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Value of Microperimetry in Detecting Early Retinal Toxicity of Hydroxychloroquine in Children with Juvenile Systemic Lupus Erythematosus

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Abstract
Purpose: To evaluate retinal sensitivity in children who are on hydroxychloroquine (HCQ) for systemic lupus erythematosus using microperimetry and compare the results with those of the Humphrey visual field (HVF) 10-2 and spectral-domain optical coherence tomography (SD-OCT). ***Procedure:*** A case-control cross-sectional study including 19 patients (less than 18 years old) on HCQ for at least 5 years. Controls were 21 normal children. Participants underwent a complete ophthalmic examination, then were investigated using HVF 10-2, SD-OCT, and microperimetry. ***Results:*** Ocular examination revealed no abnormalities. The overall mean microperimetry sensitivity of the patients (15.75 dB) was not significantly different from that of the controls (16.35 dB). The HVF 10-2 showed a significant difference in the mean deviation of the patients. ***Conclusions and Message:*** Microperimetry was not more revealing than HVF 10-2 and SD-OCT. Larger studies are required to compare the diagnostic accuracy of screening modalities of retinal toxicity in children on HCQ.

Introduction

Long-term hydroxychloroquine (HCQ) therapy has become a cornerstone in the treatment of several chronic autoimmune diseases in children such as juvenile systemic lupus erythematosus (JSLE) [1]. In 2011, the American Academy of Ophthalmology (AAO) recommended annual screening for patients taking HCQ for more than 5 years with automated 10-2 visual field and, where available, testing with one or more of the following objective tests: spectral-domain optical coherence tomography (SD-OCT), multifocal electroretinogram, or fundus autofluorescence [2].

In 2016, these recommendations have been revised and automated visual fields plus SD-OCT have been recommended as primary screening tests [3]. Nevertheless, neither of these recommendations has provided specific guidelines for pediatric patients, probably due to lack of primary literature about retinal toxicity in children.

Fundamental differences in pharmacokinetics as well as in retinal physiology and anatomy and longer life span likely result in differences in the toxic threshold in children compared to adults. Studies are extremely needed to create a comprehensive evidence-based screening program for children on HCQ therapy [1].

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Microperimetry refers to field testing with simultaneous fundus visualization, hence obtaining the exact correlation between functional deficits and corresponding morphological changes. The microperimeter allows a precise evaluation of macular sensitivity, providing an accurate detection of small scotomas [4]. Moreover, it incorporates an automated ocular tracking system that compensates for eye movement under real-time conditions, which is of special importance in children [5].

This study aims at evaluating retinal sensitivity in children who are on HCQ therapy using microperimetry and to compare the results with the data obtained from Humphrey visual field (HVF) 10-2 and SD-OCT as recommended by the AAO to find out whether it can be a better option for detecting early retinal toxicity in children.

Patients and Methods

The study protocol was approved by the Cairo University Hospital Research Committee. The study and data collection conformed to all local laws and were compliant with the principles of the Declaration of Helsinki. This is a cross-sectional case-control study that was carried out on 40 children (<18 years old) in the period from September 2014 till April 2015.

Nineteen children diagnosed with JSLE, based on the preliminary American College of Rheumatology diagnostic criteria [6], and having been treated with a maximum daily HCQ dose of 5 mg/kg or less for a minimum of 5 years, were included in the study. All patients were recruited and examined in the pediatric rheumatology and the pediatric ophthalmology clinics of Abourich Hospital, Cairo University.

The control group included 21 age- and sex-matched healthy children who were coming to the pediatric ophthalmology outpatient clinic seeking for glasses or having trivial ocular complaints. An informed consent was signed by the participants' guardians.

Real body weight, daily dose of HCQ, duration of treatment, and cumulative dose were recorded for all patients. All participants were thoroughly examined. Ophthalmological examination included measurement of best-corrected visual acuity (BCVA), Goldmann applanation tonometry for intraocular pressure measurement, color vision testing using Ishihara pseudoisochromatic color plates, slit-lamp biomicroscopy, and dilated fundus examination. Patients with visual complaints or BCVA worse than 20/25, history of diabetes or hypertension, or any macular diseases, including HCQ retinopathy, were excluded from the study. Patients who met the inclusion criteria and had normal fundus examination underwent HVF 10-2, microperimetry, and SD-OCT testing.

