Multifocal Electroretinographic Evaluation of Long-term Hydroxychloroquine Users

Raj K. Maturi, MD; Minzhong Yu, PhD; Richard G. Weleber, MD

Objectives: To observe the long-term effects of hydroxychloroquine sulfate on retinal electrical activity by multifocal electroretinography (mfERG) and to evaluate the regional variation of retinal dysfunction in subjects with hydroxychloroquine retinopathy.

Methods: Multifocal ERG with 103-hexagon stimulation was performed on 19 patients (36 eyes) treated with hydroxychloroquine for systemic lupus erythematosus, rheumatoid arthritis, or localized atypical scleroderma. Visual acuity testing, Amsler grid testing, and Ishihara color vision testing were also performed. In 2 of the patients, hydroxychloroquine was discontinued due to concerns about toxicity. Both of these patients had additional mfERG performed after discontinuation of medication.

Results: Twelve patients (19 eyes) had a normal response density in one or both eyes, including 6 patients (12 eyes) with a low lifetime dose (≤438 g) of hydroxychloroquine who had normal response densities in both eyes. Eleven patients (17 eyes) had abnormal response densities in one or both eyes, and 2 of these patients (4 eyes) had significant attenuation of response densities in almost the whole tested field; 4 patients had a normal mfERG result for one eye but had a slight decrease of response densities for the other eye. There were 4 patterns of abnormal mfERG amplitude change observed: (1) paracentral loss, (2) foveal loss, (3) peripheral loss, and (4) generalized loss. Implicit times were abnormal for pericentral responses in 3 patients. The results of color vision and Amsler grid testing were normal, except for one patient with a generalized loss pattern. In 2 subjects in whom hydroxychloroquine toxicity was suspected, response densities improved after termination of hydroxychloroquine.

Conclusions: Long-term hydroxychloroquine use may be associated with mfERG abnormalities. The mfERG appears to detect retinal physiological change earlier than visual acuity testing, color vision testing, or Amsler grid testing can. The greatest value of the mfERG is in differentiating a retinal cause and, hence, providing important evidence for hydroxychloroquine toxicity, for whatever visual field loss is apparent on perimetry.

Arch Ophthalmol. 2004;122:973-981

From the Midwest Eye Institute (Drs Maturi and Yu) and the Methodist Research Institute (Dr Yu), Indianapolis, Ind; the Ophthalmological Laboratory of the Ministry of Health and Zhongshan Ophthalmic Center, Zhongshan University, Guangzhou, People's Republic of China (Dr Yu); and Casey Eye Institute, Oregon Health & Science University, Portland (Dr Weleber). *The authors have no relevant financial interest in this article.*

ALTHOUGH CHLOROQUINE and hydroxychloroquine sulfate are 2 of several antiprotozoal drugs that have been used for many years in the treatment of malaria, their preferred usage in the United States is for treatment of various rheumatic diseases, particularly systemic lupus erythematosus and rheumatoid arthritis. However, long-term hydroxychloroquine and chloroquine use can cause severe visual loss due to a toxic effect on the outer retina and the retinal pigment epithelium. Chloroquine retinopathy was first reported by Hobbs et al[1] in 1959, and hydroxychloroquine retinopathy was first reported by Shearer and Dubois[2] in 1967. Ophthalmoscopy, slitlamp examination, some psychophysical methods (Amsler grid, perimetry, color vision testing, and visual field testing), and electrophysiology (full-field electroretinography [ERG]) have been used for the early detection of these diseases.[3,4] Because it is a sum response of the whole retina, full-field ERG cannot sensitively detect the local variation of the retinal function in subjects with early hydroxychloroquine retinopathy.[5] Focal ERG is more sensitive than full-field ERG for the detection of hydroxychloroquine toxicity in the retina[5]; however, focal ERG cannot test the function in multiple areas of the retina or provide topographical information. Kellner et al[6] observed characteristic abnormalities in the multifocal ERG (mfERG) response in 2 patients with different degrees of chloroquine retinopathy and found the mfERG to be more sensitive than Goldmann perimetry, visual acuity testing, and the full-field ERG in detecting early chloroquine retinopathy. One of us (R.K.M.) previously reported a case[7] of hydroxychloroquine retinopathy, where the response densities of the mfERG were attenuated, while the full-field ERG was normal. The patient had a normal full-field ERG

result. We postulated that the mfERG could be an objective and sensitive method for the early detection of hydroxychloroquine retinopathy. In this study, we retrospectively evaluated the mfERG results of asymptomatic and symptomatic patients who took hydroxychloroquine and identified 4 patterns of topographic changes in response density. The paracentral loss of amplitude with prolonged implicit times was the most specific for hydroxychloroquine toxicity.

METHODS

Multifocal ERG was performed on 19 patients (36 eyes; both eyes were tested in 17 patients and only one eye was tested in 2 patients) treated for systemic lupus erythematosus, rheumatoid arthritis, or localized atypical scleroderma with hydroxychloroquine sulfate (Plaquenil; Sterling Winthrop, Inc, New York, NY). Visual acuity testing and, in some patients, color vision testing, Amsler grid testing, Humphrey static perimetry (30-2), and fluorescein angiography were performed. Eyes with concomitant diseases (eg, age-related macular degeneration and histoplasmosis scars) were not included in the analysis. The response densities of the first-order kernel of mfERGs were analyzed ring by ring at each eccentricity from fixation and compared with those of our control values for response density and implicit time. Control values were obtained from 20 healthy age-matched subjects (20 eyes; mean±SD age, 50.8±14.5 years; compared with the ages of hydroxychloroquine users with a group *t* test, $P>.05$) with a normal ophthalmoscopic appearance of the fundi and normal visual acuities (20/20 or better).

For the mfERG, the test was performed monocularly as the subjects viewed the monitor screen through a video camera system that allowed monitoring of the eye position. The stimulus was presented on a 48-cm high-intensity monochromatic monitor, consisted of 103 hexagon elements, and covered the central field 44° horizontally. The fixation target was a small cross in the center hexagon. The optics of the video camera corrected the refractive error of each eye for the test distance. The hexagons were modulated between a light (400 candelas [cd]/m^2) and a dark (1 cd/m^2) state according to a binary pseudorandom m-sequence. The refresh rate was 75 Hz. The pupils were dilated, and the corneas were topically anesthetized before contact lens placement. The mfERG results were recorded with bipolar contact lens electrodes (Burian-Allen model; Hansen Instruments Inc, Iowa City, Iowa). The amplifier gain was 100 000, and the bandpass was 10 to 300 Hz. The total recording time was 7 minutes 17 seconds, divided into 16 segments.

