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Retina in rheumatic diseases: Standard full field and multifocal electroretinography in hydroxychloroquine retinal dysfunction

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Background: The purpose of this study was to evaluate and compare full-field electroretinography (ERG) and multifocal electroretinography (mfERG) results in detecting retinal dysfunction in a large number of asymptomatic patients treated with hydroxychloroquine (Hy).

Methods: Fifty eyes in 50 patients with rheumatic diseases who had been using Hy for a period of time ranging from 30 months to 15 years, and 25 eyes in 25 healthy controls, were evaluated. Receiver operator characteristic (ROC) curves were calculated to determine the sensitivity and specificity of abnormal values in patients compared to the normal controls.

Results: Signal depression was observed on the mfERG of Hy-treated patients. The most prevalent pattern was pericentral loss (19 eyes, 54.3 per cent), followed by full-field loss (11 eyes, 31.4 per cent), and central loss (five eyes, 14.3 per cent). Conversely, depression of the amplitude responses to the full field ERG was observed in only 16 per cent of the cases. The areas under the ROC curves ranged from 0.4056 to 0.9012, with the mfERG values having the largest areas, whereas the full-field ERG curves had the smallest area. The mfERG responses yielded the greatest sensitivity and specificity. In particular, the P1-N1 wave amplitude (ring 2) and root mean square (RMS) amplitude (ring 1) had specificities of 76 and 88 per cent, respectively, at sensitivities of 90 and 86 per cent.

Conclusion: A statistically significant retinal functional impairment was demonstrated by mfERG in the central two to 10 degrees in Hy-treated patients. Therefore, mfERG may provide an objective measurement of retinal dysfunction in patients receiving Hy therapy.

Key words: electroretinography, hydroxychloroquine, multifocal electroretinography, retinal toxicity, rheumatic diseases

The most common uses of hydroxychloroquine sulphate (Hy) are in the management and prophylaxis of malarial fever, rheumatoid arthritis, lupus erythematosus, Sjögren syndrome, systemic vasculitis, and mixed connective tissue disease.[1–3] Hy is in a class of drugs called antimalarials and has a prolonged half-life of up to 30 days in plasma and can persist for months after therapy.[3–5] Side-effects may include ocular, gastrointestinal, dermatological, auditory, cardio-circulatory, haematological and neuromuscular alterations. Hy has a high affinity for binding to melanin granules and therefore tends to accumulate in the iris, choroid, ciliary body and retinal pigment epithelium (RPE). Atrophic, pigmentary retinal changes of the periphery and the macula (bull's eye), attenuated retinal vessels and optic atrophy may be seen in rare cases of chronic retinal toxicity. The symptoms include difficulty in reading, photophobia, blurred distance vision,

peripheral visual field depression, central visual field scotomata and light flashes.[6–7] With low dosages of Hy only a small percentage of patients present functional alterations.[4–7] Individual susceptibility may be conditioned by other factors, including ABCA4 gene abnormalities.[8] Patients who receive less than 6.5 mg/kg per day of Hy with a treatment duration of less than 10 years and normal retinal, renal or hepatic function are not at risk for retinopathy.[9]

Since 1964, many tests were used for detecting the retinal toxic effect of Hy. The multifocal electroretinography (mfERG), introduced by Sutter,[10] is a relatively new objective measure of focal retinal function. It allows the functional mapping of the retina and contributes to the detailed evaluation of retinal function especially in regional disorders of the inner retinal layers. Maturi and colleagues[11] first studied the changes in mfERG in a patient with Hy retinopathy and subsequently other authors[12–14] confirmed its usefulness in detecting early changes of retinal function in Hy toxic retinopathy.

The purpose of this study was to investigate and compare the results of electroretinography (ERG) and mfERG in a large cohort of Hy treated patients. We also aimed to ascertain whether this relatively new test might be used as a screening examination for patients under prolonged treatment with Hy and to identify the areas of the retina that are first damaged.