Microperimetry Testing

Microperimetry was performed using the OPTOS Spectral OCT/SLO (scanning laser ophthalmoscope) Combination Imaging System (OPTOS, Inc., FL, USA) by the same examiner (A.I.H.). The test was conducted in a dark room. Following dilation with 2.5% phenylephrine and 1% tropicamide, the participants were asked to fixate on a red square while occluding the contralateral eye. They were instructed to press a button whenever they saw the stimulus, which consisted of a spot of light that is equivalent to the Goldmann III. The polar 3–12° pattern was used, which consists of 28 points arranged into 3 concentric circles (2.3°, 6.6°, and 11°). The inner circle is made of 4 points, while the middle and outer circles are composed of 12 points each (Fig. 1). The participant's sensitivity threshold was estimated at each point using a 4-2 staircase strategy.

SD-OCT Retinal Thickness Mapping

SD-OCT was then performed using the same instrument to capture both OCT and SLO images with an axial resolution of <10 μm, and a transverse resolution of 20 μm. SLO fundus image was used for alignment and registration of the OCT topographic maps. The scan protocols used were the Line scan (B-scan) and the 3-Dimensional Retinal Topography. The topography scan consisted of 200 scan lines, with 200 A-scans per line with a total of 40,000 A-scans in the area scanned. Retinal thickness values in the macula were displayed in 3 concentric circles (central, inner, and outer). The circles were centered on the fovea with diameters of 1, 3, and 6 mm, respectively. The inner and outer circles were divided into superior, temporal, inferior, and nasal subregions. Retinal thickness was averaged for the area within the central circle, inner (parafoveal) and outer (perifoveal) circles. After retinal thickness and microperimetry maps were generated, the built-in software aligned both maps so that the retinal sensitivity measured at each location was assigned to the corresponding thickness for that segment.

Humphrey 10-2 Visual Field

Visual field testing was done using standard 10-2 white III program (Humphrey perimeter; Zeiss, USA). It was done 1 or 2 days after microperimetry testing to avoid exhaustion of participants.

Statistical Methods

Statistical analysis was done using IBM SPSS v.22 (SPSS Inc., Chicago, IL, USA). Metric variables were described in the form of means ± standard deviation, categorical variables in the form of counts. Metric variables were analyzed using unpaired *t* test or Mann-Whitney test for variables that violated the normality assumption, categorical variables using Fisher exact test. Nonparametric Spearman was used to assess the correlation between microperimetry retinal sensitivity and HCQ dosage and exposure time. *p* values less than 0.05 were considered significant.

Results

Demographic Characteristics

The current study included 19 children diagnosed with JSLE; 15 girls and 4 boys with a mean age 14.37 ± 2.03 years. All of them had been treated with HCQ for a minimum duration of 5 years. The control group included 21 children; 15 girls and 6 boys with a mean age 13.94 ± 2.32 years. A summary of the clinical data is provided in Table 1.

The duration of HCQ exposure ranged from 5 to 10 years (median 5 years). The average maximum daily dose

for the patients was 293.47 ± 61.65 mg with an average cumulative dose of 6,086.46 ± 2,412.42 g. The fundus examination and color vision were normal for all patients.

All further analysis was based on the average value of the 2 eyes as no statistical significance was found between both eyes in parameters measured in 10-2 visual field, OCT thickness map, and microperimetry.

Humphrey 10-2 Visual Field

The pattern deviation maps showed no evidence of retinopathy in all patients. However, the overall retinal sensitivity as represented by mean deviation value was significantly reduced in patients (mean –2.0 ± 0.9 dB) compared to that of controls (mean –0.9 ± 1.6 dB) with $p = 0.009$. Similarly, pattern standard deviation value was reduced in patients (mean 1.2 ± 0.2 dB) when compared to controls (mean 1.4 ± 0.6 dB), but this difference lacks statistical significance ($p = 0.790$).

