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Electroretinography Findings in Patients Treated with Hydroxychloroquine

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ABSTRACT

Background: Hydroxychloroquine (HCQ) is frequently prescribed for managing rheumatic diseases such as systemic lupus erythematosus and rheumatoid arthritis. However, prolonged use of HCQ has been linked to retinal toxicity.
Objective: To assess retinal changes in patients receiving HCQ treatment using multifocal electroretinogram (mfERG).
Methods: This cross-sectional study included forty Egyptian patients with a history of one year or more of HCQ intake for conditions like systemic lupus erythematosus or rheumatoid arthritis. Patients underwent complete ophthalmic examinations and were subsequently evaluated using multifocal electroretinogram.
Results: There was no statistically significant difference in multifocal ERG abnormalities concerning the age distribution among the studied patients ($P>0.05$). However, a statistically significant difference was observed between mfERG abnormalities and the duration of HCQ treatment ($P<0.05$). Notably, patients with paracentral depression had the longest treatment duration.
Conclusions: The study findings indicate that multifocal ERG serves as a valuable screening tool for early detection of HCQ retinopathy, detecting signal depression, primarily in the paracentral region, in patients treated with HCQ for over 5 years. Importantly, even visually asymptomatic patients with no fundus abnormalities may exhibit abnormal results on mfERG.
Keywords: Electroretinography, Hydroxychloroquine, Multifocal Electroretinogram.

INTRODUCTION

Hydroxychloroquine (HCQ) is a derivative of chloroquine used primarily for rheumatologic conditions like lupus and arthritis [1]. Its expanding use includes dermatological disorders and pediatric inflammatory conditions. HCQ has shown benefits in reducing diabetes, thrombosis risk, and preserving renal function in lupus patients [2].

Administered orally as a 200 mg sulfate tablet, HCQ reaches peak concentrations within 3–5 hours. Its retinal toxicity mechanism involves inhibiting retinol uptake, leading to potential visual cycle disruption and RPE permeability [3].

Long-term use can cause HCQ retinopathy due to accumulation in ocular tissues, affecting retinal and photoreceptor cells. Screening for retinal toxicity is recommended after 5 years of therapy or earlier if additional risk factors are present, as per American Academy of Ophthalmology guidelines [4, 5].

Multifocal electroretinography (mfERG) stands out as a sensitive test for detecting early HCQ-related retinal changes, surpassing other tests like visual field analysis, autofluorescence, and Optical Coherence Tomography (OCT). It can reveal subtle electrophysiological alterations preceding visible retinopathy, making it crucial for early detection [6-8].

The goal of this study is to evaluate retinal changes in patients treated with HCQ using mfERG.

PATIENTS AND METHODS

This cross-sectional study involved forty Egyptian individuals with a history of one year or more of hydroxychloroquine intake due to rheumatic diseases like systemic lupus erythematous or rheumatoid arthritis selected from Department of Ophthalmology at Benha University Hospital. This study evaluates the abnormal results of mf ERG in patients treated with HCQ. The study was performed over one-year period January 2022 to January 2023.

Ethical considerations:

The study was done after being accepted by the Research Ethics Committee, Benha University (Approval code: MS-98-10-2021). All patients included in this study provided written informed consent prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring that their confidentiality and privacy would be protected. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The patients included in the study were adult patients over 18 years. Both sexes were included. Patients with rheumatic disease as rheumatoid arthritis and systemic lupus erythematosus. Patients treated with HCQ for 1 year duration or more.

Patients with refractive error spherical equivalent > 4.00 diopter, patients with elevated intraocular pressure, previous eye surgery, previous ocular inflammations or trauma, systemic vascular diseases, patients with renal disease, patients with diabetes mellitus, patients who refused to participate in the study and uncooperative patients were excluded.