METHODS

Study group

Fifty eyes in 50 patients (39 women and 11 men) on Hy treatment were studied (Table 1). The mean age was 51.35 ± 6.1 (SD) years and a range of 39 to 62 years. The underlying diseases were as follows: 20 rheumatoid arthritides, 18 systemic lupus erythematosus, six Sjögren syndromes, three mixed connective tissue diseases and three systemic vasculitides. None of the patients showed refractive disturbances more than either +3.00 D sphere or -5.00 D sphere or concomitant diseases such as age-related macular degeneration, retinal scars, cataracts, retinal vasculitis or glaucoma. The dose of Hy varied from two to 10 mg/kg per day. Duration of treatment ranged from 30 months to 15 years (mean 5.27 ± 3.34 years). All the patients were asymptomatic and had normal ocular and medical histories, with no sign of systemic hypertension, diabetes or other concomitant pharmacological treatment. The ocular assessments (Table 1) were all within normal range. None of the patients had fundus pigmentary changes suggesting Hy toxicity. The patients were re-examined one month after baseline assessment. The eye showing lesser level of noise was tested. Overall there were 26 right eyes and 24 left eyes.

Underlying disease	Rheumatoid arthritis 20 Systemic lupus erythematosus 18 Sjögren syndrome 6 Mixed connective tissue disease 3 Systemic vasculitis 3
Sex	39 females and 11 males
Age	39 to 62 (mean 51.35 ± 6.1 SD years)
Eye	26 right and 24 left
Duration of treatment	30 months to 15 years (mean 5.27 ± 3.34 years)
Hy dosage	2 to 10 mg/kg; daily dose adjusted for body weight. Total dosage: 360 to 1100 g; mean: 438.28 g
MfERG testing/patient	2 to 5 (mean 3.36)
Ocular examinations at baseline and follow-up	VA (6/6), colour vision (Ishihara chart), Amsler grid, intraocular pressure, slitlamp and fundoscopy, visual field Humphrey 30-2 program

Table 1. Data of the 50 patients receiving Hy therapy

All the 25 controls (14 women and 11 men) had normal ocular examinations. The mean age was 46.5 ± 7.26 years and a range of 41 to 59 years. Colour perception, Amsler grids and visual fields were all normal.

The study protocol was approved by the Ethical Committee, 'Sapienza' University of Rome (30 November 2006 Ref. 1113/30.11.06).

The investigations were performed according to the guidelines of the Declaration of Helsinki and Institutional Review Board approval was obtained.

Electrophysiological testings

Before recording, the pupils were dilated with topical tropicamide 1%. All subjects were adapted to ordinary room light for 15 minutes before testing and the corneas were anaesthetised with topical proparacaine hydrochloride 0.5 per cent. The mfERG recording was performed using an ERG Jet corneal contact lens active electrode. A skin reference or inactive electrode was attached centrally on the patient's forehead slightly above the supraorbital rims. A ground electrode was put on the patient's earlobe. The active, inactive and ground electrodes were connected with a junctional box, from which the signals were delivered to additional recording components for amplification and display. Then the subjects were dark-adapted for 30 minutes and a standard ganzfeld full field ERG was subsequently performed. MfERG and full-field ERG were analysed on the computerised Opto-electronic Stimulator Vision Monitor MonPack 120 Metrovision (Pérenchies, France) (Table 2) with reference to the ISCEV guidelines (International Society for Clinical Electrophysiology of Vision).[15–17] The first-order kernel mfERG responses were analysed using colour maps of amplitudes given as density and implicit times of N1, P1 and N2 wave peaks (Figures 1A, 1B and 2). The average responses were over a group of

Type of analysis	
(5 to 7 minutes per eye)	MfERG photopic response 61B
Modes of stimulation	Areas covering the central 25° of the retina and scaled eccentrically to simulate an array of 61 hexagons
Size of the zones	3.4 central degrees
Hexagons modulated	Between a high luminance of stimulations set at 200 cd/mq for the bright flashes and 1 cd/mq for the dark flashes state according to a binary pseudo-random m-sequence
Stimulated fields	30 degrees horizontally and 23 degrees vertically
Standard stimulation	Black/white monochrome cathode ray tube monitor with blue background to minimise rod responses and maximise cone responses
Frame frequency	High of 120 Hz to provide higher temporal resolution
Band-pass filtering	High pass cut-off 10 Hz; low pass cut-off 300 Hz; amplified with a gain of 100,000
Stimulus screen	Surrounded by a uniformly illuminated background cover with a luminance set at 30 cd/mq to eliminate the rod responses
Stimulus frequency	Set at 17 Hz to optimise the amplitude of responses
Fixation stability	Monitored with an infrared refractor camera
Optical correction	As required at 30 cm