The 103 traces were grouped from center to periphery into 6 rings (ring 1, foveal patch, 1 arc degree in diameter; ring 2, 1-6 arc degrees in diameter; ring 3, 6-12 arc degrees in diameter; ring 4, 12-21 arc degrees in diameter; ring 5, 21-31 arc degrees in diameter; and ring 6, 31-44 arc degrees in diameter). In each group, the averaged first-order kernel was analyzed. The N1-P1 (N1 indicates first negative wave; P1, first positive wave) response densities (amplitude/area, measured in nanovolts per degree squared) were measured from the N1 trough to the P1 peak. The normal ranges for these response densities and implicit times were defined by calculation of mean±95% confidence intervals of 20 age-matched control eyes.

RESULTS

Table 1 provides the clinical findings in all 19 patients, ordered according to total cumulative dose (in grams). Table 1 describes the ages of the patients, the daily dose adjusted for weight, the duration of medication use, the fundus findings, and the results of color vision testing, Amsler grid tests, and fluorescein angiography. The mean±SD age of the patients analyzed was 54.4±14.9 years. The daily dose ranged from 200 to 400 mg/d, and the duration of treatment ranged from 1 to 20 years. The daily dose adjusted for body weight ranged from 2.0 to 9.0 mg/kg per day. The cumulative dose ranged from 110 to 2920 g.

Table 2 contains the visual acuities and results of Humphrey static perimetry, where available. The corrected visual acuities ranged from 20/20 to 20/50. Also in the table are Humphrey visual fields for 15 subjects (30 eyes), and a description of the response densities.

In the 15 eyes in which 500 g or less hydroxychloroquine was used and for which mfERG and Humphrey visual field data are available, 6 had normal mfERG findings and normal automated perimetry findings, 8 had normal mfERG findings and abnormal automated perimetry findings, and 1 had abnormal mfERG findings and normal automated perimetry findings. In the 14 eyes in which more than 500 g of hydroxychloroquine was used and for which mfERG and Humphrey visual field data are available, 2 had normal mfERG findings and normal automated perimetry findings, 3 had normal mfERG findings and abnormal automated perimetry findings, 3 had abnormal mfERG findings and normal automated perimetry findings, and 6 had abnormal mfERG findings and abnormal automated perimetry findings.

Table 3 provides the control values of N1-P1 response density and P1 implicit time from the 20 control subjects. **Table 4** shows the results of the mfERGs of the 19 patients (36 eyes). Twelve patients (19 eyes) had a normal response density in one or both eyes (cumulative dose, 110-2336 g; maximum, 16 years of use). Eleven patients (17 eyes) had abnormal response densities (cumulative dose, 438-2920 g; hydroxychloroquine administration from the age of 3-20 years) in one or both eyes; 2 of these patients (4 eyes) had significant attenuation of response densities in almost the whole tested field (cumulative dose, 1533-2482 g; 11-17 years of hydroxychloroquine use); and 4 of these patients had normal mfERG results in one eye but had a slight decrease of response densities in another eye (cumulative dose, 438-2336 g; 6-16 years of hydroxychloroquine use). We identified 4 types of abnormal mfERG results (**Figures 1**, **2**, **3**, and **4**). (1) Some results showed a decrease in N1-P1 response density in the paracentral area and/or prolongations of corresponding P1 implicit times (2 patients [4 eyes]). In patient 13, the response densities and the implicit times showed paracentral change (cumulative dose, 1095 g; 7.5 years of hydroxychloroquine use) (Figure 1). In patient 18, the response densities showed generalized loss but the P1 latencies were prolonged for paracentral responses (cumulative dosage, 2482 g; 17 years of hydroxychloroquine use) (Figure 4). (2) Some results showed a decrease in the central area alone (7 patients [9 eyes]) (cumulative dose, 438-2336 g; 3-16 years of hydroxychloroquine use) (Figure 2). (3) Some results showed a decrease in the peripheral area alone (1 patient [2 eyes]) (cumulative dose, 2920 g; 20 years of hydroxychloroquine use) (Figure 3). (4) Some results showed a generalized decrease in the entire tested field (2 patients [4 eyes]) (cumulative dose, 1533-2482 g; 11-17 years of hydroxychloroquine use) (Figure 4). The implicit times for the P1 peak of the mfERG responses were normal when analyzed in the aggregate and in all indi-

Table 1. Medication Information of the 19 Patients (36 Eyes) Who Took Hydroxychloroquine Sulfate

