP) as a screening test to detecting hydroxychloroquine (HCQ) retinopathy.

Methods: Retrospective cohort study. Patients with history of HCQ use for more than 5 years and with concomitant MP and multifocal electroretinogram (mfERG) testing were retrospectively reviewed. MP was considered positive if there were 3 or more contiguous scotoma points in the parafoveal region. mfERG was used as gold standard and was considered positive if there was an increased R1/R2 ring ratio (>2.5) or reduced R1 absolute amplitude (<9.0). Sensitivity, specificity, positive predictive value and negative predictive value of MP were calculated.

Results: A total of 197 patients were reviewed. HCQ retinopathy was present in 22 (11%) patients. Their mean (SD) age was 54 (14) years and 96% were female. Their mean (SD) daily dose was 5.7 (1.3) mg/kg, cumulative dose was 2041 (1548) g and duration of use was 15 (10) years. Sensitivity, specificity, positive predictive value and negative predictive value of MP were 73%, 93%, 53% and 96%, respectively.

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Conclusions: MP has inferior sensitivity but good specificity in detecting HCQ retinopathy (compared to mfERG). As such, it may be a useful ancillary test to exclude retinopathy, especially in high-risk patients or those with conflicting results on different modalities.

Keywords

Microperimetry; Screening; Sensitivity; Specificity; Hydroxychloroquine Retinopathy; Hydroxychloroquine Toxicity

INTRODUCTION

Hydroxychloroquine (HCQ) is a commonly used medication for a range of disorders, most notably rheumatological diseases such as systemic lupus erythematosus (SLE) where it demonstrates a clear survival benefit.¹ There is also a growing body of evidence for its therapeutic effects on other conditions, particularly dermatological and oncological.² While it has few systemic adverse effects, long-term administration of HCQ can lead to irreversible retinal toxicity, the mechanism for which remains uncertain.³ It is imperative to recognize HCQ retinopathy at an early stage since the condition can progress even after the drug is stopped and the risk of visual loss is directly related to the severity of retinopathy at the time of detection.⁴

Previous estimates of HCQ retinopathy were low and it was generally considered to be a rare entity.⁵ However, modern screening techniques have shown a much higher prevalence, especially with a prolonged duration of use.⁶ The American Academy of Ophthalmology (AAO) recommends using automated visual fields and spectral-domain optical coherence tomography (SD-OCT) for routine primary screening of HCQ retinopathy.⁷

Even though standard automated 10–2 visual field is more sensitive than objective tests such as SD-OCT,⁸ their reliability is limited by fixation instability and patient cooperation.^{9,10} Microperimetry (MP) is a visual field test which integrates computerized threshold perimetry with real-time fundus imaging, allowing accurate and reliable testing of fixation stability and retinal light sensitivity as well as precise localization of functional defects.^{11,12} Several studies have demonstrated reduced retinal sensitivities on MP in patients taking HCQ, even without any evidence of retinopathy based on current recommended standards.^{13–15} Nevertheless, there is a lack of information concerning the exact sensitivity and specificity of MP in detecting HCQ retinopathy and the AAO does not currently have a position on its viability as a screening test.⁷

As HCQ use continues to grow, it is becoming increasingly important to investigate reliable and reproducible screening tests which can detect structural or functional changes before irreversible vision loss occurs. Therefore, the aim of this study was to assess the sensitivity and specificity of MP in detecting HCQ retinopathy in a large cohort of patients.

METHODS

This was a retrospective study conducted at a single center (The Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, MD). Data were collected as part of the Hydroxychloroquine

Associated Retinopathy Development **RISK** Factor retrospective (**HARD-RISK-1**) study. The study adhered to the tenets of the Declarations of Helsinki and was approved by the Johns Hopkins Institutional Review Board.

We reviewed patients who had presented to our department between January 2014 to December 2016 for HCQ retinopathy screening (with a history of HCQ use for more than 5 years) and had undergone MP and multifocal electroretinogram (mfERG) testing as part of their routine clinical care. Patients with established bull's eye maculopathy on clinical exam or concomitant retinal disorders (age-related macular degeneration, diabetic retinopathy, etc.) were excluded. Information on patient characteristics including demographics, duration and dose of HCQ therapy, and Snellen visual acuity (with current correction) was obtained from the medical records.

