Indian Journal of Ophthalmology
Journal of All India Ophthalmological Society

ORIGINAL ARTICLE
Year : 2016 | **Volume** : 64 | **Issue** : 10 | **Page** : 710--714

Screening for chloroquine maculopathy in populations with uncertain reliability in outcomes of automatic visual field testing

Paradee Kunavisarut[1], Pimploy Chavengsaksongkram[1], Aniki Rothova[2], Kessara Pathanapitoon[1],
[1] Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
[2] Department of Ophthalmology, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence Address:
Paradee Kunavisarut
Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, 110 Intawaroros Road, Chiang Mai 50200
Thailand

Abstract

Purpose: The purpose of this study was to compare screening methods for the early detection of maculopathy in patients treated with chloroquine (CQ) or hydroxychloroquine (HCQ) and to identify the risk factors for the development of toxic maculopathy. **Methods:** We performed a prospective study of all 217 patients taking CQ and/or HCQ and seen in our center between July 2011 and December 2013. All subjects underwent a complete ocular examination, as well as spectral domain optical coherence tomography (SD-OCT), fundus autofluorescence (FAF), and 10-2 Humphrey visual field (10-2 HVF). **Results:** The median age of patients was 51 years, median CQ/HCQ duration was 40 months, and median cumulative dose was 180 g. The prevalence of at least two abnormal tests was 7.4% (16/217). SD-OCT had the highest sensitivity, specificity, predictive values and accuracy while 10-2 HVF showed in 30% of nonreliable results and had the lowest specificity and positive predictive value. In multivariate analysis, an age of older than 60 years (P = 0.002), CQ duration of more than 5 years (P < 0.001), and CQ dose more than 3 mg/kg/day (P = 0.005) were associated with toxicity. **Conclusions:** In patients with unreliable outcomes of 10-2 HVF testing, SD-OCT in combination with FAF might represent a suitable alternative screening tool for toxic maculopathy.

How to cite this article:
Kunavisarut P, Chavengsaksongkram P, Rothova A, Pathanapitoon K. Screening for chloroquine maculopathy in populations with uncertain reliability in outcomes of automatic visual field testing.Indian J Ophthalmol 2016;64:710-714

How to cite this URL:
Kunavisarut P, Chavengsaksongkram P, Rothova A, Pathanapitoon K. Screening for chloroquine maculopathy in populations with uncertain reliability in outcomes of automatic visual field testing. Indian J Ophthalmol [serial online] 2016 [cited 2017 Jan 12];64:710-714
Available from: http://www.ijo.in/text.asp?2016/64/10/710/195018

Full Text

Chloroquine (CQ) and hydroxychloroquine (HCQ) are being used to treat rheumatoid arthritis, systemic lupus erythematosus, cutaneous lupus, and other connective tissue and skin disorders. Both drugs have significant retinotoxicity with HCQ being less retinotoxic [1],[2],[3],[4] because it does not cross the blood-retinal barrier.[5] Long-term CQ administration is still frequently used due to its low costs. CQ maculopathy is an uncommon complication of

this type of treatment and so far has no proven therapy. Early detection of CQ maculopathy is important because toxicity can lead to progressive and permanent vision loss despite cessation of the drug intake.[6],[7],[8] Due to the slow clearance of medication from the body, the full effects of drug withdrawal may take from 3 months to even more than 1 year.[9],[10] The aim of screening should be the detection of maculopathy in the "preclinical phase," which would allow an early cessation of the medication and prevent irreversible damage with severe visual loss. The American Academy of Ophthalmology (AAO)[10] recommends using 10-2 automated fields together with at least one of the following procedures for routine screening: (1) Multifocal electroretinogram (mfERG), (2) spectral domain optical coherence tomography (SD-OCT), or (3) fundus autofluorescence (FAF). A baseline examination is advised for all patients starting these drugs to serve as a reference point and to rule out maculopathy, which might be a contraindication to their use. Annual screening should begin after 5 years of use or earlier in the presence of additional risk factors.

The purpose of the study was to compare the usefulness of 10-2 Humphrey visual field (10-2 HVF), OCT, and FAF for early detection of macular toxicity in a tertiary center with a predominantly rural population and to identify the most appropriate screening tools within this population.

Methods

In this prospective study, we included all 217 consecutive patients taking CQ or HCQ who were examined between July 2011 and December 2013. Demographic data including age, sex, body weight, height, underlying disease, type, duration, and dosage of drug were registered. Data on CQ dosage, duration of treatment, and compliance were retrieved from the medical records and/or based on information from patients. The daily dosage per kilogram (kg) was calculated according to each patient's ideal body weight (IBW)[11] utilizing the following formula: (1) For males: 50 plus 0.91 (height in centimeters – 152.4), (2) for females: 45.5 plus 0.91 (height in centimeters – 152.4).

