Accuracy of Amsler Grid in Screening for Chloroquine Retinopathy

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Objective: *Determine the accuracy, sensitivity, and specificity of an Amsler grid testing for chloroquine retinopathy screening.*
Material and Method: *One hundred and forty patients who received chloroquine phosphate or hydroxychloroquine sulfate and attended the rheumatology clinic of BMA Medical College and Vajira Hospital between March 2008 and May 2009 were included. The patients underwent Amsler grid testing, which would be interpreted by a rheumatologist, for any evidence of chloroquine retinopathy. The results from Amsler grid testing were then compared to the results from a Humphrey 10-2 fields testing, which was subsequently performed by an experienced ophthalmologist and was used as a gold standard.*
Results: *Out of 140 patients, chloroquine retinopathy was evidenced in 11 patients (7.9%). Kappa value of the Amsler grid testing interpreted by rheumatologist and the Humphrey 10-2 fields testing interpreted by ophthalmologist was 0.89. The accuracy for screening chloroquine retinopathy by the Amsler grid testing was 98.6% (95% confidence interval [CI], 98.1-100.0%) with the sensitivity of 81.8% (95% CI,75.4-88.2%). The specificity and positive predictive value were 100.0% while the negative predictive value was 98.4% (95% CI, 96.4-100.0%).*
Conclusion: *Amsler grid testing is an accurate screening test for chloroquine retinopathy with very high specificity. The test could be achieved by a rheumatologist who could practically serve the patients in one visit at the rheumatology clinic.*

Keywords: *Chloroquine retinopathy, Screening, Amsler grid testing*

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Chloroquine is the quinine drug commonly used to treat and prevent malarial infestation. The drug is also active in other diseases, such as, rheumatoid arthritis, autoimmune disease, and dermatologic disorders[1]. Because of a relative lack of systemic side effect compared with other immunomodulating drugs[2], chloroqine has been used widely since 1951[1]. Its common side effects are tinnitus, pruritus, cutaneous hyperpigmentation, bleaching of hair, aplastic anemia, reversible diplopia, intraepithelial corneal drug deposits, and retinopathy[1].

Chloroquine retinopathy was first described by Hobbs et al in 1959[3]. Histopathologic changes depend upon drug levels and duration of exposure. This may range sequentially from multilamellar structures throughout the retina, loss of the neural retina including ganglion cells and photoreceptors, and atrophy of retinal pigment epithelium. Early clinical finding which is reversible once the drug is discontinued is bilateral paracentral scotoma without any fundus change[4]. At the irreversible stage, the retinal epithelium is depigmented in the central macula sparing small central foveal island giving a bull's eye feature. In advanced cases, the retinal depigmentation is widespread, over the entire fundus, resulting in retinal atrophy and vascular narrowing with ultimate loss of visual acuity, peripheral vision, and night vision. In some cases, despite cessation of the drug, retinal depigmentation and functional loss continued over several years[5,6]. The prolonged toxicity could be due to tight binding of the drug to melanin in the retinal pigment epithelium. It is a slow clearance of drugs from the body, which can take months to years, gradual decompensation of cells that had been injured during the period of drug exposure. Or, it could be due to a continual drug release from a reservoir in the melanin-containing tissue in the body. These effects on visual

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function of advanced chloroquine toxicity must be differentiated from retinitis pigmentosa[7].

Between the two forms of chloroquine, chloroquine phosphate can cause retinopathy more frequently than hydroxychloroquine sulfate[8]. Other predisposing factors are drug dosage[9], total duration of treatment[10], liver function, and renal function[11]. In Thailand, although hydroxychloroquine sulfate is better tolerated with fewer side effects, chloroquine phosphate is more commonly used due to its lower cost. Generally, the clinician will prescribe a daily dosage of one 250 mg tablet of chloroquine phosphate or two 200 mg tablets of hydroxychloroquine sulfate due to the convenience of pharmaceutical availability. These drug dosages could be considered as higher than the doses limiting toxicity at 3 mg/kg/day for chloroquine phosphate and 6.5 mg/kg/day for hydroxychloroquine sulfate[10,11]. The toxicity is commonly evidenced in a prolonged use over 5 years[7].