All mfERG testing had been performed using the Espion system (Diagnosys LLC, Lowell, MA, USA) in accordance with the International Society for Clinical Electrophysiology of Vision guidelines. A 61-hexagon stimulus pattern was used wherein each hexagon would elicit a waveform consisting of a negative trough (N1), followed by a positive peak (P1), followed by another negative trough (N2). The waveform amplitudes (nanovolts per degrees squared) refer to the response density measured from the trough of the N1 wave to the peak of the P1 wave. The 61 hexagon responses were grouped into 5 concentric rings (R1-R5), as shown in Figure 1. The average amplitudes within concentric rings from the center (ring 1) to the periphery (ring 5) were generated by the mfERG software. The ring ratios of the mfERG were defined as ratios of the central hexagon amplitude (R1) to each of the peripheral ring amplitudes (R2 - R5). The mfERG was considered positive for HCQ retinopathy based on the following criteria: 1) increased R1/R2 ring ratio (defined as exceeding 2.5, the 99% confidence limit for the normal population),¹⁶ or (2) reduced R1 absolute amplitude (defined as less than 9.0 nv/deg², the 99% confidence limit for the normal population).¹⁷ The normal population values were derived from a set of 36 eyes of controls ranging from 22 – 67 years (mean: 44 years) with no known ocular disease tested on our machine. For each patient, the worse eye based on mfERG criteria was chosen as the study eye.

All MP tests had been performed using the Nidek MP1 (Nidek Technologies, Padova, Italy) with our institution's standardized acquisition protocol, as described below. The test grid comprised of 68 test loci covering the central 20° of the fovea (equivalent to the 10–2 visual field pattern) and a 4–2 threshold strategy was used. The fixation target was a 2° red cross while the test stimulus was white and was set to Goldmann size III (approximately 0.4° in diameter) with a duration of 200 milliseconds. The MP was considered as positive for HCQ retinopathy if there were 3 or more contiguous scotoma points (defined as any point with sensitivity 3 standard deviations below the normal mean)¹⁸ in the parafoveal region (between 2° and 4° of fixation). Figure 2 shows an example of a positive MP along with the corresponding mfERG.

Descriptive statistics were calculated for all data. Sensitivity, specificity, positive predictive value and negative predictive value of MP were determined using mfERG as the gold standard. All analyses were performed using SPSS Version 23 (Armonk, NY: IBM Corp.).

RESULTS

A total of 197 patients were included in the study (Table 1). All patients (99%) were taking HCQ due to SLE except 2 (Sjogren's syndrome and rheumatoid arthritis). The mean (SD) age was 50 ($\pm$ 13) years and 93% were female. The majority were Caucasian (49%) followed by African American (39%). The mean (SD) weight was 75 (19) kg, the mean (SD) daily dose was 5.2 (1.4) mg/kg, the mean (SD) cumulative dose was 1902 (1175) g and the mean (SD) duration of use was 14 (8) years. Visual acuity was mostly excellent, with a median (range) of 20/20 (20/12 – 20/80). Table 1 describes the clinical characteristics of all patients.

Twenty-two eyes (11%) were considered to have HCQ retinopathy according to the study criteria based on mfERG. The mean (SD) age of these patients was 54 (14) years and 96% were female. The mean (SD) weight was 69 (18) kg, the mean (SD) daily dose was 5.7 (1.3) mg/kg, the mean (SD) cumulative dose was 2041 (1548) g and the mean (SD) duration of use was 15 (10) years. The median (range) visual acuity was 20/32 (20/20 – 20/80). It should be noted though that this was based on standard Snellen chart with the patients' current correction, not the best corrected Early Treatment Diabetic Retinopathy (ETDRS) protocol. Table 2 describes the clinical characteristics as well as the mfERG and MP results of each of these patients.

MP was positive in 16 out of the 22 eyes with HCQ retinopathy, giving a sensitivity of 73%. Out of these, 3 (19%) eyes had an inferonasal scotoma, 6 (38%) eyes had an inferotemporal scotoma, 4 (25%) eyes had a superonasal scotoma and 2 (13%) eyes had a superotemporal scotoma. All scotomas corresponded to hexagons with reduced amplitude on mfERG. Except for 2 eyes, the mfERG abnormalities extended beyond the scotoma on MP. On the other hand, MP was negative in 162 of the 175 patients with no HCQ retinopathy, giving a specificity of 93%. The positive predictive value and the negative predictive value of MP were 53% and 96%, respectively.

DISCUSSION

HCQ use is becoming increasingly common, with some tertiary centers reporting rates as high as 90% of all SLE patients.¹⁹ With an expanding list of clinical indications, an increasing confidence amongst physicians to initiate long-term therapy, and a low incidence of systemic adverse effects requiring drug cessation, the number of patients requiring ophthalmological screening for HCQ retinopathy will inevitably increase in the near future.

