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ORIGINAL ARTICLE

Retinopathy due to antimalarial drugs in patients with connective tissue diseases: are they so innocent? A single center retrospective study

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Abstract

Introduction: Antimalarial medications are basal active drugs used for the treatment of various rheumatological conditions. Their common side-effects include eye damage.

Aim: The aim of this study is to determine the safety of antimalarial medications used for rheumatological conditions and the incidence of retinopathy.

Material and methods: Eighty-five patients with rheumatological conditions, who were followed in our rheumatology clinics between 2005 and 2009 while under chloroquine (CQ) and/or hydroxychloroquine (HQ) treatment were included in the study. Indirect ophthalmoscopic examination with 90 dioptry lens, frontal segment examination and macular visual area test were applied to all patients. Severity of retinopathy was evaluated as mild initial defect in the macula, or severe visual area loss.

Results: Retinopathy findings were detected in 21 out of 85 patients (24.7%). Of these patients, 12 had mild initial defects while nine had severe visual area loss. Of 21 patients, eight were on HQ and 13 were on CQ treatment. Of the patients seen with findings of retinopathy, 17 had comorbid hypertension (HT) and six had diabetes mellitus (DM). Patients receiving CQ are under higher risk compared to those on HQ treatment ($P = 0.001$). Patient age, disease duration, HT and DM presence had no statistically significant effect on retinopathy development ($P = 0.144$, $P = 0.305$, $P = 0.258$, $P = 0.395$, respectively).

Conclusion: The incidence of retinopathy among patients using antimalarial medications as observed in this study was relatively high. Based on these results, it is essential to emphasize the importance of close monitoring in patients receiving antimalarial medications and evaluation of visual findings before treatment initiation.

Key words: antimalarial drugs, retinopathy.

INTRODUCTION

Chloroquine (CQ) and hydroxychloroquine (HQ) are antimalarial medications used to treat various connective tissue disorders, mainly systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[1] CQ was discovered in 1934 and was initially used in prophylaxis and treatment of malaria.[2] HQ was synthesized in 1946 from chloroquine phosphate and in a very short time these two drugs became indispensable first-line treatment options for connective tissue disorders.[3] Compared to other basal active drugs, it is well known that antimalarial drugs possess less toxicity.[4] For this reason, they are safely used in treatment of various rheumatological and dermatological conditions. Common side-effects of antimalarial drugs include gastrointestinal effects such as nausea and vomiting, as well as skin rashes and headache, while

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their most common and severe side-effect is retinopathy.[5] Both antimalarial medications have high affinity for melanin, thus they accumulate in melanin-rich tissues such as skin, retina and iris. Tissue clearance of antimalarial medications is very slow, so their effects continue even years after cessation of the treatment.[6] Retinopathy can show itself with early and advanced findings. In early retinopathy, paracentral scotomata can be detected in visual areas without apparent changes in fundus. In advanced retinopathy on the other hand, parafoveal retinal pigment epithelial atrophy develops along with paracentral scotomata. Different incidences of retinopathies observed between antimalarial medications have been reported in the literature.[7–9] The incidence varies between 1% and 40%, based on definition of retinopathy and diagnostic methods that have been used. Studies have shown that CQ is more effective compared to HQ; however, it is more toxic.[10] It also has been shown that retinopathy incidence observed with antimalarial medications is related to risk factors such as older age, kidney and liver dysfunction, presence of another retinal pathology, long-term antimalarial medication use and cumulative drug dose.[11] Establishing the incidence of retinopathy upon treatment with antimalarial medications, and defining the pathogenetic mechanisms, risk factors and clinical findings of this association is crucial in terms of patient follow-up. Under the light of this information, in the present study, we aimed to establish the incidence of retinopathy and associated risk factors in patients with connective tissue disorders who were receiving antimalarial medications.

MATERIALS AND METHODS

Eighty-five patients diagnosed with connective tissue disorders, who were followed in rheumatology clinics of our hospital between 2005 and 2009 while under CQ and/or HQ treatment were included in the study. Among 85 patients, 12 were diagnosed as systemic lupus erhytematosus (SLE), 35 patients had Sjögren's syndrome (SjS) and 38 had rheumatoid arthritis (RA). Eye examinations of all patients were performed biannually by an ophthalmologist. Indirect ophthalmoscopic examination with 90 dioptry lens, frontal segment examination and macular visual area test were applied to all patients. Presence and severity of retinopathy was evaluated based on early (initial) retinopathy findings and advanced (severe) retinopathy. Antimalarial medication-related retinopathy was defined as bilateral and chronic visual area abnormalities were established with two different tests. Presence of paracentral scotoma without fundus changes was considered as an early retinopathy finding. Presence of parafoveal retinal pigment epithelium (RPE) along with paracentral scotoma were considered as advanced retinopathy.