All patients were allocated to history taking involving: Personal history: Name, age, sex, residence and occupation. Past history: history of previous medical illness, history of wearing glasses, history of previous ocular investigations. Present history:

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Patient's first complaint, onset of the disease, duration and its progression, history of rheumatic disease and drugs taken (type and duration). Complete ophthalmic examinations were performed to all patients: Uncorrected and best corrected visual acuity assessment. Slit-Lamp biomicroscopic examination: full examination of the anterior segment (cornea, sclera, anterior chamber, iris, pupil and lens) to exclude any abnormalities that may affect patient visualization of the stimuli or response. Intraocular pressure measurement using Goldmann applanation tonometer and fundus examination using indirect ophthalmology (+20 D) and silt lamp biomicroscopy with + 78 diopters lens to exclude patients with fundus pigmentary changes suggesting HCQ toxicity.

Multifocal ERG of the retina:

Retinal multifocal ERG (mfERG) was conducted following ISCEV guidelines using the RETI-scan system. Prior to recording, 1% tropicamide eye drops was used to dilate the pupils. Subjects adapted to room light for 15 minutes, received topical anesthesia, and were directed to fixate on a target to minimize eye movement.

Fiber electrodes on the conjunctiva near the cornea and reference electrodes near the outer canthus were used. Ground electrodes on the forehead were connected to the recording system. Electrical activity from the central retina was recorded during stimulation, and responses were calculated using a cross-correlation technique.

Average responses per hexagon within five rings (zero to 25 degrees) were calculated. Abnormal responses were categorized as paracentral, central, peripheral, or generalized depression. P1-wave amplitude was measured in nV/deg2, while the P1-wave peak implicit time was expressed in ms.

Statistical Analysis

Data were coded, entered, and analyzed using IBM SPSS 23.0 for Windows (SPSS Inc., Chicago, IL, USA) and the jamovi project (Version 2.3, 2022). Quantitative data were presented as mean, median, range, and standard deviation (SD) and were assessed using the Kruskal–Wallis test. Qualitative variables were expressed as numbers (n) and percentages (%). A p-value < 0.05 was considered statistically significant.

RESULTS

The mean HCQ treatment duration was 5.05 years and dose of HCQ was 400 mg/day **(Table 1)**.

Table 1: Hydroxychloroquine treatment duration, Dose of HCQ and drugs taken of included patients.

	Patients (n=40)
HCQ treatment duration (Years) Mean ±SD Median (range)	 5.05±2.87 4 (2-10)
Dose of HCQ	400 mg/d

The most common abnormality among patients was paracentral depression (35%) in the right eye and 25% of patients had central and paracentral depression in the left eye **(Table 2)**.

Table 2: Frequency of multifocal ERG abnormalities among studied patients (N=40)

	Right Eye N. %	Left Eye N.%
Normal response	8 (20%)	8 (20%)
Paracentral depression	14 (35%)	8 (20%)
Peripheral depression	6 (15%)	8 (20%)
Central and paracentral depression	6 (15%)	10 (25%)
Central and peripheral depression	2 (5%)	2 (5%)
Generalized depression	4 (10%)	4 (10%)

Multifocal ERG abnormalities of right eye in relation to rheumatic diseases demonstrated that most of RA patients (43.7%) had paracentral depression, while 25% of SLE patients had peripheral, central and paracentral depression. **(Table 3)**.

While in the left eye it showed that 25% of RA patients had paracentral, central and paracentral depression, also 25% of SLE patients had peripheral, central and paracentral **(Table 3)**.

Table 3: Multifocal ERG abnormalities of right eye and left eye in relation to rheumatic diseases.

Right Eye	RA N=32 N. %	SLE N=8 N.%
Normal response	4 (12.5%)	4 (50%)
Paracentral depression	14 (43.7%)	0 (0%)
Peripheral depression	4 (12.5%)	2 (25%)
Central and paracentral depression	4 (12.5%)	2 (25%)
Central and peripheral depression	2 (6.3%)	0 (0%)
Generalized depression	4 (12.5%)	0 (0%)
Left Eye	**RA N=32 N. %**	**SLE N=8 N.%**
Normal response	4 (12.5%)	4 (50%)
Paracentral depression	8 (25%)	0 (0%)
Peripheral depression	6 (18.7%)	2 (25%)
Central and paracentral depression	8 (25%)	2 (25%)
Central and peripheral depression	2 (6.3%)	0 (0%)
Generalized depression	4 (12.5%)	0 (0%)

There was no statistically significant difference between multifocal ERG abnormalities of right and left eye in relation to age distribution among studied patients **(Table 4)**.

