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Detection of Retinal Changes in Patients on Long Term Chloroquine/Hydroxy Chloroquine Therapy Using Optical Coherence Tomography

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Abstract

Background: The best technique to diagnose chloroquine/ hydroxychloroquine-induced retinopathy changes at the earliest remains ambiguous at present. In this study, we evaluated the time-domain optical coherence tomography (OCT) to identify retinal changes associated with chloroquine and hydroxychloroquine.

Methods: One hundred patients with immunological diseases were included in the study. Fifty of them had been on chloroquine and/or hydroxychloroquine therapy for at least five years and the other 50 patients as controls. Detailed ophthalmic examination including Amsler grid , colour vision , automated threshold white perimetry using 10-2 protocol on Humphrey field analyzer, fluorescein angiography when indicated and time domain Optical Coherence Tomography was done.

Results: A statistically significant thinning was noted in the superior and inferior quadrants of the parafoveal area. Six patients had changes in fundus. When cases with normal and abnormal fundus were analyzed individually, a statistically significant thinning was noted in the inferior parafoveal region in patients on chloroquine/ hydroxychloroquine having normal fundus when compared to the controls Amsler grid, colour vision, central 10-2 perimetry, FFA were all normal in these patients. There was no significant retinal nerve fiber layer thinning in the peripapillary region Temporal macular thickness was significantly thinner in patients who received the drugs for more than 8 years.

Conclusions: Time domain OCT can be used to detect pre- clinical changes of chloroquine/ hydroxychloroquine -induced retinopathy. All patients on long term use of these drugs must undergo regular examinations to diagnose early toxicity.

Keywords: Retinopathy; Chloroquine Toxicity; Hydroxychloroquine toxicity; Optical coherence tomography

Introduction

Chloroquine, a 4-amino quinoline compound has long been used in the treatment and prevention of malaria. Hydroxy chloroquine is a hydroxylated analogue of chloroquine. Of late, these drugs are being used as disease modifying antirheumatic agents (DMARD) in diseases like rheumatoid arthritis and systemic lupus erythematosis [1].

Savarino et al. [2] showed that both chloroquine and hydroxychloroquine can cause retinal toxicity, but the potential seems to be lesser with hydroxy chloroquine. This has been supported by experimental studies which have shown that hydroxy chloroquine is a less potent enhancer of lipofuscinogenesis compared to chloroquine in the retinal pigment epithelial cells [3]. It has also been documented that both the drugs block activation of Toll like receptors (TLR) on dendritic cells and inhibit the TLR signaling [4-6]. HCQ retinopathy has been reported in more than 1% of patients after 5-7 years of usage of the drug and its incidence did not correlate with the age, daily dose or the weight of the patient [7].

Over years, several tests have been used to diagnose chloroquine retinopathy, which include Amsler grid testing, colour vision testing, and central visual field charting [2-10]. Recent studies with spectral domain Optical Coherence Tomography (SD-OCT), multifocal Electro-retinogram (mf ERG), fundus auto fluorescence show promising results in the early detection of chloroquine toxicity [8,9]. The role of time-domain OCT in establishing the diagnosis remains inconclusive, though, in a recent case report , there were suggestions of early chloroquine toxicity even on time Domain OCT [10].

The current study is designed to evaluate changes in macular and peripapillary retinal nerve fiber layers in using time-domain OCT in patients on chloroquine/hydroxy chloroquine therapy for at least 5 years.

Materials and Methods

The present case-control study was conducted in a tertiary care hospital in south India. The study protocol was approved by the Institutional Ethics Committee and an informed consent was taken from all the patients.

Fifty patients with immunological diseases receiving chloroquine or hydroxy-chloroquine and another 50 age and sex-matched controls having similar immunological diseases but not receiving chloroquine or hydroxy-chloroquine were included in the study. The inclusion criteria were: age above 18 years and chloroquine/hydroxychloroquine

therapy given for at least 5 years. The exclusion criteria were: patients with clinical evidence of any other known macular disease, presence of glaucoma or with obscurities in the visual axis, previous retinal surgery, known neurological illness and diabetics.

