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OCULAR CHANGES IN PATIENTS ON LONG TERM TREATMENT WITH HYDROXYCHLOROQUINE

Anuradha Singh[1], Sagarika Patyal[2], Vivek Vasudev[3], Vijay Sharma[4], Hemant Singh Trehan[5]

[1]*167 Military Hospital, Pathankot, Punjab, India*
[2] *Centre for Sight, New Delhi, India*
[3] *Military Hospital Bhopal, Madhya Pradesh, India*
[4] *Command Hospital (Eastern Command), Kolkata, West Bengal, India*
[5]*Command Hospital (Air Force), Bangalore, Karnataka, India*

Abstract

Introduction: *To study the ocular changes in patients on long term treatment with Hydroxychloroquine (HCQ); and detect means for early detection of toxicity.*

Methods: *We conducted a cross-sectional observational study at a tertiary care hospital, in which 100 patients, male and female, aged 35 years or more, taking HCQ for 5 years or more were included. Patients with any known ocular or systemic diseases were not included. Indication, dosage, duration and cumulative dose of HCQ intake were recorded. History of ocular symptoms, visual acuity, colour vision, complete ophthalmic examination, visual field using Amsler grid and 10-2 Humphrey's automated fields (HVF), Spectral Domain Optical Coherence Tomography (SD-OCT), colour fundus photography, fundus fluorescein angiography (FFA) and fundus autofluorescence (FAF) were recorded. The data was analyzed using descriptive and inferential analysis.*

Result: *15% of the study population showed signs of HCQ related ocular toxicity. 17%, 21% and 10% patients had abnormal SD-OCT, HVF and FAF findings respectively.*

Conclusion: *HCQ related ocular toxicity has been found in patients in the absence of symptoms. Objective tests like HVF, SD- OCT and FAF were more useful in early detection of toxicity than subjective tests such as Amsler grid, colour vision and FFA.*

Keywords: Hydroxychloroquine, Bull's eye maculopathy, Spectral Domain Optical Coherence Tomography, Fundus autofluorescence

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Correspondence to:
Anuradha Singh,
167 Military Hospital ,
Pathankot, Punjab, India
anuradha9000@gmail.com

INTRODUCTION

The eyes are target organs for damage from many systemic drugs such as Chloroquine, Hydroxychloroquine, Vigabatrin, Isotretinoin, Topiramate, Ethambutol, Amiodarone, herbal medication like Gingko biloba.[1] Hydroxychloroquine (HCQ), a drug initially developed as an antimalarial, was soon found to be effective in the treatment of a variety of systemic diseases, like rheumatoid arthritis, ankylosing spondylosis, systemic lupus erythematosus, discoid lupus, sarcoidosis, Sjogren's syndrome, photosensitivity disorders.[2,3]

It initially replaced chloroquine due to irreversible adverse effects of the latter. However, subsequently, HCQ was also found to have irreversible ocular side effects, especially retinal toxicity. It has been estimated that the prevalence of ocular toxicity due to HCQ is about 7.5% in patients taking the drug for over 5 years.[4]

The mechanism of toxicity with HCQ is not fully elucidated. The earliest changes appear to occur in the cytoplasm of photoreceptors and ganglion cells. Later, the retinal pigment epithelium (RPE) is involved, where the drug binds with melanin. It may have an adverse effect on retinal cell metabolism leading to slow and long-term toxicity.[5] HCQ, like chloroquine (CQ) is a lysomotropic drug, and is an enhancer of lipofuscinogenesis. [6]

Numerous studies have been conducted across the world to elucidate the prevalence, mechanism, progression, methods of detection and outcome of HCQ induced retinal toxicity.