The overall incidence of HCQ retinopathy using modern screening techniques has been reported to be around 7.5%, with the incidence directly proportional to the dose and duration of drug use.⁶ This is much higher than earlier estimates, which relied solely on clinical exam and visual fields. As the risk of long-term visual impairment is a direct function of the stage at which retinopathy is detected, it is important to develop screening protocols which can recognize any abnormalities as soon as possible.⁴

The first step towards formulating a screening protocol is to evaluate the sensitivity and specificity of each screening test. Browning et al. reported that 10–2 visual field, mfERG,

and SD-OCT have sensitivities of around 86%, 93% and 79% and specificities of around 93%, 97%, and 98%, respectively.²⁰ Our study is the first to report the sensitivity and specificity of MP in a large cohort of HCQ users. We found that MP has a sensitivity of 73%, which is lower than other tests, but a specificity of 93%, which is on par with them.

However, it is important to take certain aspects into consideration when comparing these estimates. First, the visual field testing by Browning et al had variations regarding the test target (white or red) and there is no clear definition as to what was considered as a positive test, which may have caused overestimation. Second, while our study had a similar prevalence of HCQ retinopathy to theirs, the method for determining HCQ retinopathy was different. This is understandable since, at present, there is no gold standard for diagnosing HCQ retinopathy and reference criteria differ from one study to the next. Browning et al. defined HCQ retinopathy as the discontinuation of the drug by the ophthalmologist and the prescribing physician based on the totality of the clinical evidence. There are certain issues with using that definition. Not only is there a certain degree of subjectivity and differences of opinion when it comes to interpreting clinical evidence, the threshold for discontinuing what is a potentially life-saving medication can vary widely between patients. Furthermore, using the totality of clinical evidence may not be an accurate representation since a physician may prefer one test over the other, which would disproportionately inflate that test's sensitivity. As such, we believed it would be better to use objective criteria.

MfERG has been used as a gold standard before in other studies since it is both an objective test as well as a direct measure of retinal function.^{16,17} Moreover, a recent systematic review suggested that it may have the ability to detect HCQ retinopathy earlier than other tests.²¹ Comparing one screening test with another is not the perfect way to analyze its independent utility since it induces circular reasoning. Additionally, the limitations of mfERG are well-documented, with some experts believing it may be too sensitive.²² Even so, with no established gold standard and the lack of consensus amongst experts on the matter, mfERG may be the best alternative available to us.

It is worth noting that the patient population for this study were taking an average daily dose of 5.2 mg/kg, which is minimally higher than the new recommended dose of 5.0 mg/kg.⁷ While this might contribute to the 11% incidence of retinopathy, one must remember that estimates for dosing are generally imperfect since they rely on data such as pills dispensed and are subject to patient compliance.⁶ Nevertheless, our data highlight the importance of dosing by patient weight.

We observed a slight predilection for the MP defect to involve the inferior retina, especially the inferiortemporal region, similar to the Humphrey's visual field.^{23,24} This predilection held true both for both true positives (56%) and false positives (62%). In the case of true positives, all MP defects corresponded to hexagons with reduced amplitude on mfERG, confirming the spatial correlation between the tests. However, except for 2 eyes, the mfERG was abnormal beyond the area of the scotoma, highlighting a relative lack of sensitivity for the MP.

The primary limitation of this study was the lack of conventional 10–2 visual field testing, which has been traditionally considered as the most sensitive test. Even though mfERG is considered similar in sensitivity and can provide objective confirmation of functional decline,^{25,26} 10–2 visual field is still currently recommended for primary screening,⁷ probably due to its easy availability and ease of interpretation. Unfortunately, comparisons of 10–2 visual field and MP have received minimal attention in the literature and doing so was beyond the scope of this study since they are considered clinically equivalent and consequently not ordered together in routine practice. A previous study comparing the two modalities in glaucoma patients did find that their results correlate well and that in some cases, MP was able to detect abnormal areas of retinal sensitivity that the 10–2 visual field did not.²⁷ However, a direct and prospective comparison between the modalities is needed to ascertain if those results translate for HCQ retinopathy as well.

It is also important to keep in mind that screening for HCQ retinopathy is usually performed by general ophthalmologists and not retina specialists.²⁸ As the MP requires expensive equipment and experienced personnel, it is not commonly available in all centers, and thus may not be suitable for routine primary screening. However, as with most other specialized tests, the primary utility of MP seems to be in its negative predictive value (96%), which can permit confident exclusion of HCQ retinopathy when the test is normal, in corroboration with other clinical characteristics and testing. This would be especially important for patients with high-risk factors or those with disparate results on different modalities where it may be difficult to make a definitive judgement.⁸ Since HCQ retinopathy is an irreversible condition, general ophthalmologists may err on the side of caution and recommend discontinuation of the drug if they see any cause for suspicion. However, considering the efficacy of the drug and the role it plays in decreasing patient morbidity and mortality, it is important to weigh the risks and benefits of treatment cessation and to work in conjunction with the patient, their primary care provider and their rheumatologist. In situations where the decision is not clear-cut, patients should be referred to retina specialists who have more experience with the condition. This is where MP may be useful, by providing important clinical information when it comes to deciding whether or not to stop HCQ for such patients.