Statistical analysis

Cross-tables were constructed for categorical data and Chi-square analysis was performed. *t*-test was used for comparison of numerical variables between two groups. The level of statistical significance was accepted to be $P = 0.05$. Pearson correlation coefficient was calculated between two numerical variables.

RESULTS

Eighty-five patients (82 women and three men) were examined. The mean age was 28.5 years (range 17–72) and mean disease duration was 3.2 years. Out of 85 patients, 21 (24.7%) were seen with findings of retinopathy. Five of these 21 patients were diagnosed as SLE, seven had SjS and nine had RA. Twelve of these patients had mild initial defects while nine had severe visual area loss (Fig. 1). Mean age and mean disease duration of the patients having retinopathy findings were 30.9 years and 2.3 years, respectively. Of 21 patients, eight were on HQ and 13 were on CQ treatment. Mean duration of HQ treatment was 1.7 years and mean duration of CQ treatment was 1.9 years. Mean cumulative HQ and CQ doses were 10.9 g and 11.4 g, respectively. Of the patients seen with findings of retinopathy, 17 had comorbid hypertansion (HT) and six had diabetes mellitus (DM). Mean age and mean disease duration of 64 patients who were not seen with retinopathy findings were 25.2 and 2.7 years, respectively. Out of these patients 42 were on HQ and 22 were on CQ treatment. Mean duration of HQ treatment among these patients was 2.09 years and mean duration of CQ treatment was 1.5 years. Five patients out of 64 had comorbid HT and two had DM. Compared to patients receiving HQ, patients using CQ were under higher risk ($P = 0.001$). Further, cumulative drug dose and treatment duration were associated with retinopathy development ($P = 0.001$, $P = 0.001$, respectively). Age, disease duration, presence of HT and DM had no statistically significant effect on retinopathy development ($P = 0.144$, $P = 0.305$, $P = 0.258$, $P = 0.395$, respectively) (Table 1).