The data collected included demographic details such as age, sex, primary diagnosis, duration of the illness, medication history (chloroquine or hydroxychloroquine or other drugs; dosage (mg/kg/day) and duration of treatment with each drug), presence of visual complaints like diminution of vision, metamorphopsia, scotomas.

Both cases and control patients underwent the following tests sequentially: 1. Best corrected Snellen's visual acuity test, 2. Amsler grid test, 3. Colour vision test using the Ishihara's pseudo isochromatic plates, 4. Automated threshold white perimetry using 10-2 protocol using Humphrey field analyzer (Zeiss Humphrey Systems, Dublin, CA), 5. Slit lamp biomicroscopic examination to study the fundus, 6. Fluorescein angiography in patients with suspicious lesions to identify subtle retinal pigment epithelial defects and 7. Optical Coherence Tomography.

The details of OCT are as follows: The examination was carried out by using a Stratus OCT (Carl Zeiss, Meditec, Dublin, CA) equipment. The patient was positioned comfortably. The chin was placed on the chin rest and forehead against the forehead strap. One eye was occluded. The patient was instructed to fix on the green target throughout the procedure.

- A fast macular thickness protocol was used to measure the macular thickness. It consisted of six radial line scans which covered a diameter of 6 mm and generated thickness reports for quantitative analysis. The thickness of the macula in the parafoveal region (1-3 mm; inner ring) was noted in the 4 quadrants (superior, inferior, nasal and inferior)
- A fast Retinal Nerve Fibre Layer (RNFL) scan protocol was used for the peripapillary measurements. It consisted of 3 consecutive 360° scans with a diameter of 3.4 mm centered on the optic nerve head, each composed of 256 A-scans taken in a single session. The RNFL thickness parameters calculated by the Stratus-OCT software (version 4.0.1) were average thickness in the temporal, superior, inferior and nasal quadrants.

A signal strength of more than or equal to 6 was taken for an acceptable scan. Average of 3 scans was taken per eye.

Statistical methods

Age of the cases and controls was compared using an independent-samples t test. Gender distribution was compared using a Chi square test. Thicknesses in the four quadrants in the macular and peripapillary areas were compared using an independent-samples t test. Macular thicknesses in the four quadrants, across the three groups – namely, patients on chloroquine with and without abnormal fundus and the controls – was compared by using a one-way analysis of variance (ANOVA) with posthoc least significant difference (LSD) testing. Pearson's test was used to correlate the duration of therapy vs macular thickness and also the dose of chloroquine/hydroxychloroquine vs retinal thickness. An independent samples t test was used to compare the retinal thickness between patients on therapy for up to 8 years vs more than 8 years. All data were expressed as mean ± SD. A p value of <0.05 was considered statistically significant. SPSS version 16.0 statistical package was used for analysis of the data.

Results

A total of 50 patients 50 controls were included in the study. The demographic characteristics of these subjects are shown in Table 1. The two groups were age and sex matched to eliminate the effect of age and gender on the retinal thickness on OCT. The distribution of the primary diagnoses between the cases and controls was also comparable. Twenty seven patients received only hydroxychloroquine, while 23 received chloroquine to begin with and were later changed to hydroxy chloroquine. The median duration of therapy with chloroquine was 3.0 years, while that of hydroxychloroquine was 6.0 years.

		Controls	Cases	Significance
Age (Years)		40.1 ± 9.3	40.4 ± 8.3	P=0.89
Sex	Male	16	13	X^2=0.355; df 1; p=0.551
	Female	34	37	
Diagnosis	Rheumatoid arthritis	30	29	
	Systemic Lupus Erythematosis	13	13	
	Sjogrens Syndrome	4	6	NS
	Systemic Sclerosis	-	1	
	UCTD/ MCTD	3	1	
Duration of treatment in years Median (IQR)	Chloroquine	-	3.0 (2.00-5.00)	
	Hydroxy-chloroquine	-	6.0 (5.00-7.00)	
Dosage ($mg.kg^{-1}.d^{-1}$)	Chloroquine	-	3.7 ± 0.7	
	Hydroxy-chloroquine	-	5.6 ± 1.1	

Table 1: Demographic characteristics of the patients.