Most studies have been aimed at comparing two or more investigative modalities to determine their relative efficacy for early detection of toxicity. This study included multiple testing methods including visual acuity, colour vision, Amsler grid testing, 10-2 Humphrey's visual fields (HVF), Spectral Domain Optical Coherence tomography (SD-OCT), slit lamp examination, dilated fundus examination, colour fundus photography, fundus autofluorescence (FAF) and fundus fluorescein angiography (FFA) to maximize the detection of toxicity. Multifocal electroretinogram (mf ERG), however, could not be done due to non-availability of the test at our hospital.

This study is different from previous studies because it exhaustively incorporates multiple methods of detection of HCQ induced retinal toxicity. It aims at studying the ocular changes in patients on long term treatment with HCQ, with the objective of determining the methods for early detection of toxicity, by eliciting a detailed history about indication, dose, duration and cumulative dose of HCQ, ocular symptoms; a detailed ocular examination with visual acuity and colour vision testing, Amsler grid testing, anterior and posterior segment examination over the slit lamp and indirect ophthalmoscopy. Investigations carried out for every patient were Humphrey's 10-2 HVF, SD-OCT, FFA, FAF.

METHODS

Our study was a cross sectional observational study of 100 patients over a duration of one and a half years, carried out in the Department of Ophthalmology at a tertiary care hospital in New Delhi, India. 100 patients who were undergoing long term treatment with HCQ were referred from the Department of Rheumatology of the hospital. Male and female patients, aged 35 years or more, who were on treatment with HCQ for any rheumatological or inflammatory condition for 5 years or more were included in the study.

The exclusion criteria included patients on treatment with HCQ for less than 5 years; any known diseases or anomalies affecting the optic nerve, viz. optic neuropathy, optic disc drusen, optic disc pit or coloboma; any known retinal diseases like diabetic retinopathy, retinitis pigmentosa, age related macular degeneration, ocular occlusive vascular diseases; other ocular diseases like uveitis, glaucoma or glaucoma suspects, any past history of intraocular or refractive surgery, any media opacity that may preclude a high quality OCT examination, history of diabetes mellitus or hypertension, deranged liver or renal function tests.

Patients were informed about the investigations they would undergo, including the potential risks with FFA. A written informed consent was taken. The study had the ethical approval from the Ethics committee of the hospital, and was carried out in

accordance with the ethical standards stated in 1964 Declaration of Helsinki. The patients were counselled about the toxic effect of the said drug, the progressive and irreversible nature of the condition and the rationale of screening for drug toxicity. The patients underwent an exhaustive ophthalmic examination which included a history of visual complaints, visual acuity testing with Snellen's chart and near vision including best corrected visual acuity, colour vision assessment using Ishihara plates, Amsler grid assessment, slit-lamp examination for anterior segment evaluation, indirect ophthalmoscopy with a 20 diopter lens to look for irregularity in macular pigmentation, blunting of foveal reflex (early finding), Bull's eye maculopathy (classic finding), peripheral pigment irregularity and bone spicule formation, vascular attenuation, optic disc pallor (late finding), 10-2 HVF, SD-OCT, colour fundus photography, FFA, FAF.

Descriptive and inferential statistical analysis were carried out in the study. Results on continuous measurements are presented on Mean ± Standard Deviation (Min-Max) while results on categorical measurements are presented in Number (%).

RESULTS

A total of 125 patients were considered for the study, of which 100 patients fulfilled the eligibility criteria detailed above. The patients were examined and investigated in a single sitting; hence, no cases were lost to follow up.

The mean age of our study population was 52.9 ± 10.30 years, with the age group ranging from 36-76 years. The study population was predominated by females (89%). The mean daily intake of HCQ was 212 ± 47.73 mg over a mean duration of 8.25 ± 3.58 years (Table 1).

Table 1**. Variables related to disease and treatment history**

Variable	No of patients	Mean	Std Dev	Min	Max
Age of patient (years)	100	52.9	10.30397	36	76
Duration of disease (years)	100	12.65	6.475088	5	40
Daily dose of HCQ (mg)	100	212	47.73665	200	400
Duration of HCQ (years)	100	8.36	3.543439	5	20
Cumulative dose of HCQ (grams)	100	623.23	268.3256	365	1460

The cumulative dose intake was 623.23 ± 268.32 g, with minimum and maximum cumulative doses of 365g and 1460g respectively.