Table 4: Multifocal ERG abnormalities of right eye and left eye in relation to age among studied groups.

Right Eye	Age Median (range)	P-value
Normal response (n=8)	35 (25-55)	0.2
Paracentral depression (n=14)	41 (29-52)	
Peripheral depression (n=6)	45 (38-50)	
Central and peripheral depression (n=2)	44 (44-48)	
entral and paracentral depressio (n=6)	50 (44-56)	
Generalized depression (n=4)	55.5 (53-58)	
Left Eye	Age Median (range)	P-value
Normal response (n=8)	35 (25-44)	0.08
Paracentral depression (n=8)	40 (38-55)	
Peripheral depression (n=8)	51 (29-55)	
Central and peripheral depression (n=2)	44 (44-48)	
entral and paracentral depressio (n=10)	57 (36-58)	
Generalized depression (n=4)	39 (32-45)	

MfERG abnormalities in relation to HCQ treatment duration among studied groups showed that patients with paracentral depression had the highest HCQ treatment duration and this difference was statistically significant **(Table 5)**.

Table 5: Multifocal ERG abnormalities of right eye and left eye in relation to HCQ treatment duration among studied groups

Right Eye	Duration of HCQ intake Median (range)	P-value*
Normal response (n=8)	2 (2-8)	0.03
Paracentral depression (n=14)	9 (6-10)	
Peripheral depression (n=6)	5 (2-10)	
Central and peripheral depression (n=2)	3 (3-5)	
Central and paracentral depression (n=6)	6 (2-10)	
Generalized depression (n=4)	5 (6-10)	
Left Eye	Duration of HCQ intake Median (range)	P-value*
Normal response (n=8)	2.5 (2-4)	0.02
aracentral depression (n=8)	9 (2-10)	
Peripheral depression (n=8)	4.5 (2-10)	
Central and peripheral depression (n=2)	3 (3-5)	
Central and paracentral depression (n=10)	5 (2-10)	
Generalized depression (n=4)	6 (5-10)	

*: Statistically significant difference, post hoc test was used to compare each group.

DISCUSSION

In the right eye, 50% showed paracentral depression in mfERG signals: 35% paracentral, 15% central and paracentral, with 20% normal response, 15% peripheral, 5% peripheral and central, and 10% generalized depression. For the left eye, 45% exhibited paracentral depression: 25% paracentral and central, 20% paracentral, 20% peripheral, 20% normal response, 10% generalized, and 5% peripheral and central depression. Damage in mfERG was categorized as central, paracentral, pericentral, and peripheral, based on specific criteria within rings from the fovea to the middle periphery [9].

A study compared between fundus autofluorescence and (mfERG) for early detection of retinal alterations in 25 patients using chloroquine (HCQ) treatment (duration, more than 1 year). The (mfERG), pericentral, central, or generalized amplitude reductions were detected in all patients with FAF abnormalities and in an additional four patients with normal FAF. Also revised recommendation on screening for chloroquine and HCQ mentioned that mfERG can objectively document localized paracentral ERG depression in early CQ and HCQ retinopathy [5,10].

In the present study, the right eye of (43.7%) of RA patients had paracentral depression, while (25%) of SLE patients had peripheral, and (25%) had central and paracentral depression. However, the left eye of (25%) of RA patients had paracentral and (25%) had central and paracentral depression, also (25%) of SLE patients had peripheral and (25%) had central and paracentral depression. (50%) in the SLE and only (12.5%) of RA patients had normal response in each eye, this may indicate that retinopathy in RA patient has a higher rate than in those with SLE but probably because SLE patients had a history of a drug duration below five years and represent only (20%) of the sample size.