Visual acuity

There was no statistically significant difference between the cases and controls except for one patient with bull' s eye maculopathy in the study group, who had a Snellen's visual acuity of 5/60 in his right eye and 4/60 in his left.

Dilated fundus examination

Six patients had fundus changes. One patient had a typical bull's eye maculopathy in both eyes. Four others showed pigmentary stippling at the macula in both the eyes. One patient had a pigment epithelial detachment in the right eye.

Amsler grid testing

The two patients with pigmentary changes at macula had metamorphopsia on Amsler grid testing. The patient with bull's eye maculopathy had a central scotoma. In the rest of the patients, the test was normal.

Colour vision

Colour vision was normal in all the patients other the patient with bull's eye maculopathy. In this patient, colour vision could not be recorded due to the poor vision.

Automated visual fields

Visual fields were normal in all the patients. In the patient with bull's eye maculopathy, central visual fields could not be charted due to the poor vision.

Fluorescein angiography

In those patients with pigmentary stippling, fluorescein angiography was inconclusive.

Optical Coherence Tomography findings

The macular findings on OCT are shown in table 2. In the cases, a statistically significant thinning was noted in the superior and inferior quadrants of the parafoveal macula (inner ring) compared to the controls (superior: 252 ± 34 in the chloroquine group vs. 261 ± 23 in the control group; p value 0.033 & inferior: 252 ± 32 in the chloroquine group vs. 262±26 in the control group; p value of 0.016). The measures in the temporal and nasal quadrants were not significantly different between the study and control groups.

	S(superior)	T (temporal)	I (inferior)	N (nasal)
Chloroquine Group	252 ± 34	242 ± 32	252 ± 36	255 ± 32
Normal Group	261 ± 23	248 ± 24	262 ± 26	260 ± 26
Significance (p value)	0.033	0.157	0.016	0.219

Table 2: Macular changes associated with chloroquine therapy.

Six cases had changes in their fundus. Further analysis on macular changes was carried out to compare the cases with and without abnormalities of fundus with control patients. The results are shown in Table 3.

Study Group	Fundus	Superior	Temporal	Inferior	Nasal
Chloroquine Group	Abnormal Fundus N=10 eyes	254 ± 24$	249 ± 21	251 ± 24$	253 ± 18
Chloroquine Group	Normal fundus N=88eyes	253 ± 34*	243 ± 32	253 ± 37*	257 ± 32$
Control Group	N=100 eyes	261 ± 22	248 ± 23	262 ± 26	260 ± 24*
		$p=0.456 vs. control *p=0.074 vs. control	NS	$p=0.282 vs. control *p=0.048 vs. control	$p=0.700 vs.Chloroquine abnormal fundus *p=0.473 vs. Chloroquine-abnormal fundus

Table 3: Comparison of macular thickness in cases with or without fundus changes and control group.

One patient had a bull's eye maculopathy; OCT in this patient revealed an atrophic macula (OD: superior: 199, temporal: 186, inferior: 209, nasal: 195 with a Total Macular Volume {TMV} of 5.51 and a foveal thickness of 110. OS: superior: 189, temporal: 178, inferior: 198 and nasal: 195, TMV: 5.31 and foveal thickness of 112). Since this patient had already an advanced disease, he was excluded from the rest of the analysis, the results of which are as follows: The average macular thickness in all quadrants in the parafoveal (inner ring) region in patients with abnormal fundus on chloroquine/hydroxychloroquine was lesser than in the controls. However it did not reach statistically significant levels probably due to the small sample size (N=10). A statistically significant thinning was noted in the inferior parafoveal region in patients on chloroquine but having normal fundus when compared to the controls (253 ± 37 vs. 262 ± 26; p=0.048). A trend towards the same was observed in the superior parafoveal region (253 ± 34 vs 261 ± 22; p=0.074).

Changes in peripapillary retinal nerve fibre layer are shown in table 4.

	Superior	Temporal	Inferior	Nasal
Chloroquine Group	130 ± 27	68.4 ± 19	131 ± 26	85.4 ± 27
Control Group	124 ± 23	66.3 ± 14	133 ± 14	89.4 ± 21
Significance (p value)	0.124	0.262	0.523	0.249

Table 4: Changes in peripapillary retinal nerve fibre layer.