Patient No./ Eye/Age, y/ Disease	Daily Dose Adjusted for Weight, mg/kg of Body Weight	Period of Hydroxy-chloroquine Use, y/Total Cumulative Dose, g	Description of Response Density (Eye)	Fundus Change		Color Vision		Amsler Grid		Fluorescein Angiography	
				R	L	R	L	R	L	R	L
1/L + R/62/RA	2.2	1.5/109.5	Normal (L + R)	Normal	Normal	12/12	12/12	Normal	Normal	NA	NA
2/L + R/56/SLE	4.1	1/146	Normal (L + R)	Normal	Normal	NA	NA	Normal	Normal	NA	NA
3/R/49/SLE	6.2	1/146	Normal (R)	Flecklike changes in the macula	Flecklike changes in the macula	NA	NA	Normal	Normal	NA	NA
4/L + R/41/SLE	2.0	2.5/182	Normal (L + R)	Normal	Normal	12/12	12/12	Normal	Normal	Normal	Normal
5/L + R/54/RA	2.9	3/219	Normal (L + R)	Drusen in the macula	Drusen in the macula	NA	NA	Normal	Normal	NA	NA
6/L + R/58/SLE	2.9	3/219	Normal (L + R)	Normal	Normal	NA	NA	Normal	Normal	NA	NA
7/L + R/72/RA	3.2	3/438	Foveal loss (L + R)	Rare drusen	Rare drusen	13/14	13/14	Normal	Normal	Normal	Normal
8/L + R/56/RA	5.6	3/438	Normal (L + R)	Rare drusen	Rare drusen	11/11	11/11	Normal	Normal	NA	NA
9/L + R/56/RA	3.0	6/438	Normal (R) and foveal loss (L)	Rare drusen	Rare drusen	14/14	14/14	Normal	Normal	Normal	Normal
10/L + R/54/RA	3.6	5/730	Foveal loss (L + R)	Drusen	Few flecks	NA	NA	NA	NA	Normal	Normal
11/L/44/SLE	6.2	5/730	Foveal loss (L)	Normal	Normal	14/14	14/14	Normal	Normal	POHS scar in macula	Small window defect
12/L + R/15/SLE	6.3	5/730	Normal (R) and foveal loss (L)	Normal	Normal	13/14	13/14	Normal	Normal	NA	NA
13/L + R/73/SLE	8.0	7.5/1095	Paracentral loss (L + R)	Normal	Normal	10/12	10/12	Normal	Normal	NA	NA
14/L + R/60/SLE	4.1	8/1168	Normal (L + R)	Normal	Normal	10/16	11/16	Normal	Normal	Staining 2° drusen	Staining 2° drusen
15/L + R/61/LAS	3.8	10.5/1533	Generalized loss (L + R)	Normal	Normal	14/14	14/14	Normal	Normal	Normal	Normal
16/L + R/67/RA	4.4	15/2190	Normal (R) and foveal loss (L)	Normal	Normal	14/14	14/14	Normal	Normal	NA	NA
17/L + R/60/SLE	4.7	16/2336	Normal (R) and foveal loss (L)	Normal	Normal	12/12	12/12	Normal	Normal	Significant for a few areas of RPE pigment mottling in the early and late frames without any evidence of significant leakage	Significant for a few areas of RPE pigment mottling
18/L + R/25/RA	8.0	17/2482	Generalized loss (L + R)	Normal	Normal	14/14	12/14	Wavy	Distortion	NA	Hyperfluorescence in the area of atrophy temporal to fixation
19/L + R/70/SLE	9.0	20/2920	Peripheral loss (L + R)	Normal	Normal	14/14	14/14	Normal	Normal	NA	NA

Abbreviations: L, left eye; LAS, localized atypical scleroderma; NA, data not applicable; POHS, presumed ocular histoplasmosis syndrome; R, right eye; RA, rheumatoid arthritis; RPE, retinal pigment epithelium; SLE, systemic lupus erythematosus.

viduals except for patients 13 (Figure 1, **Figure 5**, and **Table 5**), 18 (Figure 4), and 15 (rings 4 and 5 in the left eye only). The results of color vision testing were normal in all patients. The results of Amsler grid testing were normal for all eyes, except for 1 patient (2 eyes) with 17 years of hydroxychloroquine use who demonstrated a gen-

Table 2. Visual Acuity and Static Perimetry Results

Patient No.	Snellen Visual Acuity		Perimetry		Description of Response Density
	R	L	R	L	
1	20/20	20/25	Scattered defects	Scattered defects	Normal (L + R)
2	20/20	20/20	Normal	Defect in the upper nasal field	Normal (L + R)
3	20/50	20/30	Normal	Scattered temporal defects	Normal (R)
4	20/25	20/20	Scattered defects	Scattered defects	Normal (L + R)
5	20/20	20/25	Normal	Scattered defects	Normal (L + R)
6	20/40	20/30	Normal	Normal	Normal (L + R)
7	20/25	20/25	NA	NA	Foveal loss (L + R)
8	20/25	20/20	Scattered defects	Scattered defects	Normal (L + R)
9	20/20	20/20	Normal	Normal	Normal (R) and foveal loss (L)
10	20/25	20/25	NA	NA	Foveal loss (L + R)
11	20/25	20/25	Mild peripheral constriction	Mild peripheral constriction	Foveal loss (L)
12	20/20	20/20	Normal	Normal	Normal (R) and foveal loss (L)
13	20/30	20/40	NA	NA	Paracentral loss (L + R)
14	20/20	20/20	Mild peripheral constriction	Mild peripheral constriction	Normal (L + R)
15	20/25	20/20	NA	NA	Generalized loss (L + R)
16	20/50	20/40	Scattered defects	Perifoveal loss and scattered defects	Normal (R) and foveal loss (L)
17	20/20	20/20	Normal	Scattered defects	Normal (R) and foveal loss (L)
18	20/30	20/30	Central loss	Central loss	Generalized loss (L + R)
19	20/25	20/40	Normal	Normal	Peripheral loss (L + R)

Abbreviations: See Table 1.

Table 3. Values of P1-N1 Response Density and P1 Implicit Time From 20 Healthy Control Subjects (20 Eyes)*

Ring	Response Density†	Implicit Time, ms
1	163.8 ± 32.6	28.2 ± 1.6
2	83.5 ± 14.2	28.5 ± 1.6
3	54.4 ± 8.7	27.3 ± 1.1
4	42.8 ± 7.1	27.4 ± 0.9
5	35.1 ± 6.5	27.9 ± 1.0
6	33.8 ± 7.4	28.4 ± 1.1

*Data are given as mean ± SD.
†Measured in nanovolts per degree squared.

eralized pattern loss (patient 18). A decrease in visual acuity, when present, was usually because of anterior segment findings.

In 2 of the patients (patients 9 and 13) who underwent a longitudinal mfERG study, the response densities demonstrated a trend toward improvement after the cessation of hydroxychloroquine use. **Figure 6** shows the change of their averaged response density in rings 1 and 2 relative to the period of termination of hydroxychloroquine use. Significant prolongations of implicit times occurred for patient 13, particularly for those responses that correspond to rings 2, 3, and 4. At this time, early hydroxychloroquine retinopathy was clinically recognized on this patient (Figures 1C and 5 and Table 5). The patient stopped drug treatment and follow-up mfERGs continued to demonstrate prolonged implicit times. The visual acuities for these 2 patients improved mildly in the same period. An additional patient (patient 18) with a generalized loss pattern stopped using hydroxychloroquine due to mfERG findings and central visual field loss. Follow-up mfERG test results were not available for this patient.