Another possible limitation of this study was the fact that we only considered HCQ retinopathy as a parafoveal entity whereas Asian eyes are typically affected in a more peripheral pattern.^{29,30} Despite the fact, we do not expect that to affect our results since only 2% of our patients were Asians and all of them had normal testing on both modalities.

In conclusion, this study demonstrates that MP has a slightly inferior sensitivity yet a comparable specificity in detecting HCQ retinopathy. Therefore, for patients with high-risk factors or with uncertainty regarding diagnosis, MP may be a useful ancillary test.

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Abbreviated Title:**HCQR**

Microperimetry screening for

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Figure 1. Multifocal electroretinogram with 61-hexagon stimuli arranged in rings from R1-R5. Each hexagon comprises a waveform with a negative trough (N1) followed by a positive peak (P1) followed by another negative trough (N2). The amplitude (nanovolts per degrees squared) refers to the response density measured from the trough of the N1 wave to the peak of the P1 wave.

Figure 2. Microperimetry test graded positive for hydroxychloroquine retinopathy with corresponding multifocal electroretinogram.

Table 1.

Clinical Characteristics

Characteristic	HCQ retinopathy* (n=22)	No HCQ Retinopathy (n=175)
Age (years), mean (SD)	54 (14)	50 (13)
Females, n (%)	21 (96)	162 (93)
Race, n (%)	7 (32)	90 (51)
Caucasian	12 (55)	64 (37)
African American	3 (13)	21 (12)
Other		
Weight (kg), mean (SD)	69 (18)	76 (19)
Duration of HCQ Use (years), mean (SD)	15 (10)	14 (8)
Daily Dose (mg/kg), mean (SD)	5.7 (1.3)	5.2 (1.4)
Cumulative Dose (g), mean (SD)	2041 (1548)	1885 (1123)
Visual Acuity (Snellen), median (range)	20/20 (20/125 –20/16)	20/20 (20/125 –20/12)

* As identified using mfERG criteria

Table 2:

Patients with HCQ retinopathy*

Patient ID	Age (yrs)	Sex	Weight (kg)	Duration (years)	Daily Dose (mg/kg)	Cumulative Dose (g)	Visual Acuity	mfERG			MP
								R1 (nv/deg ²)	R2 (nv/deg ²)	R1/R2	
31	59	M	66	21	6.1	3066	20/20	8.7	5.1	1.7	Positive
32	42	F	48	13	4.2	949	20/25	7.8	4.2	1.9	Positive
40	45	F	67	7	6.0	1022	20/32	20.0	7.3	2.7	Positive
62	66	F	86	11	4.6	1606	20/25	7.4	2.9	2.6	Negative
69	56	F	76	12	5.3	1752	20/25	24.4	9.5	2.6	Positive
73	38	F	70	10	5.8	1460	20/80	8.1	5.6	1.4	Positive
76	26	F	57	10	5.9	1241	20/25	8.9	4.8	1.9	Negative
100	54	F	71	33	5.6	4818	20/63	4.6	4.0	1.2	Positive
107	58	F	105	5	3.8	730	20/40	8.4	6.2	1.4	Negative
114	45	F	102	5	3.9	730	20/20	19.8	7.7	2.6	Positive
122	63	F	65	8	6.2	1168	20/32	9.7	3.5	2.8	Negative
139	76	F	101	16	4.0	2336	20/40	6.2	3.4	1.8	Positive
141	31	F	76	19	5.2	2774	20/20	18.9	3.3	5.7	Positive
146	68	F	67	12	6.0	1752	20/32	4.2	1.6	2.6	Positive
147	56	F	80	47	5.0	6862	20/20	5.4	3.8	1.4	Positive
156	68	F	62	14	6.4	2044	20/50	7.0	8.0	0.9	Positive
159	40	F	44	5	9.1	730	20/25	7.7	5.6	1.4	Negative
173	57	F	46	15	4.5	1133	20/20	8.8	8.6	1.0	Positive
177	71	F	55	30	7.2	4380	20/40	4.5	3.4	1.3	Positive
186	74	F	73	15	5.5	2190	20/32	8.4	8.0	1.1	Positive
189	60	F	54	9	7.4	1314	20/50	8.9	9.5	0.9	Negative
193	33	F	53	6	7.4	854	20/40	5.3	5.3	1.0	Positive

* As identified using mfERG criteria (abnormal values in bold)