Of the 100 patients studied, 37 patients presented with ocular complaints. These were mostly subjective in nature, ranging from difficulty in reading, dimness, discomfort to bright light, and occasionally, a scotoma in the field of vision.

A reduction in visual acuity was noticed in 82% patients using Snellen's distant visual acuity chart at 6m and Jaeger chart for near vision at 33 cm. However, most patients could be given a satisfactory best corrected visual acuity with spectacles. If not, the diminished vision could be attributed to the presence of senile cataract or posterior sub capsular cataract which may be due to concomitant oral steroid use. 02 out of 100 patients had diminished vision which could be attributed to the presence of HCQ related retinal toxicity.

Presence of corneal deposits was not detected in any of the 100 patients on slit lamp examination. Fundus evaluation done with indirect ophthalmoscope with 20 diopter lens and slit lamp biomicroscope with 90 diopter lens revealed the following findings:

92% patients showed no abnormal pigmentary changes at the macula (Fig 1). Of the 8% patients who had irregular macular pigmentation, 1 patient had unilateral changes while the rest 7 patients had bilateral changes. Blunting of foveal reflex as an early feature of retinal toxicity was seen in 9 out of 100 patients (9%). The remaining 91 patients had normal foveal reflex on fundoscopy. Bull's eye maculopathy was noticed bilaterally on clinical examination in one patient (1%), along with vascular attenuation and optic atrophy (Fig 2). Changes in peripheral retina and bony spicule pigmentation was not detected in any of the study subjects. The subtlety of clinical findings in our patients was found to be in agreement with a study published by Mavrikakis et al in 2003.[7]

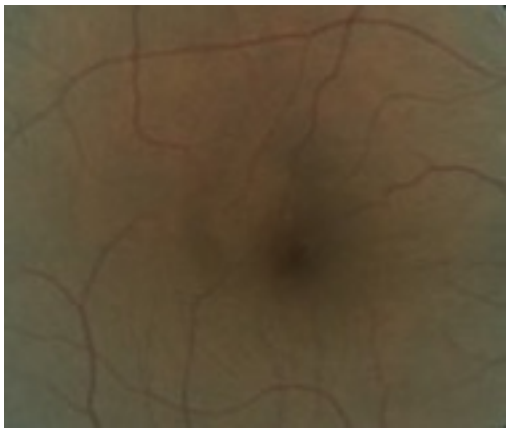

Figure 1: **Pigmentary changes at macula**

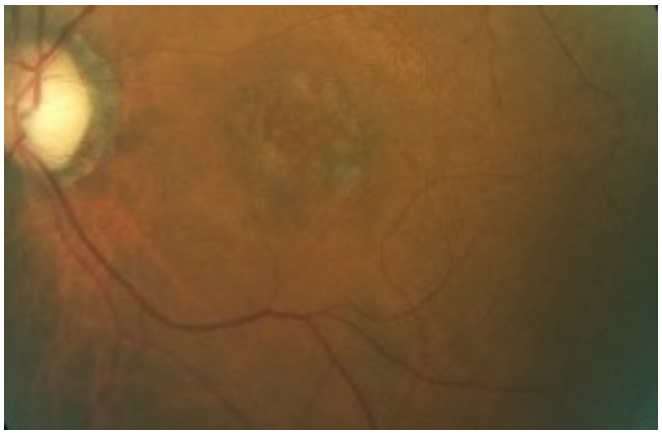

Figure 2: **Bull's eye maculopathy with vascular attenuation and optic disc atrophy in left eye**