COMMENT

Although hydroxychloroquine originally was thought to be a safer drug than chloroquine, retinal toxicity from hydroxychloroquine can occur. The long-term safety of hydroxychloroquine and most effective means of screening for retinal toxicity are still subject to debate. In the study by Johnson and Vine,[8] patients receiving dosages up to 400 mg/d (≤6.5 mg/kg per day) seemed to tolerate massive cumulative doses (1054-3923 g) of hydroxychloroquine without developing abnormalities in their visual acuity, Amsler grid result, color vision testing, and visual field testing. Toxicity has been shown when a cumulative dose of more than 800 g of the drug is ingested.[9] Also, a toxic reaction has been reported for those undergoing long-term therapy (10 years, for a total cumulative dose of 1460 g) in whom the adjusted daily dose was never greater than 6.3 mg/kg per day.[10] This suggests that other factors, possibly genetic and acquired, may influence which patients develop retinal toxicity. For example, Shroyer et al[11] have suggested that the carrier state for mutation of the gene *ABCA4* (the gene that is defective in Stargardt disease) may increase susceptibility to hydroxychloroquine and chloroquine retinal toxicity. Furthermore, because hydroxychloroquine is cleared through renal and hepatic functions, those with severe kidney or liver disease may be at greater risk of toxicity.

Most of our patients (10 of 11) who had abnormal mfERG results had taken hydroxychloroquine for at least 5 years. This implies that, in the first 5 years of hydroxychloroquine use, the incidence of retinopathy caused by toxicity of the drug is low or nonexistent. This finding supports the recommendation from the American Academy of Ophthalmology[12] that, for individuals using less than 6.5 mg/kg of hydroxychloroquine per day, screening can be modified for the first 5 years to account for the minimal risk of a toxic reaction at this dose.

Table 4. P1-N1 Response Density of the 19 Hydroxychloroquine Sulfate Users

Patient No.	Eye	Ring* 1	2	3	4	5	6	Relative Cumulative Dose, g/kg
1	R	154.6	86.0	56.6	43.2	37.5	38.5	1.2
	L	107.0	65.4	45.0	34.1	28.1	26.5	1.2
2	R	117.6	104.4	79.0	62.1	52.5	51.3	1.7
	L	130.7	79.1	57.7	47.3	40.8	38.6	1.7
3	R	117.1	71.3	47.7	38.6	32.1	30.8	2.3
4	R	214.5	127.7	96.2	77.2	68.7	60.8	1.8
	L	202.3	119.0	86.0	72.4	64.2	58.3	1.8
5	R	193.6	93.7	62.6	50.4	40.2	33.8	3.2
	L	147.4	89.7	68.3	50.3	39.1	38.4	3.2
6	R	144.9	71.9	42.6	30.3	27.8	25.8	3.2
	L	163.2	73.2	41.4	31.8	28.0	27.0	3.2
7	R	87.5†	64.0	47.0	39.4	36.4	40.2	2.3
	L	87.9†	61.3	48.8	40.9	37.8	42.3	2.3
8	R	159.3	85.0	61.4	56.2	48.1	47.4	6.2
	L	150.5	79.8	55.6	51.2	43.4	40.4	6.2
9	R	186.1	97.5	60.7	40.8	33.4	32.4	6.6
	L	89.7†	70.2	46.3	36.3	26.2	29.0	6.6
10	R	78.3†	49.0†	38.2	31.2	26.4	27.0	6.6
	L	50.3†	52.7†	47.7	34.6	31.1	29.7	6.6
11	L	87.7†	67.8	50.8	42.3	35.8	34.0	11.3
12	R	186.1	97.5	60.7	40.8	33.4	32.4	11.6
	L	53.8†	45.8†	36.7†	29.0	26.5	27.7	11.6
13	R	140.3	64.2	32.3†	30.6	33.9	32.0	21.9
	L	139.5	74.8	36.3†	38.5	34.9	32.1	21.9
14	R	195.4	87.0	51.3	37.1	26.4	21.2	12.0
	L	165.8	72.2	45.6	33.3	25.8	20.2	12.0
15	R	91.3†	51.6†	17.5†	11.9†	11.3†	13.9†	14.7
	L	73.3†	36.3†	14.5†	7.6†	7.0†	9.0†	14.7
16	R	119.6	82.7	63.1	47.9	40.3	43.6	24.1
	L	79.1†	64.7	50.4	40.4	35.4	36.4	24.1
17	R	110.6	66.3	42.1	36.4	32.0	29.8	27.1
	L	101.0	50.4†	32.4†	30.6	26.5	24.4	27.1
18	R	69.4†	18.8†	6.4†	7.1†	9.2†	12.2†	49.7
	L	22.1†	8.6†	5.4†	5.6†	7.0†	7.0†	49.7
19	R	123.7	46.5†	25.0†	23.5†	19.6	15.2†	65.6
	L	105.5	44.1†	27.0†	21.2†	16.2†	11.3†	65.6

Abbreviations: See Table 1.
*Data are given as nanovolts per degree squared.
†Outside the normal range.

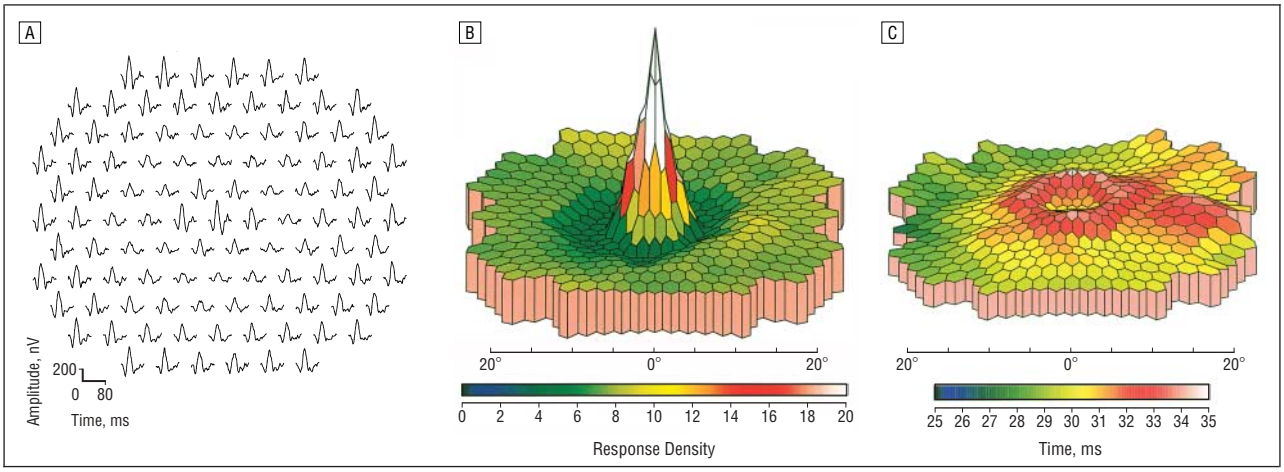

Figure 1. Multifocal electroretinogram of the right eye of patient 13 (taken February 1, 2002), showing subnormal response densities and prolonged implicit times in the paracentral area. A, Trace array. B, Three-dimensional scalar product plot. The response density is measured in nanovolts per degree squared. The total response was 7.72 nV per degree squared. C, Latency plot. The implicit times for P1 were mildly, but significantly (Table 5), delayed for rings 2, 3, 4, and 5.