All patients were evaluated with visual acuity testing (best-corrected Snellen acuity), fundus examination with slit-lamp biomicroscopy and 78D magnifying lens, color fundus photography, SD-OCT, FAF, and 10-2 HVF testing. The mfERG was not available at our institute during the study. Dilated ocular examination and color fundus photography were performed to detect associated retinal disorders. Patients with ocular morbidities potentially affecting the results of the examinations were excluded from this study.

The used tests consisted of SD-OCT, FAF, and 10-2 HVF because other tests such as fundus photography, fluorescein angiography, Amsler grid, and color vision testing have been shown to be insensitive for the detection of toxicity.[10]

All three tests were classified by a masked researcher for the identity of patient and results of other investigations. SD imaging was performed using the Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany), which displayed the subfield thickness maps and high-resolution gray scale cross-section images. We defined the abnormal results when one or more of following characteristics were present: Inner segment/outer segment (OS) disruption (disruption of the ellipsoid zone), "flying saucer" sign,[12] and parafoveal thinning. FAF was recorded using a Spectralis unit (Heidelberg Engineering). We defined the abnormal results as the development of a patch of hyperfluorescence and/or hyperfluorescence around the fovea and/or more extensive hyperfluorescence with the dark parafoveal ring. Visual field testing was performed using 10-2 HVF (Humphrey perimeter; Carl Zeiss Meditec Inc., Dublin, CA, USA). We excluded all unreliable or noninterpretable results which were recommended by Humphrey instruments such as fixation loss error (>20%) and/or false positive/negative error (>33%). For the remainder (interpretable HVF), we defined the abnormal results as the development of decreased sensitivity at least of three decibels for at least three consecutive points or decreased sensitivity of at least ten decibels for at least two consecutive points on pattern deviation. Macular toxicity was defined as at least two abnormal tests were detected.

The study was approved by the Ethics Committee and conformed to the provisions of the Declaration of Helsinki.

Statistical analyses were performed using paired t-test, continuity corrected Chi-square test, Fisher's exact test, and logistic regression by a software package, SPSS 13.0 (SPSS Inc., Chicago, IL, USA). The statistical significance level was set at $P < 0.05$.

Results

Our study included 217 patients consisting of 183 females (84%) and 34 males (16%). The patient demographics are given in [Table 1]. The combination of three abnormal tests was found in 9/217 (4.1%) patients, two abnormal tests were found in 7/217 patients (3.2%), and one abnormal test was noted in 8/217 patients (3.7%). All patients with only one abnormal test result had abnormal 10-2 HVF.{Table 1}

In total, an abnormal 10-2 HVF was noted in 18 patients (18/217; 8.3%) while 65/217 (30%) had unreliable 10-2 HVF results. Of these 18 patients with abnormal 10-2 HVF, 10 patients exhibited at least one additional abnormal test result, specifically SD-OCT (n = 10) or FAF (n = 9) while 8 had no other abnormal test. The eight patients with solely abnormal 10-2 HVF test result underwent second 10-2 HVF test within 4 weeks. Seven out of eight (88%) exhibited a normal result of the second test and the remaining patient who was CQ-taking still had paracentral scotoma in the same location when retested. SD-OCT showed an abnormal result in 16 patients (16/217; 7%), FAF in 15 patients (15/217; 7%). From all patients with two abnormal tests, 6 patients had abnormal results with OCT and FAF (together with nonreliable results of 10-2 HVF) and 1 patient had abnormal result in OCT and 10-2 HVF while FAF showed normal results. Macular toxicity visible at fundoscopy was observed in three patients; all had abnormal results with all three tests performed.

The performance of the tests is given in [Table 2]. SD-OCT had higher specificity and higher positive predictive values compared to 10-2 HVF. FAF gave slightly lower performance compared to SD-OCT.10-2 HVF gave not interpretable results in 30% of patients and had, in consequence, the lowest positive predictive value. We also found that all patients with obvious parafoveal anatomical damage as diagnosed by SD-OCT had abnormal results in the 10-2 HVF and/or FAF; all were diagnosed with CQ toxicity.{Table 2}

The clinical characteristics comparing the toxicity and nontoxicity groups are shown in [Table 3]. All patients who developed macular toxicity were CQ-taking, were significantly older, and had a longer duration of medication exposure, higher daily dose, and higher daily dose per IBW as well as higher cumulative dosage than those with no toxicity.{Table 3}

Univariate analysis revealed that age older than 60 years, CQ duration of more than 5 years, CQ dose more than 3 mg/kg/day (MKD), and cumulative CQ dose more than 460 g (g) were the risk factors of CQ toxicity (P = 0.004, odds ratio [OR] 4.72, 1.66–13.42; P < 0.001, OR 28.7, 3.71–221.81; P = 0.003, OR 13.71, 1.78–105.8; and P < 0.001, OR 21.12, 6.32–70.59, respectively). In multivariate analysis, age older than 60 years, CQ duration of more than 5 years, and CQ dose more than 3 MKD were associated with macular toxicity (P = 0.002, OR 8.64, 2.14–34.87; P < 0.001, OR 68.69, 7.66–615.88; and P = 0.005, OR 22.05, 2.58–188.78, respectively).