17% patients showed abnormality on OCT macula, which ranged from early parafoveal and perifoveal thinning to foveal atrophy in advanced case with bull's eye maculopathy (Fig 3). The classical "flying saucer" sign described by Eric Chen et al was not detected in any of the subjects.[8] 21% patients showed field defects on 10-2 HVF, which ranged from small paracentral defects to paracentral ring and arcuate scotomas as well as central scotomas (Fig 4). 10% of the patients gave an abnormal fundus auto fluorescence, in the form of a ring of hyperautofluorescence surrounding a zone of central hypoautofluorescence at the macula (Fig 5, 6). No significant abnormality was detected on FFA, Amsler grid, colour vision testing using Ishihara plates among any of the patients. among any of the patients. 10-2 HVF,

Amsler grid and colour vision assessment could not be done in 01 patient with bull's eye maculopathy due to low vision.

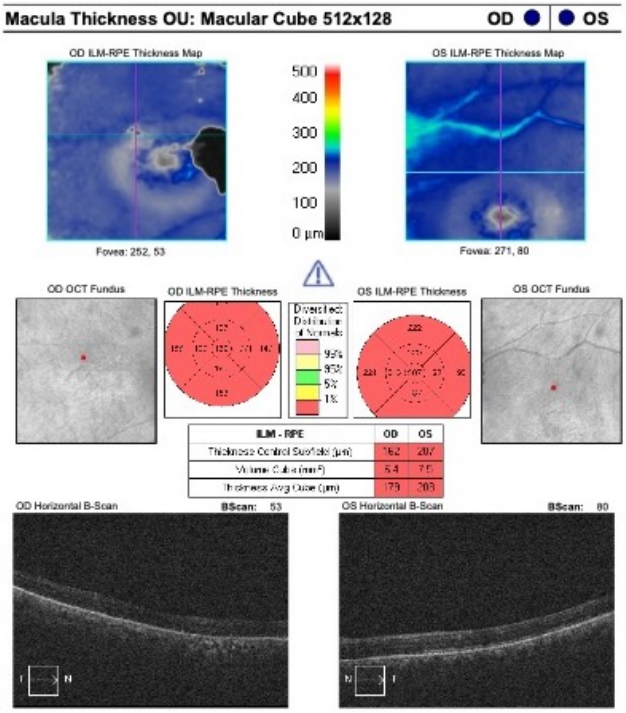

Figure 3. **SD-OCT macula showing severe foveal, perifoveal and parafoveal thinning**