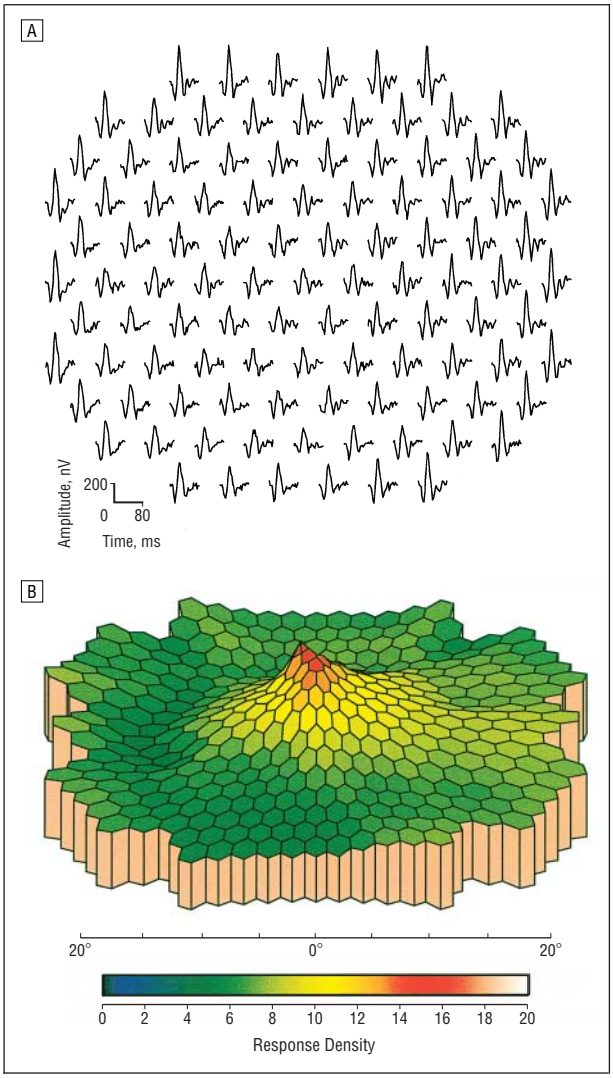

Figure 2. Multifocal electroretinogram of the left eye of patient 16, showing a decrease of response densities in the central area alone. A, Trace array. B, Three-dimensional plot. The response density is measured in nanovolts per degree squared. The total response was 8.72 nV per degree squared.

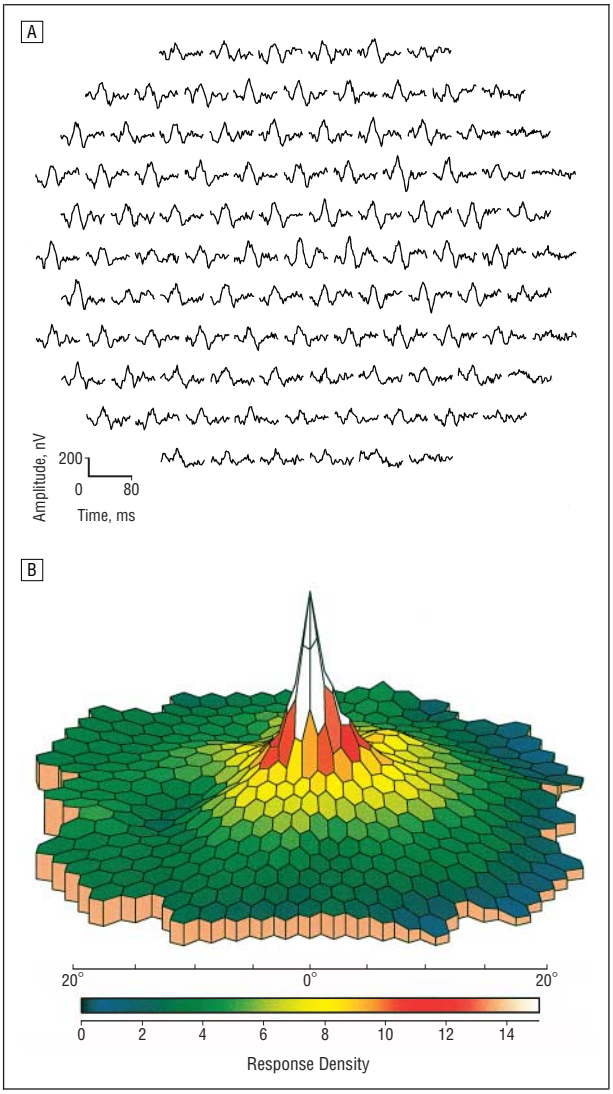

Figure 3. Multifocal electroretinogram of the left eye of patient 19, showing a decrease of response densities in the peripheral area alone. A, Trace array. B, Three-dimensional plot. The response density is measured in nanovolts per degree squared.

Three of the patients with abnormal mfERG results (patients 13, 18, and 19) were ingesting higher dosages (8.0, 8.0, and 9.0 mg/kg per day, respectively) than recommended at the time of our study. Both subjects with paracentral loss were taking a higher daily dose by weight, as were the 2 subjects with the highest cumulative doses. However, overall, the incidence of retinal dysfunction did not correlate significantly with the daily dose adjusted for weight. Although the daily dose adjusted for weight may be an important risk factor for toxicity, we found foveal loss or generalized loss of response density for 8 patients taking less than 6.5 mg/kg per day. Hydroxychloroquine is not retained in fatty tissues.[12] The daily dose adjusted for weight is, thus, relatively lower for obese patients, and this index will not reflect the real dose in lean weight. Thus, we conclude that the duration of hydroxychloroquine use and the total cumulative dose are still important risk factors for hydroxychloroquine retinopathy.