Despite the fact that chloroquine retinopathy could occur and cause a major public health problem, only few data were available[12,13]. Thus, screening for early chloroquine retinopathy is crucial. Several diagnostic tools for chloroquine retinopathy are available, *e.g.* fundus examination by indirect ophthalmoscope and slit lamp biomicroscope with high plus lens[4,7,8], automated perimetry[7,8,10,15], electrophysiological testing[4,7,8], and color vision test[4,7,8,16]. Humphrey perimetry 10-2 program is a standard test to detect chloroquine retinopathy. However, it is time consuming, expensive, and difficult to perform. Amsler grid[7,11], which is the test to evaluate macula disease was reported to be useful to screen chloroquine retinopathy[15,17]. Because Thailand has few ophthalmologist, any cost-effective screening test that could be conducted by a clinician or a para-medical personnel would be very useful. Nevertheless, the test should yield acceptable diagnostic performances to serve the purpose.

The purpose of the present study was to determine the accuracy, the sensitivity, and the specificity of Amsler grid testing interpreted by rheumatologist for chloroquine retinopathy screening.

Material and Method

The present study was conducted after an approval from the Ethics Committee on Researches Involving Human Subjects of the institution and the Bangkok Metropolitan Administration. One hundred and forty patients who attended the rheumatology clinic, BMA Medical College and Vajira Hospital between March 2008 and May 2009 were included. Inclusion criteria were rheumatic patients who received chloroquine phosphate or hydroxychloroquine sulfate, and were consulted at the Ophthalmology Department of the institution for detection of chloroquine retinopathy. All patients were required to give informed consent prior to entering into the present study. The patients were tested by a standard Amsler grid at the rheumatology clinic each eye at a time. The rheumatologist, who had been introduced and educated how to conduct an Amsler grid testing, would ask the patients for any area (s) of the patient's visual defect, and mapped the defected square (s) by himself. The Amsler grid, designed by Marc Amsler of Zurich, is a 10 x 10 cm white grid containing 400 small squares on a black background. Each individual square corresponds to 1° of visual angle with an overall of 20° per total grid area. Chloroquine retinopathy was diagnosed in any patient with faded or absent squares on the Amsler grid in both eyes. After Amsler grid testing, the patients underwent Humphrey 10-2 fields with white light test performed by an experienced ophthalmologist. An indirect ophthalmoscopy and a slit lamp biomicroscopy with high plus lens were performed after retinal dilatation to examine for the gross clinical pathologic change of retina. Evidence of bilateral paracentral scotomas on Humphrey 10-2 fields testing was used as gold standard for diagnosis of chloroquine retinopathy. Data collected were age and gender of the patients, weight, type and total dose of chloroquine drug, and duration of treatment.

Statistical analysis was performed using STATA software package version 7 (College Station, Texas, USA). Demographic data of age was expressed as mean with standard deviation. The other characteristic features were categorized into groups and presented as numbers with percentages. The agreement of the two methods was expressed as Kappa value while the diagnostic performances of the Amsler grid were expressed as accuracy, sensitivity, specificity, positive predictive value, and negative predictive value with their 95% confidence intervals (CIs).

Results

Of the 140 patients who met inclusion criteria, 135 of them were female (96.4%). Mean age of all patients was 46.9 $\pm$ 12.4 years. The majority of them received chloroquine phosphate (114 patients or 81.4%), with the prescribed dosage of more than 3 mg/kg/day in 90/114 patients (78.9%). Among 26 patients (18.6%) who

received hydroxychloroquine sulfate, approximately 1/3 of them (38.5%) had it more than 6.5 mg/kg/day. Basic demographic data of the patients are shown in Table 1.

From the Amsler grid testing by rheumatologist, chloroquine retinopathy was reported in nine patients (6.4%) while the diseases were evidenced in 11 patients (7.9%) from the Humphrey 10-2 fields testing by the ophthalmologist. Among the 11 patients affected by chloroquine retinopathy, bull's eye maculopathy were observed in two patients. The number of patients being diagnosed as chloroquine retinopathy by the Amsler grid testing and the Humphrey 10-2 fields testing are shown in Table 2. Only two patients being affected by chloroquine retinopathy were missed from the Amsler grid testing (false negative). All of the nine patients who were diagnosed as having retinopathy were confirmed by the Humphrey testing.

