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Evaluation of Several Tests in Screening for Chloroquine Maculopathy

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Summary

Patients receiving antimalarial therapy, specifically hydroxychloroquine, for different periods were evaluated using contrast sensitivity test (CST) and results were compared with those of electro-retinography (EOG), and pattern visual evoked potential (PVEP), and a matching age control group. The results indicated CST to be most sensitive of the evaluated techniques particularly in patients under 40 years old. In 44.4% of the cases CST revealed macular dysfunction of which the other two methods of examination were not capable. Our findings suggest the CST is a reliable and practical method which could be used as an additional screening test for chloroquine maculopathy.

Clinicians are making every possible effort to achieve early diagnosis of chloroquine retinopathy which is particularly important in the early stages of this condition, when there is still a possibility for reversal.

With the recently increasing use of chloroquine and chloroquine derivatives in the treatment of connective tissue diseases,[1,2] early diagnosis of chloroquine maculopathy has become imperative. In an attempt to achieve this, many tests have been proposed, including visual fields, colour vision, Amsler grid, and fluorescein angiography.[3,4,5,6,7]

Electro-oculography (EOG) is one of these tests, and has been reported to be a sensitive test,[8] although this is still controversial.[9] The test is still used in several centres for the detection of functional disturbances induced by the storage of chloroquines in the retinal pigment epithelium.[10]

The spatial contrast sensitivity test (CST), using sinusoidal gratings, is frequently recommended as a sensitive means of detecting and evaluating several macular diseases.[11,12] The pattern visual evoked potential (PVEP) has also been suggested for testing macular disorders.[13,14]

We report the results and relative sensitivity of the CST, EOG and PVEP tests in revealing early chloroquine maculopathy in 27 patients treated for long periods with hydroxychloroquine, which is a less toxic derivative of chloroquine.

Patients and Methods

Twenty-seven patients, ranging in age from 21 to 80 years and suffering from rheumatoid arthritis, systemic lupus erythematosus, familial Mediterranean fever and other collagen diseases, were examined (Table I). The subjects were treated with hydroxychloroquine at a dosage of 200 mg./day for periods ranging from 1 to 9 years.

A second, randomly chosen, group of 28 patients, of similar age, served as a control (Table II). Some of these subjects suffered

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Table I *Results of various evaluations and duration of treatment in patients under antimalarial drugs*

Age	Years of treatment	corrected V.A. RE	corrected V.A. LE	E.O.G. RE	E.O.G. LE	Arden Ind.* RE	Arden Ind.* LE	C.S.T. RE	C.S.T. LE	P.V.E.P. BE
Subgroup A										
21	2	6/6	6/6	270	290	46	46	normal		
21	2	6/6	6/6	340	340	55	55	··		
21	2	6/6	6/6	290	300	64	67+	··		
34	1.5	6/6	6/6	260	260	57	59	··		
37	4	6/6	6/6	190	180	61	60	··		
39	1.5	6/9	6/9	240	210	63	66+	··		
40	3	6/9	6/9	200	220	75	65+	Sub ··		
Subnormal B										
41	3	6/9	6/9	290	280	53	56	normal		
41	7	6/6	6/6	320	350	51	54	··		
43	2	6/6	6/6	245	285	47	45	··		
43	7	6/6	6/6	210	200	42	45	··		
43	3	6/9	6/9	190	285	59	60	··		
47	2	6/6	6/6	220	230	58	59	··		
48	4	6/9	6/9	300	330	62	58	··		
50	8	6/6	6/6	200	180	63	68+	··		
51	1	6/6	6/6	235	235	67	64+	··		
53	2	6/6	6/6	220	235	48	53	··		
53	6	6/9	6/12	230	180	116	118+	··		
54	8	6/12	6/12	285	230	74	64+	··		
55	3	6/9	6/9	265	220	52	51	··		
59	2	6/24	6/7.5	275	268	50	61	··		
60	3	6/6	6/6	156	145+	77	67+	··		
64	2	6/12	6/9	133	150+	108	101+	··		
64	1	6/9	6/9	172	172+	90	100+	··		
68	8	6/9	6/9	225	257	76	82+	Sub ··		
74	9	6/12	6/12	270	200	50	41	normal		
80	3	6/15	6/12	130	125+	85	91+	··		

* Arden Ind.: Arden Index
† Subnormal or borderline values.

from dry eyes or various types of conjunctivitis, others were referred for a driving license test.

Each patient underwent a full ophthalmological examination, including visual acuity, ocular pressure, slit lamp biomicroscopy and direct and indirect fundus ophthalmoscopy, with emphasis on the appearance of the macula. Among the treated patients the average intraocular pressure ranged between 14 and 22 mmHg; the anterior segments were normal in all patients except for mild lenticular sclerosis seen in 4 patients, though their visual acuity was maintained at a 6/6–6/12 level. The fundus findings were within normal limits in all these patients, but two patients showed fine pigmentary stippling of the macula and age-related peripheral pigmentary changes.