Table 2. mfERG parameters on the computerised Optoelectronic Stimulator Vision Monitor MonPack 120 Metrovision (Pérenchies, France)

up to five rings from zero to 25 degrees of eccentricity relative to fixation. The analysis generates a histogram for each of the extended zones indicating the average amplitude of the N1, P1, N2 peaks and of the root mean square (RMS) in nanoVolts per degree squared (nV/deg^2). The RMS characterises the energy content of each response (Figures 1A and 1B). Several visualisation modes were obtained with 2-D and 3-D maps. There were four patterns of abnormal mfERG amplitude responses observed and these were classified as paracentral loss, foveal loss, peripheral loss and generalised loss, as described by Maturi, Yu and Weleber.[13]

Statistical analysis

The Mann Whitney U test was used to assess possible differences between patients and controls. Spearman's correlation was used to calculate the relationship between the mfERG response and the cumulative Hy dose. Data from normal

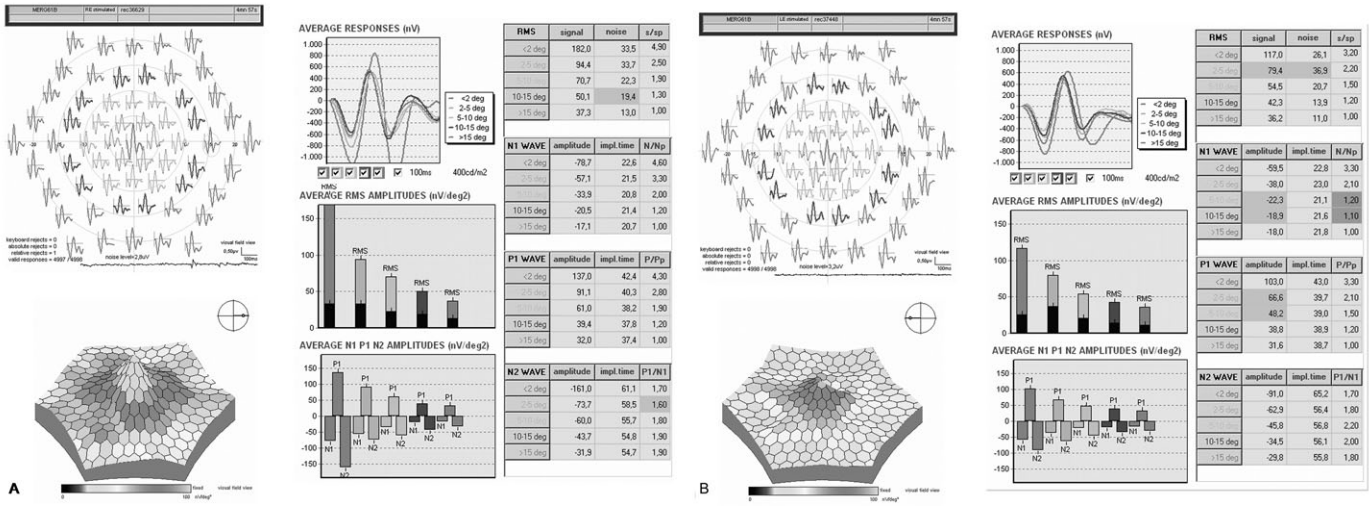

Figure 1. Example of mfERG recordings from a control (eye right) (panel A) and mfERG recordings from a Hy-treated patient (eye left) (panel B).