There was no significant retinal nerve fiber layer thinning in the peripapillary region in patients on the drug as compared to the controls. There was no significant correlation between the dose of chloroquine or hydroxychloroquine (in mg/kg) and the thickness of retina when analyzed by a Pearson's correlation test (Table 5).

	Superior	Temporal	Inferior	Nasal
Dose of Chloroquine therapy				
r value	0.23	0.203	0.179	0.202
p value	0.109	0.157	0.213	0.159
Dose of Hydroxychloroquine therapy				
r value	0.008	0.046	0.035	0.021
p value	0.941	0.65	0.733	0.836

Table 5: Correlation of the drug-dose with macular thickenss.

A correlation was attempted between the retinal thickness and the total duration of chloroquine or hydroxychloroquine therapy. The patients were divided into two groups (patients on therapy for 8 years or more vs. therapy for <8 years); temporal macular thickness was significantly different between the two groups (235 ± 31 vs. 249 ± 31 respectively; p<0.022) (One-way ANOVA with posthoc LSD test).

Discussion

Hydroxychloroquine is a commonly used medication in the management of various immunological disorders. The American academy of ophthalmology is concerned that retinal toxicity, although

rare, may be more common than previously recognized, based on a study by Wolfe et al which found that the risk exceeded 1% after 5 years [7]. Early chloroquine retinopathy is still inadequately described.

There are numerous tests used for screening but the sensitivity and specificity of each of these objective tests for retinal toxicity is still being debated. Early detection and discontinuation of the drugs can halt further visual loss.

Chloroquine/ hydroxy chloroquine accumulate in the retinal pigment epithelium and disrupts its function [11].

It has been shown that ganglion cell loss occurs in long term chloroquine users using scanning laser polarimetry [12]. Ganglion cell density is highest in the disc. Retinal thickness measurements in this region may reveal early toxicity before functional defects occur which are irreversible.

A recent study using high-speed ultra-high-resolution OCT showed discontinuity or loss of perifoveal photoreceptor inner segment/outer segment junctions and thinning of the outer nuclear layer in patients receiving hydroxychloroquine with normal fundus [9].

A recent report showed significant thinning in the perifoveal and outer macula especially in inferior and temporal quadrants in a patient on chloroquine therapy using time domain OCT [10].

In our patients there was a statistically significant thinning in the parafoveal macula (inner ring) especially in the inferior and superior quadrants among cases. It is important to note that these patients had a normal fundus, red Amsler grid test, perimetry and colour vision test. Since an acquired paracentral scotoma on automated field charting has been described as an early manifestation of retinopathy [13], it is evident that OCT can detect changes even before automated fields can.

Although previous studies have shown peripapillary thinning in patients on the drug [14], our study also found such changes.

When our patients were divided into two groups (patients on therapy for 8 years or more vs. therapy for <8 years), temporal macular thickness was significantly different between the two (235 ± 31 vs. 249 ± 31 respectively; p <0.022). This finding reinforces the recommendations of AAO that patients on chloroquine/hydroxy chloroquine should be evaluated for retinopathy after 5 years of usage of the drug [15].

The current study is the largest case series so far in the literature.

Optical coherence tomography could detect the retinopathic changes at the pre-clinical stage of maculopathy when all other tests like Amsler grid, colour vision, automated visual fields, fundus fluorescein angiography were normal.

In conclusion, macular thickness in patients receiving chloroquine/ hydroxychloroquine therapy was significantly thinner than in control group patients. Thinning was more evident if the patient was on the therapy for more than 8 years. Optical coherence tomography could identify the retinopathy even before changes are evidenced in the automated visual fields. Peripapillary nerve fiber layer thickness is not significantly different between chloroquine users and controls. Routine screening for toxicity should be emphasized for patients on long term chloroquine/ hydroxychloroquine therapy. Our study suggests that OCT should be a part of routine screening for retinopathy. Longitudinal studies will be helpful to further establish the role of time domain OCT in early diagnosis of chloroquine retinopathy.

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