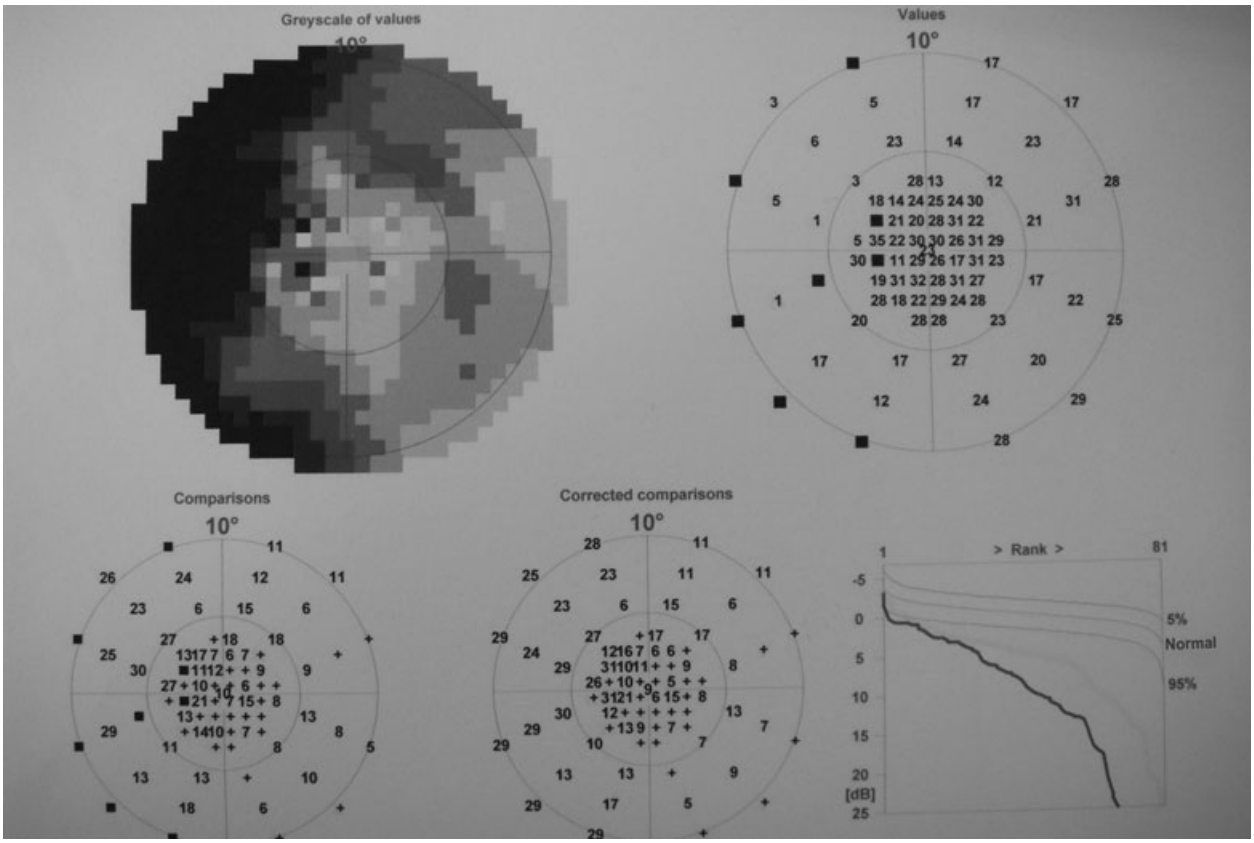

Figure 1 Visual field test showing advanced retinopathy findings.

DISCUSSION

In the present study, incidence of retinopathy among patients using antimalarial medications was determined as 24.7%. CQ was more toxic compared to HQ. Risk factors for antimalarial retinopathy were also evaluated in this study. Although comorbid HT and DM were more frequent among patients who developed retinopathy compared to those who did not, this difference was not statistically significant. Patient age and disease duration did not have a statistically significant effect on retinopathy development. Cumulative drug dose and treatment duration were associated with retinopathy development. No association was found between gender and retinopathy development. Contradictory results have been reported in the literature for antimalarial medication-related retinopathy. The incidence of retinopathy development associated with antimalarial medications in SLE and RA patients was found to be 24% and 13%, respectively.[12] Car *et al.*[13] reported retinopathy incidence as 50%. Mackenzie *et al.*[14]suggested that patients receiving HQ at doses < 6.5 mg/kg/day are not under retinopathy risk. Mantyjarvi *et al.*[15] have detected retinopathy in one out of 63 patients. According to Bernstain,[16] patients under HQ treatment at a dose < 6.5 mg/kg/day for less than 10 years who have normal kidney functions

Table 1 Demographic and clinical findings of 85 patients with connective tissue disease treated with antimalarial drugs

	Retinopathy-positive (n = 21)	Retinopathy-negative (n = 64)	P-value
Female/male	20/1	62/2	0.561
Mean age (years)	30.9	25.2	0.144
Mean disease duration (years)	2.3	2.7	0.305
HQ/CQ user	8/13	42/22	0.001
Hypertension	17	5	0.258
Diabetes mellitus	6	2	0.395

HQ, hydroxychloroquine; CQ, chloroquine.

are not under risk of retinopathy. Easterbook *et al.*[17] observed retinopathy in 62 of 1650 patients (3.76%) receiving antimalarial medications. There are paradoxical opinions regarding development of antimalarial medication-related retinopathy. Some authors suggest that retinopathy development is associated solely with drug dose.[9] The safe drug dose established for HQ and CQ is 6 mg/kg/day and 4 mg/kg/day, respectively. All patients in our study group received similar daily doses per kilogram of both antimalarial drugs. Further, there wre no limitations (such as renal insufficiency) for drug doses in our patients. Some authors on the other hand, suggest that retinopathy development is associated with cumulative drug dose rather than daily dosage.[18] There are different and contradictory opinions regarding pathogenesis of retinopathy. Based on a widely accepted hypothesis, antimalarial medications accumulate in RPE and they bind to melanin granules. Loss of phagocytic functions of RPE cells and resultant RPE functional insufficiency leads to loss of rods and cones.[19,20] According to another opinion, accumulation of lipid complexes in retinal neuronal and glial cells is the most important factor triggering retinopathy. This results in DNA toxicity and necrotic cell death. Other suspected mechanisms include increase in intracellular pH, decrease in enzymatic activity and prostaglandin synthesis.[21] Effects of antimalarial drugs on cellular mechanisms are not yet completely known. For this reason, selection of functional tests that show early retinal changes is difficult. Meanwhile, systemic disease alone can trigger some ischemic changes in the retina. Such changes have been demonstrated in SLE and RA patients.[22,23] These ischemic changes result in electrophysiological abnormalities and may effect the functional tests that have been applied. Consequently, it becomes difficult to differentiate between retinal changes associated with the systemic disease and those associated with the antimalarial medications. The only means to make this differentiation is to cease treatment and monitor visual findings. There are some limitations to the present study. Since it was a single-center and retrospective study, the results cannot be generalized. In addition, this study was not a population-based study but clinical research, hence the proportion of severe cases is higher.

As a conclusion, there are still contradictory opinions regarding retinopathy associated with antimalarial medications. Duration and interval of patient follow-up, and ophthalmologic methods to be used during follow-up examinations are not yet completely agreed upon. Multicenter and prospective studies should be performed to provide further clarification on this topic.

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