A. Normal mfERG trace array with waveforms and 3-D density plots of 61 local responses exploring rings 1 to 5 (from zero to 25° central). The analysis generates a histogram for each of the extended zones indicating the average amplitude of the N1, P1, N2 peaks and the average of the energy content of each response RMS in nV/deg^2. To determine the presence of a response against noise, it is important to compare the RMS measurement of the response with colour bars and signal column. The RMS measurement of noise (black bars) is performed over a time window where no response should be present from 200 to 290 ms after stimulation

B. Trace array with wave forms and 3-D density plots of 61 local responses, exploring rings 1 to 5 (from zero to 25° central). The amplitudes are reduced, particularly in rings 2 and 3. Decrease of response densities for the P1 peaks in the paracentral area in rings 2 and 3 (two to 10° central).

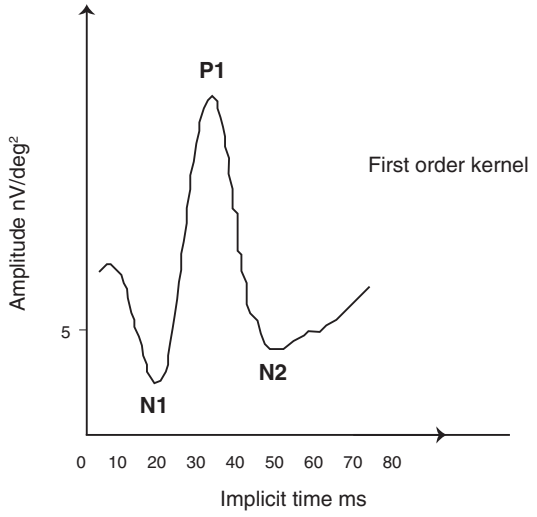

Figure 2. The 'waveform' analysis. This analysis performs an automated identification of the waveform and detects the N1, P1 and N2 peaks. It also determines automatically the amplitudes and the implicit times of these peaks.

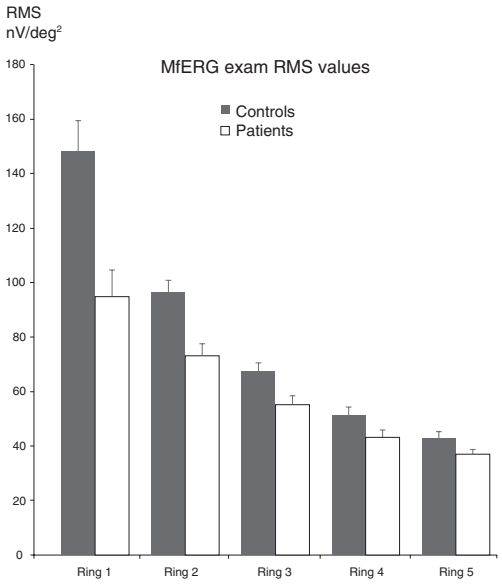

Figure 3. Controls versus Hy-treated patients (RMS). RMS mean value and 95 per cent CI in control and patient groups. A significant reduction in RMS responses was demonstrated at the mfERG for all the rings (central 2° to 25°) in Hy-patients versus controls.

Ring	Amplitude P1-N1	SD	Implicit time P1	SD	Amplitude RMS	SD
< 2°	128.28	±24.70	47.75	±2.24	148.16	±28.56
2–5°	85.62	±11.54	42.18	±1.58	96.32	±10.75
5–10°	60.38	±7.65	40.56	±1.61	67.18	±8.07
10–15°	45.12	±7.88	39.61	±1.81	50.95	±8.01
> 15°	38.38	±7.08	39.60	±1.76	42.60	±6.78

Ring 1 = < 2°; Ring 2 = 2° – 5°; Ring 3 = 5° – 10°; Ring 4 = 10° – 15°; Ring 5 = > 15°
Amplitude P1-N1 (nV/deg2); Implicit time P1 (ms); Average RMS (nV/deg2). RMS = Root mean square characterises the energy contained in the response signal.

Table 3. Normal mfERG. Mean P1-N1 wave response (amplitude and implicit time) and mean RMS (amplitude) response values in 25 healthy controls.

eyes and Hy-treated patients did not vary significantly with age. The subjects' ages ranged from 39 to 62 years.