In the line with our study results, a prospective and comparative study included patients who were using HCQ for the treatment of SLE (35 patients) and RA (40 patients) and healthy subjects who were not using any drugs and their results revealed that HCQ use caused retinal toxicity more frequently in RA patients compared to SLE patients. This result may relate to the mean HCQ exposure time, which is 7 months longer in RA patients. On the contrary in another study conducted by a study included 110 patients with a mean age of 43.5±10.1 years and predominantly females aimed to estimate the prevalence of HCQ retinopathy in a cohort of Indian patients and analyze the associated factors demonstrated that there was no significant association between underlying rheumatological disease and the occurrence of HCQ retinopathy similar to other study by **Browning and Lee** [11-13].

According to statistical analysis of the current study there was no statistically significant difference between multifocal ERG abnormalities of both eyes in relation to age distribution among studied patients.

A study included thirty-five eyes of 35 female SLE patients with a mean age of 57.02 ± 4.33 years (SLE group), 40 eyes of 40 female RA patients with a mean age of 59.23 ± 3.24 years (RA group) and 20 eyes of 20 healthy female subjects with a mean age of 56.17 ± 4.13 years (control group) were included in this study. There was no statistically significant difference in mean age and gender between groups (P>0.05). A study reported that the age was excluded as an independent 'major risk factor' in the AAO revised guidelines, 2016 although it was considered a major risk factor in the 2011 AAO guidelines. One study of 32 individuals taking HCQ found that electroretinography was able to detect changes over the course of treatment in elderly patients (over 65 years), not present in younger patients. Maculopathy, and deteriorating renal function may be associated with increasing age and both considered independent major risk factors [11,14].

Regarding current study, there was statistically significant difference between ERG abnormalities in relation to HCQ treatment duration (P<0.05). Eight patients with normal response; six of them were taking HCQ for less than 5 years and only two cases more than 5 years at right eye, while at the left eye all patients with normal response were taking HCQ for duration less than 5 years. Despite that MfERG abnormalities were detected in 14 cases with HCQ usage less than 5 years. Also, abnormal responses were detected in all patients above 5 years; only two cases made the exception by having unilateral normal response with HCQ usage duration more than 5 years. Patients with paracentral depression had the highest duration of HCQ intake.

In the line with our results, a study concluded that the risk of toxicity has been found to be associated with the duration of HCQ use. It was shown that the toxicity incidence was very low within the first 5 years of use and could increase rapidly after 5 years to 1%. However, the toxicity incidence may be higher (ranged from 20 to 60%) even less than 5 years of CQ/HCQ usage when using (mfERG) as a screening tool [15, 16].

A landmark epidemiological study included patients who had used HCQ continuously for greater than 5 years. The overall prevalence of HCQ retinopathy in this study was 7.5% but increased to around 20% after 20 years of therapy. Duration of use >5 years is considered one of the major risk factors for HCQ retinopathy [5].

Brilliant study was conducted to localize the damage in progressive HCQ retinopathy on and off the drug and concluded that outer retinal thinning while using HCQ initially involves the parafovea but becomes diffuse across the macula as damage progresses or after drug cessation [17].

Another study was performed to evaluate HCQ retinopathy by using mf ERG concluded that multifocal ERG objectively demonstrates depression of signals in the perifoveal region in visually symptomatic patients with long-term HCQ use. Even patients with normal visual acuity and no fundus abnormalities can have abnormal results [18].

CONCLUSION

Based on the study results, it can be concluded that multifocal ERG is an objective test that detected depression of signals mostly in paracentral region in patient treated with HCQ for period more than 5 years, even if the patients were visually asymptomatic and had no fundus abnormalities they can have abnormal results. Multifocal ERG is a good screening test that may help in early detection of HCQ retinopathy before toxicity is clinically apparent.

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