All of the patients in this study had visual acuities between 20/20 and 20/50 and normal color vision results, as tested. We believe that color vision testing and fluorescein angiography show findings indicative of toxic changes typically late in the course of the disease. Thus, color vision testing, although useful in defining visual function in cases of suspected drug toxicity, may not have a significant benefit as a screening tool for early disease. One subject had a change on fluorescein angiography. Amsler grid testing has been suggested to show change earlier in the disease process and has been suggested for home screening.[12] However, only one subject in our series had an Amsler grid change.

Humphrey visual field testing was somewhat useful as a method for evaluating early drug toxicity. Our study, in most cases, did not incorporate retesting of visual fields or mfERG to evaluate the reproducibility of abnormal findings. However, many cases of abnormal visual fields can be noted for patients in whom no hydroxychloroquine toxicity is expected. In some cases, repeat testing of visual fields (data not shown) gave results that were still abnormal but difficult to interpret. In the lower-dose hydroxychloroquine users in whom retinal toxicity was not expected, we

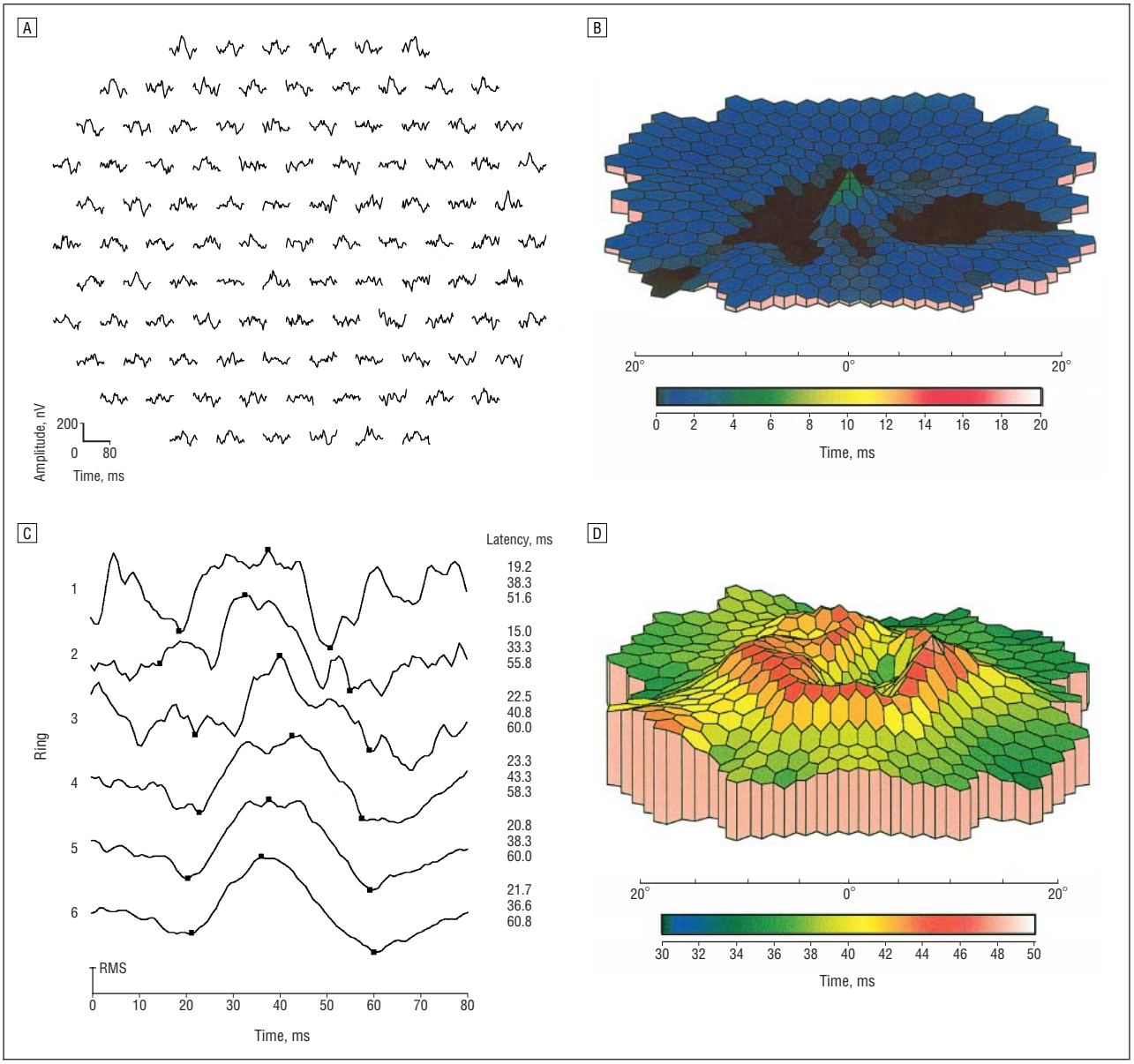

Figure 4. Multifocal electroretinogram of the left eye of patient 18, showing a decrease of response densities in the entire tested field. A, Trace array. B, Three-dimensional plot. The response density is measured in nanovolts per degree squared. The total response was 2.34 nV per degree squared. C, Normalized ring averages. The implicit times for P1 were markedly delayed for all ring averages. RMS indicates root mean square. D, Latency plot.

found many instances in which perimetry showed scattered defects. In these instances when the Humphrey visual field was abnormal and the mfERG was normal, we were confidently able to reassure patients that the retina was still functioning well and that they could continue hydroxychloroquine therapy despite the abnormal visual field.

In the higher-dose group of patients, we found 3 eyes in which perimetry found abnormalities while the results of mfERG testing were normal. In 2 of these eyes (patient 14), the perimetry results showed scattered abnormalities with no other clinical findings of hydroxychloroquine toxicity. We believed that the patient displayed no signs of hydroxychloroquine toxicity. In the third eye (the right eye of patient 17), it is possible that the mfERG did not detect early hydroxychloroquine changes that were apparent on perimetry (the findings on both tests showed abnormalities in the fellow eye). Thus, while it is possible for perimetry to demonstrate changes associated with hydroxychloroquine use earlier than mfERG, in most cases, mfERG supplemented and confirmed abnormalities found on visual field testing. In addition, in the patient for whom we were concerned about toxicity (patient 19), mfERG showed abnormalities that were not detected on visual field testing. The greatest value of the mfERG is in differentiating a retinal cause and, hence, providing important evidence supportive of hydroxychloroquine toxicity, whenever visual field loss is apparent on perimetry.