Receiver operator characteristic (ROC) curves were constructed describing sensitivity and specificity of abnormal values for the control group versus patients, with optimal cut-off points chosen among normal and abnormal responses. Areas under the curves were used to compare different rings. Stata 10.1 was used in all analyses.

RESULTS

In all subjects, there were no significant differences between the tests at baseline and at follow-up. Table 3 summarises the average values of RMS and of P1-N1 of the mfERG responses for each ring obtained in the 25 healthy controls.

Among the Hy-treated eyes, 70 per cent (35 eyes) had abnormal mean response densities for one or more of the rings on mfERG, while among the Hy-treated eyes, 16 per cent (eight eyes) had an abnormal full field ERG. Characteristic patterns of loss were identified, similar to those described previously.[13,18] The most prevalent pattern was pericentral loss (19 eyes, 54.3 per cent), followed by full-field loss (11 eyes, 31.4 per cent), and central loss (five eyes, 14.3 per cent). Eyes with loss only in the periphery were not seen in the analyses.

A significant reduction (Mann-Whitney U test) in RMS and P1 amplitude responses were demonstrated at the mfERG for rings: 1 (central 2°), 2–3 (2° to 10°) and 4–5 (10° to 25°) in Hy-patients versus controls (Figures 3 and 4).

The total cumulative Hy dose correlated negatively with both RMS responses

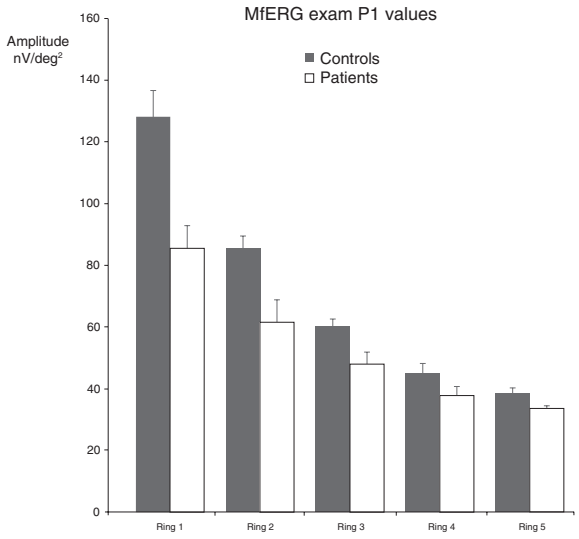

Figure 4. Controls versus Hy-treated patients (P1-N1). Amplitude mean value and 95 per cent CI in control and patient groups. A significant reduction in P1-N1 waves amplitude responses was demonstrated at the mfERG for all the rings (central 2° to 25°) in Hy-patients versus controls.

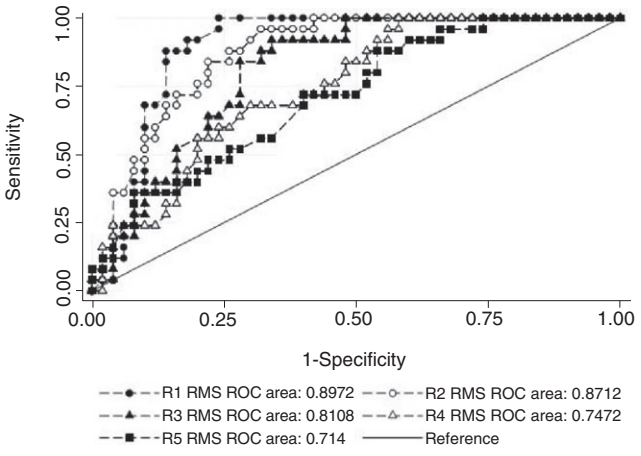

Figure 5. ROC curves of mfERG (RMS). ROC curves describing sensitivity and specificity of RMS values for the control group versus Hy-treated patients. The areas under the ROC curves range from 0.714 to 0.8972.