Discussion

Our results documented that in our setting, SD-OCT had higher specificity and higher positive predictive values for early detection of CQ maculopathy than 10-2 HVF. SD-OCT was easy to perform and gave reliable results while 10-2 HVF was identified as the least reliable method and required repeated testing in one-third of the patients. FAF gave results similar to SD-OCT but required better-schooled technicians and interpreters.

The ideal screening test should be quick and easy to perform and moreover should have a high sensitivity and specificity for early detection of toxicity. Until 2011, a routine screening test for CQ toxicity in our institute consisted of 10-2 HVF, but the major problems comprised the necessity to perform multiple tests due to low 10-2 HVF reliability in a considerable number of patients. Due to low 10-2 HVF reliability, patients were asked to come back for repeated examinations, which in our situation (with most patients living in the far rural areas) lead frequently to loss of follow-up. There is no doubt about the efficacy and sensitivity of 10-2 HVF when reliable results are accomplished. In accordance, none of our patients with normal 10-2 HVF was diagnosed with CQ toxicity. In contrast, we identified one patient with normal SD-OCT and FAF images, who had repeatedly abnormal 10-2 HVF, which suggests that a reliable 10-2 HVF might be more sensitive than SD-OCT. This possible higher sensitivity of reliable 10-2 HVF in a proportion (up to 10%) of patients was already reported previously.[13] In theory, the SD-OCT-based approach might miss the very early stage of macular toxicity in a scarce number of patients. However, a recent study [14] demonstrated that OCT with ganglion cell analysis showed a concentric thinning even before any abnormality on 10-2 HVF.

The prevalence of toxic maculopathy observed in our country and other populations varied from 2.4%–31.4%[15],[16],[17],[18],[19],[20],[21] and 0.001%–40%,[2],[22],[23] respectively, depending on socioeconomic circumstances, health care, and variations in methods used for the prevention and diagnosis of maculopathy. In our study, the prevalence of at least two abnormal tests was 7.4% (16/217). In fact, the real prevalence might have been slightly higher if all of our

patients with noninterpre[table 10]-2 HVF were retested.

Since 2011, we included two objective tests (SD-OCT and FAF) in our screening.[10] Of these, SD-OCT gave the best results, while the performance of FAF was slightly lower than SD-OCT and needed more experience from the photographer and the interpreter [Table 2]. Several reasons support the usefulness of SD-OCT as a primary test for detection of CQ/HCQ maculopathy. First, its objective characteristics as the SD-OCT needs less cooperation from the patient than the 10-2 HVF. Second, the SD-OCT is less time consuming than the 10-2 HVF, and finally, it has high sensitivity and specificity as demonstrated in the present study.[12],[24],[25],[26],[27] In addition, the SD-OCT is easy to perform and to interpret. The low reliability of 10-2 HVF testing in our population might be caused by a large number of patients living in remote areas, having a low education and no experience with similar procedures. In addition, our results show that only 1 out of 217 patients had abnormal 10-2 HVF only in combination with normal results of OCT and FAF.

AAO in 2011[10] reviewed the risks of CQ/HCQ maculopathy and concluded that high-risk group had a duration of medication use of more than 5 years, the cumulative dose exceeded 460 g for CQ and 1000 g for HCQ, daily dose more than 3.0 MKD for CQ and 6.5 MKD for HCQ, elderly, kidney or liver dysfunction, and preexisting retinal or macular diseases. We found similar results except for kidney or liver dysfunction ($P = 0.135$), but could not evaluate for preexisting retinal or macular diseases, because in the present series, the patients with retinal disorders were excluded.

Based on our results, in our institute, we adapted AAO guidelines for CQ toxicity screening to save cost and time together with retaining high sensitivity and specificity as indicated in [Figure 1]. Our adapted guidelines might be of value for ophthalmologists caring for patients with uncertain or poor performance in visual field testing. Although the preferred screening method recommended by AAO consists of a combination of reliable 10-2 HVF testing with other objective tests of the macular area (SD-OCT, FAF, mfERG), in a center serving a population in which unreliable 10-2 HVF results are common, another approach, based on an objective test such as SD-OCT, might be more suitable. {Figure 1}