The Kappa value between the two tests was 0.89%. The accuracy for screening chloroquine retinopathy by the Amsler grid testing was 98.6% (95% confidence interval [CI], 98.1-100.0%) with the sensitivity of 81.8% (95% CI, 75.4-88.2%). The specificity and positive predictive value were 100.0% while the negative predictive value was 98.4% (95% CI, 96.4-100.0%).

Of note, all of the 11 patients who had chloroquine retinopathy received chloroquine phosphate; 10 of them were female, nine (81.8%) had the drug dosage of more than 3 mg/kg/day, and six (54.5%) had a prolonged usage of more than 5 years. Out of the nine patients who had scotoma from Amsler grid test, eight had an excellent correlation of the field defects with the Humphrey 10-2 filed test regarding the area and extent of involvement.

Table 1. Demographic data of rheumatologic patients having chloroquine retinopathy screening (n = 140)

Variables	Number	Percentage
Gender		
Male	5	3.6
Female	135	96.4
Drugs, dosages, and duration of treatment		
Chloroquine phosphate	114	81.4
Dose > 3 mg/kg/day	90	78.9
Duration > 5 years	33	28.9
Hydroxychloroquine sulfate	26	18.6
Dose > 6.5 mg/kg/day	10	38.5
Duration > 5 years	5	19.2

Discussion

Since long-standing retinopathy could result in visual loss, any effective programs to prevent, to screen, and confirm early detection would be useful. A timely cessation of the drug causing retinopathy has been proven to be effective in reducing the risk of visual loss[14].

Many rheumatologic patients who receive chloroquine frequently present with chloroquine retinopathy in advanced stage, which is irreversible or may progress after treatment is discontinued[7]. Since chloroquine retinopathy can reverse by stopping the drug, it is important to detect the initial changes so that medication can be halted to normalize or prevent further loss of visual function. Although there is consensus concerning the cost-effectiveness of the screening, the best method has not been established[15]. Amsler grid testing is a simple screening test, which was reported to be a cost effective for chloroquine retinopathy[15,17].

The prevalence of chloroquine retinopathy in the present study was 7.9%, which was in the range of 0.001-40%[18] that had been reported. However, the present study finding was much lower than the two previous studies in Thailand that reported chloroquine

Table 2 Comparison of chloroquine retinopathy diagnosed with Amsler grid testing interpreted by rheumatologist and the Humphrey 10-2 fields testing interpreted by ophthalmologist (n = 140)

Amsler grid testing	Humphrey 10-2 fields testing (gold standard)		
	No chloroquine retinopathy (n)	Chloroquine retinopathy (n)	Total
No chloroquine retinopathy	129	2	131
Chloroquine retinopathy	0	9	9
Total	129	11	140

retinopathy as high as 14.2%[13] or 20.4%[12]. This difference might lie on the strict criteria of diagnosis in each study. Bernstein[8] reported lower risk of chloroquine retinopathy with hydroxychloroquine sulfate than chloroquine phosphate. The American Academy of Ophthalmology[7] reported that the great majority of hydroxychloroquine toxicity had occurred in individuals taking more than 6.5 mg/kg/day and most chloroquine toxicity has occurred with doses above 3 mg/kg/day and the drug being used for least 5 years. All of the 11 patients affected by chloroquine retinopathy received chloroquine phosphate, nine of them using more than 3 mg/Kg/day and seven of them used it for more than 5 years. One obvious reason is the availability of pharmaceutical preparation tablets, which are considered too strong for the Thai or Asian people with a smaller body build than the Western people.

The present study was done to evaluate the diagnostic performance of Amsler grid testing by rheumatologist for chloroquine retinopathy screening. The agreement between the Amsler grid testing and the Humphrey 10-2 fields testing, which was used as a gold standard, was almost perfect (Kappa value = 0.89). The high Kappa value was probably due to the Amsler grid testing that had high efficacy in screening for chloroquine retinopathy.

The accuracy of screening chloroquine retinopathy by Amsler grid testing in the present study was 98.6% while the sensitivity and the specificity were 81.8% and 100.0%, respectively. The sensitivity and specificity of the Amsler grid in the present study were higher than the values that had been previously reported[15,19]. The others reported 60-79% sensitivity and 95-100% specificity[15,19]. Excellent correlation of area and extent field defect from the Amsler grid and Humphrey 10-2 fields testing in the present study (8/9 cases) was consistent with Easterbrook study, which also found good correlation of the scotoma from both tests[15].