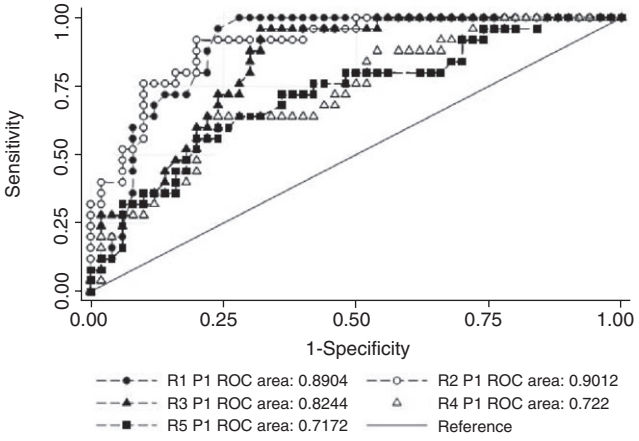

Figure 6. ROC curves of mfERG (P1-N1). ROC curves describing sensitivity and specificity of P1-N1 wave amplitude values for the control group versus Hy-treated patients. The areas under the ROC curves range from 0.7172 to 0.9012.

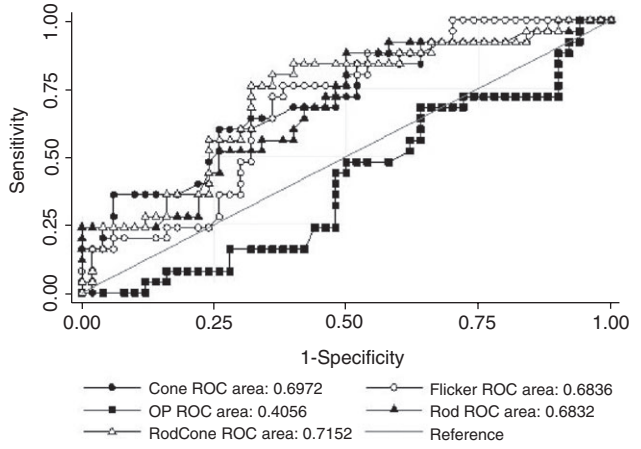

Figure 7. ROC curves of full field ERG. ROC curves describing sensitivity and specificity of full field ERG wave amplitude values for the control group versus Hy-treated patients. The areas under the ROC curves range from 0.4056 to 0.7152.

and P1 amplitudes for all the rings at mfERG. Spearman's correlations for the RMS signals were: rings 1 to 5 = -0.07, -0.34 , -0.25, -0.24 and -0.28, respectively. Spearman's correlations for the P1 amplitudes were: rings 1 to 5 = -0.20, -0.32, -0.26, -0.18 and -0.24, respectively. The strongest correlation was observed for ring 2 with both RMS and P1-N1 amplitude responses.

The results from the 50 Hy-treated patients and from the 25 controls were used to construct ROC curves for the responses as shown in Figures 5, 6 and 7. The proportion of eyes classified as

Average RMS responses	Cut-off nV/deg2	Sensitivity percentage	Specificity percentage	Correctly classified percentage
Ring 1	127	86.00	88.00	86.67
Ring 2	89.3	84.00	72.00	80.00
Ring 3	61	72.00	84.00	76.00
Ring 4	50	80.00	56.00	72.00
Ring 5	45.6	92.00	36.00	73.33
Amplitude P1-N1	**Cut-off nV/deg2**	**Sensitivity percentage**	**Specificity percentage**	**Correctly classified percentage**
Ring 1	104	76.00	96.00	82.67
Ring 2	78	90.00	76.00	85.33
Ring 3	57.6	80.00	60.00	73.33
Ring 4	42.9	76.00	64.00	72.00
Ring 5	41.7	94.00	32.00	73.33

Table 4. Correctly classified, sensitivity, specificity, and optimal cut off point chosen between normal and abnormal RMS and P1-N1 amplitude values for different rings