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Rynes RI. Ophthalmologic considerations in using antimalarials in the United States. Lupus 1996;5 Suppl 1:S73-4.
2 Finbloom DS, Silver K, Newsome DA, Gunkel R. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. J Rheumatol 1985;12:692-4.
3 Tobin DR, Krohel G, Rynes RI. Hydroxychloroquine. Seven-year experience. Arch Ophthalmol 1982;100:81-3.
4 Levy GD, Munz SJ, Paschal J, Cohen HB, Pince KJ, Peterson T. Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. Arthritis Rheum 1997;40:1482-6.
5 Raines MF, Bhargava SK, Rosen ES. The blood-retinal barrier in chloroquine retinopathy. Invest Ophthalmol Vis Sci 1989;30:1726-31.
6 Tehrani R, Ostrowski RA, Hariman R, Jay WM. Ocular toxicity of hydroxychloroquine. Semin Ophthalmol 2008;23:201-9.
7 Farrell DF. Retinal toxicity to antimalarial drugs: Chloroquine and hydroxychloroquine: A neurophysiologic study. Clin Ophthalmol 2012;6:377-83.
8 Michaelides M, Stover NB, Francis PJ, Weleber RG. Retinal toxicity associated with hydroxychloroquine and chloroquine: Risk factors, screening, and progression despite cessation of therapy. Arch Ophthalmol 2011;129:30-9.
9 Marmor MF, Carr RE, Easterbrook M, Farjo AA, Mieler WF; American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: A report by the American Academy of Ophthalmology. Ophthalmology 2002;109:1377-82.
10 Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF; American Academy of Ophthalmology. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology 2011;118:415-22.

11 Pai MP, Paloucek FP. The origin of the “ideal” body weight equations. Ann Pharmacother 2000;34:1066-9.

12 Chen E, Brown DM, Benz MS, Fish RH, Wong TP, Kim RY, *et al.* Spectral domain optical coherence tomography as an effective screening test for hydroxychloroquine retinopathy (the “flying saucer” sign). Clin Ophthalmol 2010;4:1151-8.

13 Marmor MF, Melles RB. Disparity between visual fields and optical coherence tomography in hydroxychloroquine retinopathy. Ophthalmology 2014;121:1257-62.

14 Brandao LM, Palmowski-Wolfe AM. A possible early sign of hydroxychloroquine macular toxicity. Doc Ophthalmol 2016;132:75-81.

15 Puavilai S, Kunavisarut S, Vatanasuk M, Timpatanapong P, Sriwong ST, Janwitayanujit S, *et al.* Ocular toxicity of chloroquine among Thai patients. Int J Dermatol 1999;38:934-7.

16 Chiowchanwisawakit P, Nilganuwong S, Srinonprasert V, Boonprasert R, Chandranipapongse W, Chatsiricharoenkul S, *et al.* Prevalence and risk factors for chloroquine maculopathy and role of plasma chloroquine and desethylchloroquine concentrations in predicting chloroquine maculopathy. Int J Rheum Dis 2013;16:47-55.

17 Srikua U, Aui-Aree N. Timing of chloroquine and hydroxychloroquine screening. Thai J Ophthalmol 2008;22:61-8.

18 Leecharoen S, Wangkaew S, Louthrenoo W. Ocular side effects of chloroquine in patients with rheumatoid arthritis, systemic lupus erythematosus and scleroderma. J Med Assoc Thai 2007;90:52-8.

19 Thongsin S. Chloroquine maculopathy in Chiang Rai Regional Hospital. Lampang Med J 2010;31:98-103.

20 Suansilpong A, Uaratanawong S. Accuracy of Amsler grid in screening for chloroquine retinopathy. J Med Assoc Thai 2010;93:462-6.

21 Samsen P, Ruangvoravate N, Chiemchaisri Y, Parivisutti L. Chloroquine keratopathy. Thai J Ophthalmol 1995;9:167-73.

22 Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. Am J Med 1983;75:25-34.

23 Cox NH, Paterson WD. Ocular toxicity of antimalarials in dermatology: A survey of current practice. Br J Dermatol 1994;131:878-82.

24 Stepien KE, Han DP, Schell J, Godara P, Rha J, Carroll J. Spectral-domain optical coherence tomography and adaptive optics may detect hydroxychloroquine retinal toxicity before symptomatic vision loss. Trans Am Ophthalmol Soc 2009;107:28-33.

25 Marmor MF. Comparison of screening procedures in hydroxychloroquine toxicity. Arch Ophthalmol 2012;130:461-9.

26 Rodriguez-Padilla JA, Hedges TR 3rd, Monson B, Srinivasan V, Wojtkowski M, Reichel E, *et al.* High-speed ultra-high-resolution optical coherence tomography findings in hydroxychloroquine retinopathy. Arch Ophthalmol 2007;125:775-80.

27 Pasadhika S, Fishman GA. Effects of chronic exposure to hydroxychloroquine or chloroquine on inner retinal structures. Eye (Lond) 2010;24:340-6.