In the control group six patients aged 58 years and above had mild lenticular sclerosis which affected their visual acuity to the level of 6/12.

Patients with media opacity, ocular or macular pathology or any other aetiology which affected their visual acuity, or appeared to affect the CST, were excluded from the study.

The CST was performed using AO contrast sensitivity test plates, with each plate at a test distance of about 57 cm. from the eyes, producing a 2c/degree at plate 2 and up to 6.4c/degree at plate 7. The test was conducted at the recommended illumination level of 100 ft. candles. After explanation and presentation of the demonstration plate (plate 1) to the patient, each plate was slowly drawn from the original box at a full plate exposure speed of 15 seconds. In elderly patients the plate exposures were repeated twice, in order to

Table II *Control Group Evaluations*

Age	Visual acuity RE	LE	E.O.G. RE	Arden Ind.* LE	C.S.T. RE	LE	P.V.E.P. BE
Subgroup C							
20	6/6	6/6	210	210	54	54	normal
20	6/6	6/6	220	215	59	58	··
21	6/7.5	6/6	230	200	53	44	··
23	6/6	6/9	195	200	59	54	··
25	6/6	6/6	190	185	58	60	··
28	6/6	6/6	240	225	46	48	··
33	6/6	6/6	210	205	51	58	··
35	6/7.5	6/7.5	195	210	56	53	··
39	6/6	6/6	200	215	49	53	··
40	6/6	6/6	210	220	60	57	··
Subgroup D							
41	6/6	6/6	235	215	61	59	··
41	6/6	6/6	190	205	55	53	··
45	6/6	6/6	210	220	56	56	··
47	6/6	6/6	185	195	62	61	··
48	6/6	6/9	190	200	40	45	··
50	6/9	6/6	225	215	49	51	··
53	6/6	6/6	230	245	55	59	··
55	6/6	6/6	215	220	61	62	··
58	6/7.5	6/9	230	240	54	57	··
58	6/6	6/6	200	195	68	71+	··
60	6/12	6/9	223	215	50	52	··
63	6/7.5	6/6	194	195	53	56	··
66	6/6	6/6	205	207	61	58	··
71	6/12	6/9	170	175+	75	80+	··
73	6/9	6/9	185	180	57	59	··
75	6/9	6/6	195	205	57	56	··
78	6/12	6/12	175	168+	84	79+	··
80	6/9	6/9	215	210	63	60	··

* Arden In.: Arden Index
† Subnormal or borderline values.

avoid learning difficulty and to get a consistent performance of the test. The score was recorded as the patient's first response. The total score for all the plates was taken as the final result. A score of 62 or less was considered normal, that between 63–78 was considered suspect, and above that was definitely abnormal.

The EOG was performed by sitting patients at a distance of one metre from the screen, with two fixation points at a distance of 30° one from the other. The electrodes were attached to the medial and lateral canthus of each eye, and an indifferent electrode was attached to the ear. At a given rhythm, the patient was instructed to alternate his fixation between the two points, for one minute at a time. The examination was performed in a dark room for 15 minutes and repeated in a lighted room for a further 15 minutes. The Arden index was calculated by dividing the light peak/dark trough. A score of 1.8 or 180% was considered the lower normal limit (0.2 or 20% is the standard deviation in our laboratory).

The PVEP was performed in a semi-sitting position, at a distance of 1.5 m from a TV checkerboard screen stimulator with 95% contrast and 1.88 c/sec frequency and 36 sec check size. The electrodes were attached to the scalp with pentonate paste 5 cm above the 3 cm lateral to the inion on each hemisphere. The reference electrode was attached to the forehead and the indifferent electrode to the ear. Each eye was stimulated separately, and the unexamined eye was covered with a heavy black tissue and the patient's palm. The average response following 100 stimuli was

recorded on a film, with 110 msec considered the normal first major peak latency.

Results

As shown in Table I, the CST was normal in 15 of the 27 treated patients, suspect in seven patients, and definitely abnormal in five patients—all five having been on antimalarial treatment for periods ranging from one to eight years.

The EOG results were normal in 23 out of 27 patients. One patient showed a borderline Arden index (1.7), and the remaining three patients showed definitely pathologic Arden indices, two of these three patients had been on antimalarial medication for two years, and the third for three years. These four patients were also included in the five cases which showed a pathologic CST.

The PVEP was normal in 25 out of 27 patients. In two patients there was a latency of more than 110 msec. In these two cases the EOG was normal, but the CST was suspect. No pathology was discerned which could account for the abnormal PVEP.