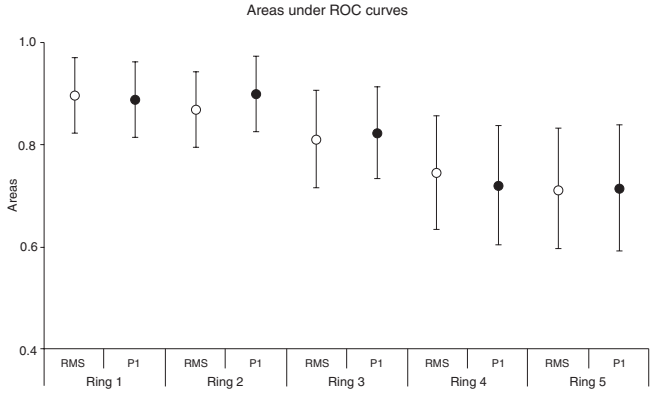

Figure 8. Areas under ROC curves of RMS and P1-N1 values. The numeric difference plot shows strong statistical agreement with P1-N1 area for retinal functional impairment.
RMS; Ho: area(r1 rms) = area(r2 rms) = area(r3 rms) = area(r4 rms) = area(r5 rms)
$\chi^2_4 = 8.02$; Prob > $\chi^2_4 = 0.0907$
Amplitude; Ho: area(r1 p1) = area(r2 p1) = area(r3 p1) = area(r4p 1) = area(r5 p1)
$\chi^2_4 = 13.65$; Prob > $\chi^2_4 = 0.0085$

abnormal or true positive rate (sensitivity) was plotted against the proportion of control eyes classified as abnormal or false positive rate (1-specificity).

The curves were constructed by varying the cut-offs defining abnormal RMS and P1-N1 wave amplitude values (rings 1 to 5; from zero to 25° central) and full-field ERG (photopic and scotopic tests). The areas under the ROC curves ranged from 0.4056 to 0.9012 (Figures 5, 6 and 7) with the mfERG values having the largest area (Figure 6), whereas the full-field ERG curves had the smallest area (Figure 7). The mfERG responses yielded the greatest sensitivity and specificity ratio as seen in Table 4. In particular, the P1-N1 wave amplitude (ring 2) and RMS amplitude (ring 1) had specificities of 76 and 88 per cent, respectively, at a sensitivity of 90 and 86 per cent (Table 4).

The RMS and P1-N1 amplitude ROC curves (rings 1, 2 and 3) were fairly similar to each other, as were their areas under the ROC curves (Figures 5 and 6), whereas the full-field ERG (photopic and scotopic tests) curves had the smallest area (Figure 7). The RMS and P1-N1 amplitude values of the rings 1, 2 and 3 presented the best area, sensitivity and specificity (Figures 5 and 6 and Table 4). The numeric difference plot (Figure 8) showed strong statistical agreement with P1-N1 area value for retinal functional impairment ($p > \chi^2 = 0.0085$).

The average RMS amplitude of the central hexagon ring 1 and the ratio of ring 1 to each of the successive concentric ring was calculated. The ratios, ring 1/ring 2, ring 1/ring 3, ring 1/ring 4, and ring 1/ring 5, were compared with limits derived from control eyes with p value of 0.003 or less (Mann Whitney test) (Table 5). Figure 9 shows the values for each ring ratio in normal eyes and those of Hy-treated patients.

DISCUSSION

In our study, mfERG proved to be more sensitive and specific than standard full field ERG in detecting Hy retinal dysfunction in asymptomatic patients. Abnormal mfERG responses were detected in 70 per cent of the clinically asymptomatic eyes, whereas the full-field ERG examination revealed retinal functional changes in only up to 16 per cent of the eyes. Our results are in agreement with those of other authors.[13,17,18] In fact, the retinal areas between the central two to 10 degrees

Ring ratio	Controls		Patients		p value*
	Mean	SD	Mean	SD	
R1/R2	1.54	±0.25	1.30	±0.36	0.003
R1/R3	2.22	±0.43	1.74	±0.62	< 0.001
R1/R4	2.96	±0.61	2.24	±0.85	< 0.002
R1/R5	3.54	±0.74	2.64	±1.02	< 0.003