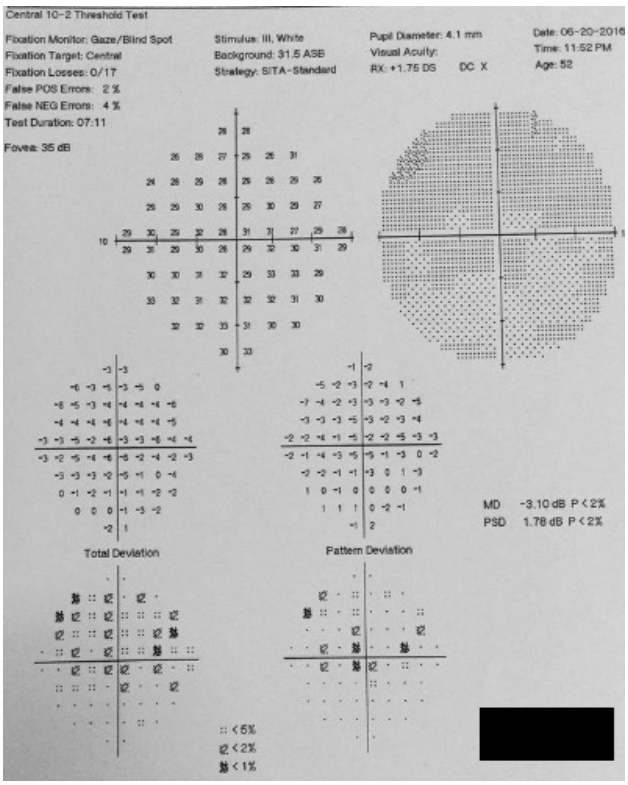

Figure 4. **Visual field defects in a patient with HCQ toxicity**

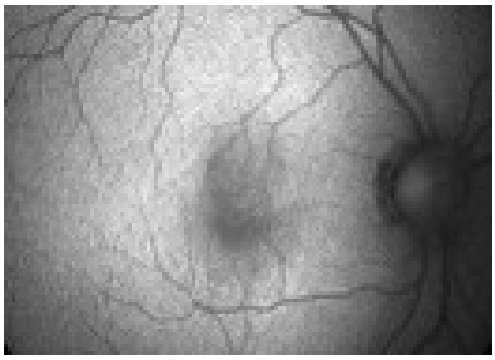

Figure 5: **Fundus autofluorescence of right eye showing hyperautofluorescence at macula**

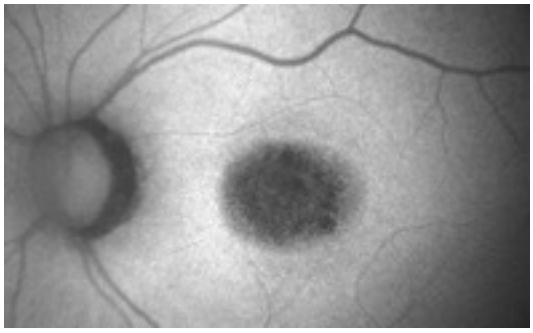

Figure 6: **Fundus autofluorescence of left eye of a patient with Bull's eye maculopathy**

Based on SD-OCT, 10-2 HVF and FAF findings, we detected features of HCQ toxicity in 15% of the subjects under evaluation. 17%, 21% and 10% patients showed abnormal SD-OCT, automated perimetry and FAF findings respectively. The results did not have a direct correlation with age, weight, daily dose and cumulative dose of the drug (Table 2).

Table 2. **Cases of HCQ toxicity based on investigation findings**

S No	Age/ Sex	Diag	BCVA	Duration of treatment (years)	Daily dose (mg)	Cumu-lative dose (g)	SD-OCT	10-2 HVF	FAF
1	52/F	RA	6/6, 6/6	8	200	576	+	+	+
2	38/F	RA	6/6, 6/6	6	200	438	+	+	+
3	50/F	RA	6/6, 6/6	13	200	949	+	+	+
4	55/F	RA	6/9, 6/9	10	200	730	+	+	-
5	44/F	RA	6/9, 6/12	10	200	730	+	+	+
6	50/F	RA	6/6, 6/6	13	200	949	+	+	+
7	66/F	RA	6/6, 6/6	10	200	730	+	+	-
8	47/F	RA	6/6, 6/6	10	200	730	+	+	-
9	60/F	RA	6/6, 6/6	9	200	660	+	+	-
10	73/M	RA	2/60, 3/60	11	200, 400	1168	+	NR	+
11	42/F	SLE	6/6(P), 6/6(P)	7	200, 400	653	+	+	+
12	48/F	RA	6/6, 6/6	10	200	730	+	+	+
13	43/F	RA	6/6, 6/6	6	200	438	+	+	+
14	56/F	RA	6/6(P), 6/9(P)	9	200	660	+	+	+
15	62/F	RA	6/9(P), 6/18(P)	14	200	1008	+	+	-

DISCUSSION

This was a cross sectional observational study conducted in a tertiary care teaching hospital in New Delhi, India. A sample size of 100 patients on long term HCQ treatment was clinically examined and screened for retinal toxicity using a battery of investigative modalities after written informed consent. The findings of the study were analyzed using descriptive analysis. The mean age was 52.9 ± 10.30 years. Females predominated the study (89%). The mean daily intake of HCQ was 212 ± 47.73 mg over a mean duration of 8.25 ± 3.58 years. The cumulative dose intake was 621 ± 261.80 g. Majority of the patients were asymptomatic, reduced visual acuity due to HCQ related toxicity was found in 02 cases. SD-OCT, 10-2 HVF and FAF picked up retinal abnormality in 17%, 21% and 10% cases respectively. Amsler grid, colour fundus photography, colour vision and FFA failed to detect abnormalities in these patients.