In the control group (Table II), the CST was subnormal in two and borderline in one of the 28 cases. One of the 28 control patients was considered normal though the right eye scored 63, just above the upper limit (62), and the left eye was within the normal range at 60. the EOG was subnormal in only two of the 28 controls. The PVEP was normal in all the controls.

When the two groups were subdivided, using 40 years as the separating age, the treated group was now divided into seven young patients, (subgroup A), and 20 older patients (subgroup B) (see Table I). The control group included ten patients under 40 years of age (subgroup C), and 18 patients over 40 (subgroup D) (see Table II).

A comparison of these subgroups showed the CST to be subnormal or borderline in three out of seven treated patients in subgroup A, and in nine of the 20 patients in subgroup B. In the untreated control patients the results of this test proved normal in all the C control subgroup, and pathologic or borderline in three of the 18 in D control subgroup.

On the other hand, normal EOG was seen in all subgroup A patients, and subnormal EOG in four of the 20 subgroup B subjects (Table I). In the control subgroups (C, D) the EOG was normal in the entire C subgroup, and subnormal in two of the 18 in D control subgroup (Table II).

The PVEP was subnormal in one patient of each of the A and B treated subgroups, and normal in all the subgroup C and D control patients.

Discussion

Plaquenil maculopathy, which is difficult to detect at the early, occasionally reversible stage, presents a challenge and a major medicolegal problem for ophthalmologists.

In screening for this maculopathy, one of the many tests used is EOG. However, its merits have recently been questioned, with the discovery of low values in untreated patients suffering from rheumatoid arthritis.[15]

The CST has been described as a sensitive test for several ocular conditions, including media haziness,[16,17] maculopathies,[11] glaucoma[18] and diseases of the optic nerve.[19,20]

Our study of 27 patients treated with hydroxychloroquine for long periods, ranging from one to nine years, showed that it was possible to detect abnormal macular function far more readily by screening these patients with the CST than with either the EOG or PVEP tests. These findings were highly significant as shown by χ-square statistical analysis of the three tests, and in a comparison between the control and treated groups.

In the treated patients the CST was pathologic or suspect in 44.4% of the cases (12 out of 27), a significantly high percentage compared with the 14.8% (four out of 27) found in the EOG test ($p<0.02$), or the 7.4% (two out of 27) in the PVEP test ($p<0:01$).

In the untreated control group, the frequency of pathologic or suspected CST was 10.7% (three out of 28), as compared with 44.4% in the treated group, the difference between the two groups revealing a high statistical significance ($p<0.005$).

On the other hand no significant difference in the frequency of pathological changes in the EOG ($p<0.99$) was found between the control group (7.1%, two out of 28) and the treated group (14.8%).

Since no pathological changes were found

in the two subnormal PVEP subjects in the treated group, the results of the test were not considered to be of any significance.

It should be emphasised that the abnormal results were detected in fundi of normal appearance.

The reason for the three positive CST cases detected in the control group (Table II) is not clear. In two nuclear sclerosis may be the underlying cause, or in all three just a poor performance. Senile changes in the pigment epithelial cells, such as the accumulation of lipofuscein deposits, might account for the two positive EOG results among the control group.

The findings were more striking on comparison of the treated and untreated subgroups. The EOG proved normal in all the treated A subgroup and control C subgroup, with no difference between the two, whereas the CST was abnormal in 42.88% (three out of seven) of the treated A subgroup, but normal in the entire matching control C subgroup ($p<0.05$), statistically very significant.

Although significant, the difference was less conspicuous when the older subgroups were considered, with the EOG subnormal in 20% (four out of 20) of the treated B subgroup, compared with 11.1% (two out of 18) in the control D subgroup ($p<0.5$). The CST was subnormal in 45% (nine out of 20) of the treated B subgroup, compared with 16.7% (three out of 18) in the control D subgroup ($p<0.1$).

It should be noted that improvement in the CST performance was evident in patients following discontinuation of medication, and in some of them the re-establishment of treatment caused reduction in the CST performance (data under evaluation, not included here), a fact which may lend support to the notion that the abnormal results are related to the antimalarial treatment.

Although the group studied was relatively small, the results support the fact that the CST is more effective and sensitive than the EOG in detecting macular hypofunction induced by antimalarial drugs. It should be borne in mind that the CST may show some false positive results with advancing age (Table II), although in patients under 40 its accuracy is much better. Using this test, macular abnormality was detected in 45% of the treated patients under 40, but none in the control subgroup ($p<0.05$).

In conclusion, we consider that the CST is a suitable test for evaluation and follow up of chloroquine-induced maculopathy. It is sensitive, easy to perform and less time consuming than other tests. In addition, although not included in our study, it is less psychologically traumatic for the paediatric age group, which constitutes a considerable proportion of patients under antimalarial treatment.

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