SD-OCT Retinal Thickness Mapping

The average foveal thickness measured in the central circle for patients (192.9 ± 20.0 μm) was not significantly different from controls (193.0 ± 16.9 μm) with $p = 0.883$. Additionally, the average parafoveal and perifoveal thicknesses were not significantly different for the patients (264.2 ± 16.7 μm and 287.2 ± 17.9 μm, respectively) as compared to the controls (266.2 ± 17.9 μm and 279.5 ± 19.8 μm, respectively; $p = 0.461$ and 0.428, respectively).

Microperimetry Data

The overall retinal sensitivity values for the patients (15.8 ± 1.2 dB) and controls (16.4 ± 0.9 dB) were not significantly different ($p = 0.187$). Similarly, the retinal sensitivity at the inner (15.9 ± 1.6 dB vs. 16.9 ± 1.1 dB), middle (16.0 ± 1.4 dB vs. 16.3 ± 0.7 dB), and outer rings (15.1 ± 1.6 dB vs. 15.9 ± 0.9 dB) were also lower for patients versus controls, but this difference was statistically insignificant ($p = 0.75$, 0.798, and 0.1, respectively). No significant relationship was found between the overall retinal sensitivity and either duration of exposure ($p = 0.499$), daily dose ($p = 0.906$), or cumulative dose ($p = 0.303$).

Discussion

In 2016, recommendations on screening of chloroquine (CQ) and HCQ retinopathy have been revised and released by the AAO in light of new data concerning prevalence of toxicity, risk factors, racial differences, and efficacy of screening tests [3].

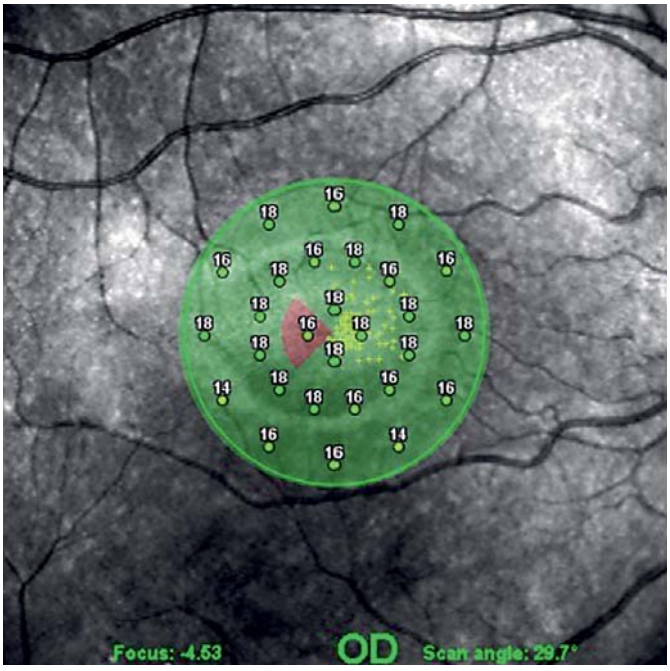

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Fig. 1. Microperimetry polar 3–12° test (patient No. 15) superimposed on scanning laser ophthalmoscope infrared image. The test points are arranged within the macula showing sensitivity values in 3 concentric circles centered on the fovea, with a mean retinal sensitivity of 16.9 dB.

Table 1. Clinical data of patients

Serial number	Age, years	Sex	Years of exposure	Maximum daily dose of HCQ, mg/day	Cumulative dose, g
1	13	F	5	258	4,700.00
2	16	F	5	300	5,400.00
3	15	F	8	318	9,000.00
4	17	F	10	312	9,500.00
5	13	F	5	252	4,650.00
6	11	F	7	159	4,050.00
7	15	F	5	318	6,900.00
8	16	F	5	324	2,371.68
9	16	F	5	318	5,800.00
10	12	F	7	252	6,400.00
11	14	F	5	306	5,500.00
12	15	F	7	324	8,200.00
13	17	M	8	384	9,995.00
14	16	F	7	294	7,500.00
15	14	M	8	315	9,000.00
16	10	F	5	192	1,756.00
17	15	M	5	390	7,000.00
18	16	M	5	360	5,000.00
19	12	F	5	200	2,920.00

HCQ, hydroxychloroquine.