We believe that mfERG testing can detect change in retinal function far sooner than any other electrophysiological modality in use. However, the clinician is required to interpret these changes and to determine whether the mfERG abnormalities are significant enough to warrant discontinuation of hydroxychloroquine therapy. In this retrospective study, 3 patients (patients 9, 13, and 18)

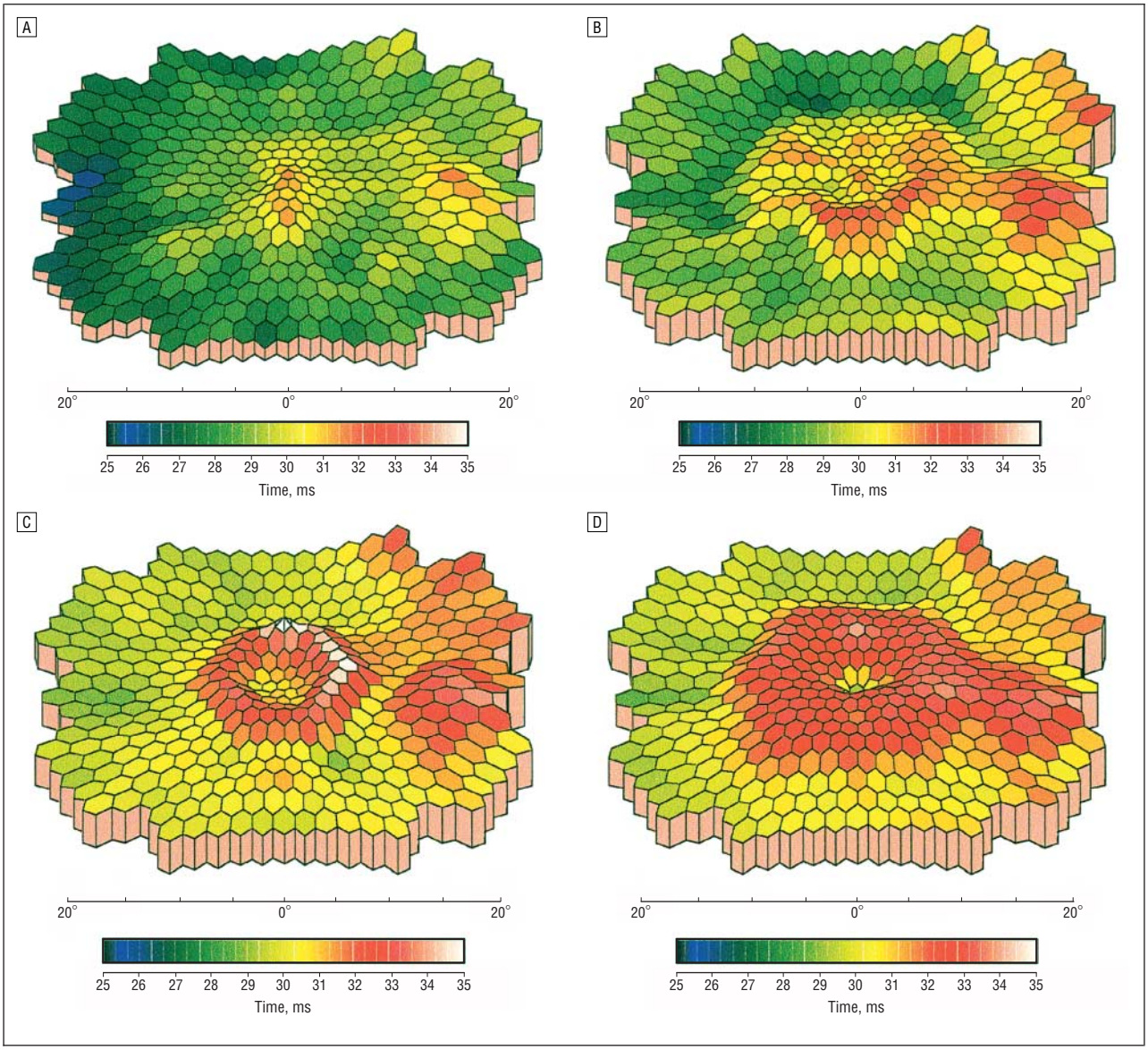

Figure 5. Longitudinal change in the latency plots of the right eye of patient 13 during the evolution of retinal toxicity. Time is given relative to the cessation of medication on August 1, 2001. A, Minus 5 months (February 23, 2001). B, Minus 6 weeks (June 15, 2001). C, Plus 2 weeks (August 15, 2001). D, Plus 10 months (June 12, 2002).

stopped using the medication for various reasons. Abnormalities were seen in the mfERG for each of these patients. Two of these patients (whose medication duration ranged from 6-17 years) returned for subsequent mfERGs, which, for both, showed an improvement in response density. Serial repeat studies in these 2 hydroxychloroquine users who stopped using the drug showed a trend toward electrophysiological recovery of mfERG response (Figure 6). This suggests that in early cases, the loss of retinal response densities associated with hydroxychloroquine use may be reversible. We did not observe significant reduction in the prolonged implicit times in the subjects. Implicit time recovery, however, if it is to occur at all for hydroxychloroquine toxicity, may not take place within the same time frame as recovery of response density, and the observation period in our patients may have been too short. Other retinal degenerations often show lack of correlation of latency prolongations and changes in amplitudes.[13]

We were not able to determine whether a particular pattern of mfERG abnormality preceded another pattern, except that foveal loss may be an early feature and generalized decrease in response density is the final pattern. Paracentral loss of amplitude (rings 2-4), particularly with prolonged implicit times, however, is the most specific pattern for hydroxychloroquine toxicity. We have not encountered this latter specific pattern in more than 800 mfERGs that we have obtained (for various diseases) in the past few years. Seeliger et al[14] reported that the latencies for P1 show low topographical variability in control subjects. Thus, prolongations in latencies for the pericentral responses seem to be a particularly diagnostic feature of focal retinal dysfunction. The fact that the most characteristic loss on mfERG is located in the paracentral rings would suggest that, for screening for hydroxychloroquine toxicity, the Humphrey visual field 10-2 test may be a better program than the 30-2 test.