The outcomes of this study conformed to those of some other studies while they varied from some others. The incidence of retinal toxicity with HCQ is estimated to be 0.5% after 5 years of therapy.[9] A retrospective cohort study of 234 Thai rheumatology patients revealed the incidence of HCQ retinopathy to be 3.28% with cumulative doses from 80-130g over a period of 660-828 days.[10] We found an overall incidence of toxicity of 15% in our study group. Age and weight of the patient, and daily dosage of the drug were not found to have strong correlation in our study, which was similar to a study conducted by Frederick Wolfe and Michael F. Marmor.[11] A study conducted by Doo-ri et al over 310 Korean patients and published in March 2017, found a much lesser prevalence of toxicity (9 out of 310 patients). However, the demographic profile, cumulative dose and duration of treatment, visual acuity and findings on OCT, HVF and FAF revealed similar outcomes among those with toxicity.[12] The study population was predominated by females (89%) which was similar to the study published by Doo-ri et al (92.3%)[12] and also reflected a greater prevalence of rheumatological disorders among women.[13] Majority of our patients were asymptomatic, as also seen in a study by Mavrikakis et al.[14]

Clinical examination revealed absence of corneal deposits as a consistent finding, as also seen in a study published by Rynes RI in 1983.[15] Irregular macular pigmentation and blunting of foveal reflex were seen in 8% and 9% patients respectively. Bull's eye maculopathy along with vascular attenuation and optic disc pallor was seen in 1% of the cases; while peripheral pigment abnormality and bone spicule formation were not seen in any cases. The subtlety of clinical findings in our patients was found to be in agreement with a study published by Mavrikakis et al in 2003.[16]

On investigation, although abnormalities on OCT macula were seen in 17% patients, the classic 'flying saucer' sign described by Eric Chen et al was not detected in any of the subjects.[17] The results of the above investigative modalities highlighted the usefulness of the newer modalities of detection of HCQ related retinal toxicity over the previously practiced methods like Amsler grid, colour vision, fundus photography and fundus fluorescein angiography. The study found SD-OCT, 10-2 automated perimetry and FAF to be superior to the aforementioned techniques in detection of toxicity. This was in agreement with the latest guidelines issued by the American Academy of Ophthalmology in 2016 for screening of HCQ related retinal toxicity.[18]

The study was the first of its kind to incorporate a comprehensive battery of evaluation and investigation modalities. In this regard, we were able to clearly delineate the relative importance of these methods for early detection of toxicity, including the novel methods of investigation. We were also able to detect significant retinal toxicity in seemingly asymptomatic patients. The main limitations of the study were a small sample size of the study, non-availability of a normal distribution of patient population and absence of linear relationship between different variables leading to difficulty in correlation analysis.

CONCLUSIONS

Long term HCQ treatment should always be viewed with concern, as the risk of toxicity may remain despite a lower than maximum daily dose if given over a prolonged period of time. In our study, majority of the patients were on treatment with 200mg/day dose of HCQ. Even so, features suggestive of retinal toxicity were detected in 15% of the cases. Also, this study highlights the greater utility of newer modalities of investigation over the previously used subjective methods of assessment. The latest guidelines issued by the American Academy of Ophthalmology are of greatest relevance in the present-day scenario till the time

new research brings into light better ways of earlier detection of this cause of irreversible vision loss.

Conflicts of interest- The authors have no personal or financial conflicts of interest.

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