The new recommendations consider microperimetry as a test that should be useful and more valuable than automated perimetry theoretically, but practically it is similarly complicated and has not proven as yet to be more revealing [3].

This study was conducted before the release of the new recommendations. We were comparing the results of HVF 10-2 and SD-OCT with those of microperimetry between pediatric patients receiving HCQ for more than 5 years and visually normal controls.

In our study, overall retinal sensitivity as well as retinal sensitivity at the inner, middle, and outer rings, as measured by microperimetry, was reduced in patients when compared to controls; however, this difference lacked statistical significance.

These results were contradictory to the results of two studies [7, 8] that were conducted in 2013 and used microperimetry as a novel screening test for retinal toxicity caused by antimalarial drugs. Both studies concluded that microperimetry, though not being a recommended test of screening, could provide important information regarding visual function in patients on HCQ therapy [7, 8].

Our study was different in many aspects, the most important of which is study population. In both studies, patients were adults and were treated with HCQ for different autoimmune diseases, not SLE only [7, 8]. Literature to date regarding relation of age to HCQ toxicity is deficient and paradoxical. A recent demographic study found that age is not correlated with retinal toxicity [9]. However, in newly released AAO recommendations on screening, age has been considered as a lesser risk factor as aged tissue could be less resistant to the toxic effect of a drug [3].

Moreover, in the study conducted by Jivrajka and colleagues [7], patients were of different races. Racial differences do have an impact on pattern of toxicity, where a pericentral pattern of HCQ toxicity was described in Korean and Asian patients rather than the traditional parafoveal pattern [10]. That is why wider HVF programs (24-2 or 30-2) are recommended for Asian patients [3].

In the study done by Martínez-Costa and associates [8], they included patients receiving CQ as well and they did not exclude patients already having CQ/HCQ retinal toxicity, which might have led to biased results. Another important difference is that they used a different microperimetry machine covering only the central 10° and recorded 3 different indices which were average threshold, fixation stability, and macular integrity [8].

Using HVF (10-2), toxicity means partial or full ring scotomas, mainly involving the parafoveal region, which can be evaluated by pattern deviation [11]. None of our patients showed such signs on HVF. However, we believe that mean deviation value, being a representative of overall retinal sensitivity, may also be helpful. In our study, a statistical significant difference was found between patients and controls in mean deviation but not in pattern standard deviation.

For SD-OCT, toxicity is usually detected by parafoveal thinning of the outer retina and loss of photoreceptor outer segment marker lines [12]. None of our patients had these abnormalities.

In summary, the only parameter that was statistically significantly different between patients and controls was mean deviation measured by HVF; however, being a sign of toxicity in absence of pattern deviation abnormalities remains to be verified. Microperimetry and OCT-SD parameters have not been more revealing.

This discrepancy in results of different screening tests is more or less in line with the study conducted by Marmor [13], who compared the results of individual screening tests (not including microperimetry) of early HCQ retinopathy and concluded that patients are more or less sensitive to different tests. He recommended using multiple screening modalities for more definitive results when there is a concern for toxicity [13]. Accordingly, one should bear in mind that there is no established gold standard test for screening. Although it is crucial to be sensitive to signs of toxicity, it is equally important to verify such signs with more than one test or by repeating the same test [3].

This is of particular importance in children as daily dose and duration of use are considered major risk factors for toxicity [3, 9]. Given the longer life span of children when compared to adults, they are, at least theoretically, at higher risk due to longer duration of drug use.

One of the major limitations of this study is small sample size, which is due to the strict inclusion criteria used. To the best of our knowledge, this is the first study that uses microperimetry for screening of HCQ toxicity in children. Large-scale demographic studies are required to identify risk factors for the development of HCQ toxicity in children. Moreover, larger prospective studies should be conducted to compare the diagnostic accuracy of different screening modalities in the detection of early HCQ toxicity in children. Therefore, a comprehensive evidence-based program could be tailored for screening of children on HCQ therapy.

Disclosure Statement

The authors declare no conflict of interest.

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