Of 11 chloroquine retinopathy patients diagnosed by Humphrey 10-2 fields testing, two of them were missed from the Amsler grid testing. Paracentral scotoma in these two patients was missed from the Amsler grid leading to false negative result. Type of Amsler grid might have an effect on the result. Almony et al[17] suggested that Amsler grid of threshold type is more sensitive for the detection of scotoma than the standard type, which was used in the present study. Of note, 2/11 (18.2%) chloroquine retinopathy in the present study had bull's eye maculopathy found from an ophthalmoscopic examination. One patient received 2.5 mg/kg daily dose of chloroquine phosphate for 9 years while the other received 3.7 mg/kg daily dose for 2 years. These data supported information that both drug dosages and duration of treatment are very important risk factors. Hence, the clinician (both rheumatologist and ophthalmologist) should be very careful in prescribing the drug and surveillance for its toxicity as indicated since this degree of damage is irreversible and will certainly affect the patients' quality of life.

The present study showed that the Amsler grid testing could serve as a screening test for chloroquine retinopathy to identify patients with retinopathy for referral for ophthalmic evaluation and management. The test could be applied in rheumatology clinic.

Conclusion

Amsler grid testing is a convenient screening test for a diagnosis of chloroquine retinopathy. The test could be achieved by rheumatologist who could practically serve the patients in one visit at a rheumatology clinic.

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ความแม่นยำของการใช้ Amsler grid ในการคัดกรองจอตาเสื่อมจากยาคลอโรควิน

อภิชาติ สวนศิลป์พงศ์, สมชาย เอื้อรัตนวงศ์

วัตถุประสงค์*: เพื่อหาความแม่นยำ ความไว ความจำเพาะของการใช้ Amsler grid เพื่อตรวจคัดกรองโรคภาวะจอตาเสื่อมที่มีสาเหตุจากยาคลอโรควิน*

วัสดุและวิธีการ*: ศึกษาในผู้ป่วยโรคข้อจำนวน 140 ราย ที่ได้รับยา chloroquine phosphate หรือ ยา hydroxychloroquine sulfate จากคลินิกโรคข้อ วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล ระหว่างเดือนมีนาคม พ.ศ. 2551 ถึง เดือนพฤษภาคม พ.ศ. 2552 ผู้ป่วยได้รับการตรวจ หาภาวะจอตาเสื่อม จากยาคลอโรควิน โดยใช้ Amsler grid และแปลผลโดยแพทย์โรคข้อ แล้วจึงได้รับการตรวจโดยวิธีมาตรฐานจากจักษุแพทย์ นำข้อมูลที่ได้ทั้งหมดมาวิเคราะห์เปรียบเทียบทางสถิติ*

ผลการศึกษา*: ค่าความชุกของภาวะจอตาเสื่อมจากยาคลอโรควิน เท่ากับร้อยละ 7.9 จากผู้ป่วยโรคข้อ 140 ราย ค่าความสอดคล้อง ระหว่างการตรวจทั้งสองวิธี เท่ากับ 0.89 ค่าความแม่นยำ และความไวในการคัดกรองของภาวะจอตาเสื่อมจากยาคลอโรควิน เท่ากับ ร้อยละ 98.6 และร้อยละ 81.8 ตามลำดับ ในขณะที่ค่าความจำเพาะและค่าการทำนายผลบวกเท่ากับ ร้อยละ 100.0 ส่วนค่าการทำนายผลลบเท่ากับ ร้อยละ 98.4*

สรุป*: การใช้ Amsler grid ในการคัดกรองภาวะจอตาเสื่อมจากยาคลอโรควิน เป็นวิธีที่มีความแม่นยำและความจำเพาะสูง การคัดกรองสามารถทำโดยแพทย์โรคข้อซึ่งสามารถทำการตรวจรักษาโรคข้อ และคัดกรองจอตาเสื่อมจากยาคลอโรควิน ได้ในการมาตรวจเพียงครั้งเดียวกันของผู้ป่วย*