Table 5. P1 Implicit Time for Patient 13 During the Evolution of a Toxic Reaction in the Retina

Ring	Eye	Implicit Time, ms: Patient 13* 2-23-01	6-15-01	8-15-01	2-1-02	6-12-02	Control Subjects (n = 20)†	Upper Limit of the Normal Range
1	R	30.8	30.8	30.0	30.0	29.2	28.2 ± 1.6	31.4
	L	30.0	29.2	30.8	30.0	30.8		
2	R	30.0	30.0	30.8	31.7‡	31.7‡	28.5 ± 1.6	31.6
	L	30.8	30.8	31.7‡	30.8	31.7‡		
3	R	29.2	30.8‡	33.3‡	33.3‡	32.5‡	27.3 ± 1.1	29.4
	L	29.2	31.7‡	31.7‡	32.5‡	32.5‡		
4	R	28.3	30.0‡	30.0‡	30.8‡	32.5‡	27.4 ± 0.9	29.1
	L	28.3	28.3	30.0‡	30.8‡	30.0‡		
5	R	28.3	28.3	30.0‡	30.0‡	30.0‡	27.9 ± 1.0	29.8
	L	28.3	29.2	29.2	29.2	30.0‡		
6	R	27.5	29.2	30.0	29.2	30.0	28.4 ± 1.1	30.5
	L	28.3	29.2	29.2	30.0	29.2		

Abbreviations: See Table 1.
*Dates are given as M-DD-YY.
†Data are given as mean ± SD.
‡Outside the normal range.

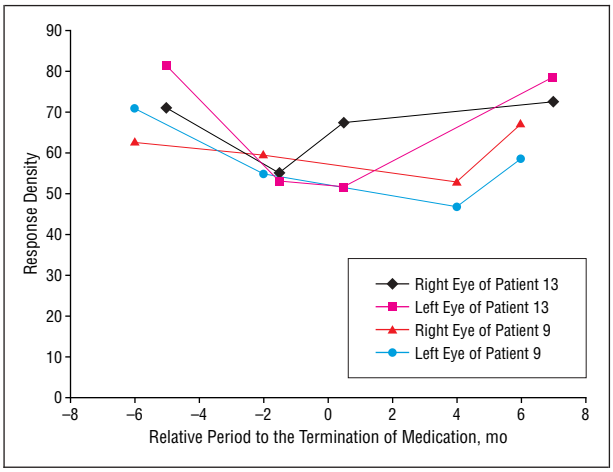

Figure 6. Longitudinal change of the mean response densities in rings 1 and 2 in patients 9 and 13. The x-axis shows the relative period to cessation of hydroxychloroquine sulfate use. The response density is measured in nanovolts per degree squared.

The abnormalities in retinal electrophysiology, as detected by the mfERG, occurred earlier than any morphologic fundus change using ophthalmoscopy. We believe that the mfERG may be the most sensitive objective test for the early detection of hydroxychloroquine retinopathy. Patients who take hydroxychloroquine in higher than the recommended dose (>6.5 mg/kg per day) or for a long duration (>5 years) should be considered for periodic mfERG testing for the early detection of hydroxychloroquine retinopathy.

In summary, the evidence supports periodic testing with mfERG, when possible and available, in patients undergoing long-term hydroxychloroquine therapy, particularly if there is any clinical suggestion of drug toxicity. An mfERG is also an excellent choice for confirming the absence of retinal toxicity when perimetry or other tests detect abnormalities. Further study is necessary to evaluate the sensitivity of the mfERG in early detection of hydroxychloroquine retinopathy and to determine the role of mfERG in screening.

Submitted for publication September 5, 2002; final revision received November 24, 2003; accepted January 7, 2004.

This study was supported by the Methodist Research Institute and Midwest Eye Foundation, Indianapolis, Ind; The Foundation Fighting Blindness, Owings Mills, Md; and Research to Prevent Blindness, New York, NY.

Correspondence: Raj K. Maturi, MD, Midwest Eye Institute, 201 Pennsylvania Pkwy, Indianapolis, IN 46280 (rmaturi@indyretina.com).

REFERENCES

1. Hobbs HE, Sorsby A, Freedman A. Retinopathy following chloroquine therapy. *Lancet.* 1959;2:478-480.
2. Shearer RV, Dubois EL. Ocular changes induced by long-term hydroxychloroquine (Plaquenil) therapy. *Am J Ophthalmol.* 1967;64:245-252.
3. Hart WM Jr, Burde RM, Johnston GP, et al. Static perimetry in chloroquine retinopathy. *Arch Ophthalmol.* 1984;102:377-380.
4. Weiner A, Sandberg MA, Gaudio AR, et al. Hydroxychloroquine retinopathy. *Am J Ophthalmol.* 1991;112:528-534.
5. Sassaman FW, Cassidy JT, Alpern M, et al. Electroretinography in patients with connective tissue diseases treated with hydroxychloroquine. *Am J Ophthalmol.* 1970;70:515-523.
6. Kellner U, Kraus H, Foerster MH. Multifocal ERG in chloroquine retinopathy. *Graefes Arch Clin Exp Ophthalmol.* 2000;238:94-97.
7. Maturi RK, Folk JC, Nichols B, et al. Hydroxychloroquine retinopathy. *Arch Ophthalmol.* 1999;117:1262-1263.
8. Johnson MW, Vine AK. Hydroxychloroquine therapy in massive total doses without retinal toxicity. *Am J Ophthalmol.* 1987;104:139-144.
9. Mills PV, Beck M, Power BJ. Assessment of the retinal toxicity of hydroxychloroquine. *Trans Ophthalmol Soc U K.* 1981;101:109-113.
10. Thorne JE, Maguire AM. Retinopathy after long term, standard doses of hydroxychloroquine. *Br J Ophthalmol.* 1999;83:1201-1202.
11. Shroyer NF, Lewis RA, Lupski JR. Analysis of the *ABCR* (*ABCA4*) gene in 4-aminoquinoline retinopathy. *Am J Ophthalmol.* 2001;131:761-766.
12. Marmor MF, Carr RE, Easterbrook M, et al. Recommendation on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2002;109:1377-1382.
13. Hood DC, Holopigian K, Greenstein V, et al. Assessment of local retinal function in patients with retinitis pigmentosa using the multi-focal ERG technique. *Vision Res.* 1998;38:163-179.
14. Seeliger MW, Kretschmann UH, Apfelstedt-Sylla E, Zrenner E. Implicit time topography of multifocal electroretinograms. *Invest Ophthalmol Vis Sci.* 1998;39:718-723.