*Mann Whitney test

Table 5. RMS ring ratios of Hy-treated patients compared to the controls

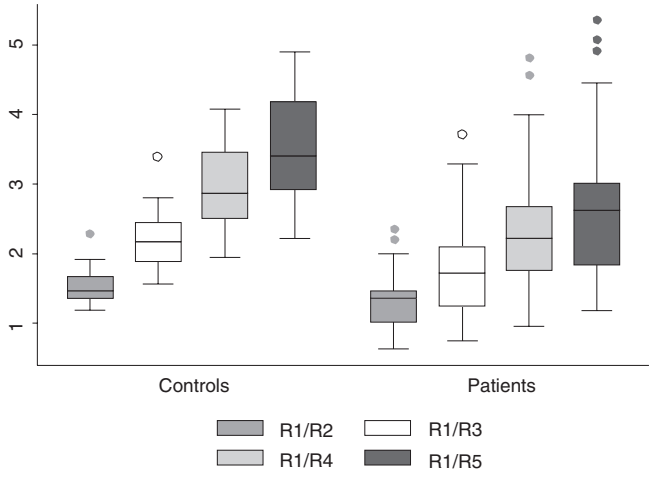

Figure 9. RMS ring ratios (controls versus patients). Scatterplot demonstrating values from zero to 25° central of each RMS ring ratio in control eyes and eyes of patients taking Hy.

appeared to be mostly affected (Figure 5, 6 and 7).

Several authors[12–14,19–26] agreed that the functional abnormalities in Hy-treated patients can be detected earlier on the mfERG than with other tests and even affect subjects with normal retina at fundoscopy and/or normal visual fields. Our data are similar to those already described and are based on a relatively large and homogenous number of patients (range from 39 to 62 years), when compared to some of the previously published investigations.[23,27–29] The increased sensitivity of mfERG with respect to other instrumental examinations may be the result of the on- and off-bipolar cellular contribution to the mfERG response as demonstrated by Hood and associates[30] in 10 rhesus monkeys. According to Kellner, Kraus and Foerster[19] and Kellner, Renner and Tillack,[28] retinal toxicity from antimalarial drugs is initiated by the vascular supply of the drug to the ganglion cells. Thinning of the retinal fibre layer could subsequently increase the drug level at the photoreceptor level, with consequent atrophy of the cones and RPE reactive proliferation and loss.

Other authors[31] argued that systemic immune diseases, such as rheumatoid arthritis, may contribute to a low scotopic ERG (rod response) or an abnormal electroculogram (EOG) ratio, independent of the use of antimalarial drugs, even in the presence of a bull's eye foveal lesion.[14,31]

Recent works[18,27] demonstrated an improvement of mfERG parameters in both symptomatic and asymptomatic patients after discontinuation of Hy treatment. The latter observation confirms the role of mfERG in the early detection of Hy toxicity in clinically asymptomatic patients. Elevated cumulative Hy doses (beyond 1250 g) have lately been indicated as more predictive of mfERG abnormalities than the daily dose adjusted for weight.[18,25,27] We also found a negative correlation between cumulative Hy dose and both RMS responses and P1 amplitudes for paracentral rings at mfERG.[18] Similar results were obtained by Lyons and Severns[18] in 2009, though in other work[23] the correlation appeared to be significant for all rings. In addition, Lyons and Severns[18] found the use of ring ratios to be a sensitive measure of retinal dysfunction in Hy patients. Because the macular area is usually less involved in the disease process, normalising the averaged ring amplitudes by the central amplitude further reduces the measurement variability and increases sensitivity. This is scheduled for completion (Table 5 and Figure 9).

The American Academy of Ophthalmology task force guidelines[32] recommend that patients exceeding five years of usage be screened annually. Whenever available, mfERG testing should be considered in addition to the psychophysical methods for the early detection and tracking of the progression of macular changes.[17,18]

More recently, Rüther and co-workers[25] reported a study on 21 patients and concluded that there is a high variability of cumulative doses and therefore, regular visual acuity, fundoscopy and electrophysiological testing should be performed once a year. The mfERG turned out to be the most important test in this regard.[17,18,25,26]

More research is needed to determine whether the patients with electroretinographic abnormalities will show progression even when the drug is discontinued. Significant, either reversible or irreversible central visual loss associated with antimalarial drugs is very rare but an important side-effect that can warrant discontinuation of therapy.[24,33]

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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