

Multifocal Electroretinogram in Hydroxychloroquine-related Macular Toxicity

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Prolonged use of hydroxychloroquine is common in patients with rheumatoid arthritis. Retinal toxicity due to hydroxychloroquine is known, and is monitored by investigations such as visual acuity, Amsler chart, colour vision, automated perimetry, full-field electroretinogram, and electrooculogram. Multifocal electroretinogram can suggest macular toxicity due to hydroxychloroquine even when the other investigations have normal results. Hence, multifocal electroretinogram has a role in the screening and follow-up of patients with suspected hydroxychloroquine toxicity.

Key words: Drug toxicity, Electroretinography, Hydroxychloroquine

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Introduction

Antimalarial agents are often used for a prolonged period in patients with rheumatoid arthritis. Hydroxychloroquine (HQ) is less toxic than chloroquine and some other disease-modifying drugs. Common systemic side effects of HQ include gastrointestinal upset, skin rash, and headache.¹ Keratopathy in the form of corneal deposits, lens opacities, and maculopathy causing a bull's eye lesion are the known ocular side effects of prolonged use of HQ.²

Retinal toxicity with prolonged chloroquine and HQ use is due to primary retinal photoreceptor damage or damage to the retinal pigment epithelium. These drug effects are irreversible and progressive, even after cessation of the drug.³ Therefore, timely intervention is needed to avoid any visual handicap.

Diagnosis of retinal toxicity poses a challenge to ophthalmologists, and is difficult to diagnose in the early stages as the drug effects may be localised and not easily picked up by conventional electro-diagnostic procedures, which rely on the mass response of the retina. Investigations such as visual acuity, Amsler chart, colour vision, visual field analysis, and fundus examination are used to determine retinal toxicity in patients with a history of HQ intake. A paracentral scotoma on visual field testing may be the first indication of retinal toxicity secondary to HQ.⁴

There is a need for investigations that can document the focal toxic effects of HQ. This report highlights the role of multifocal

electroretinogram (mfERG) in evaluating retinal toxicity in a patient with prolonged HQ intake.

Case Report

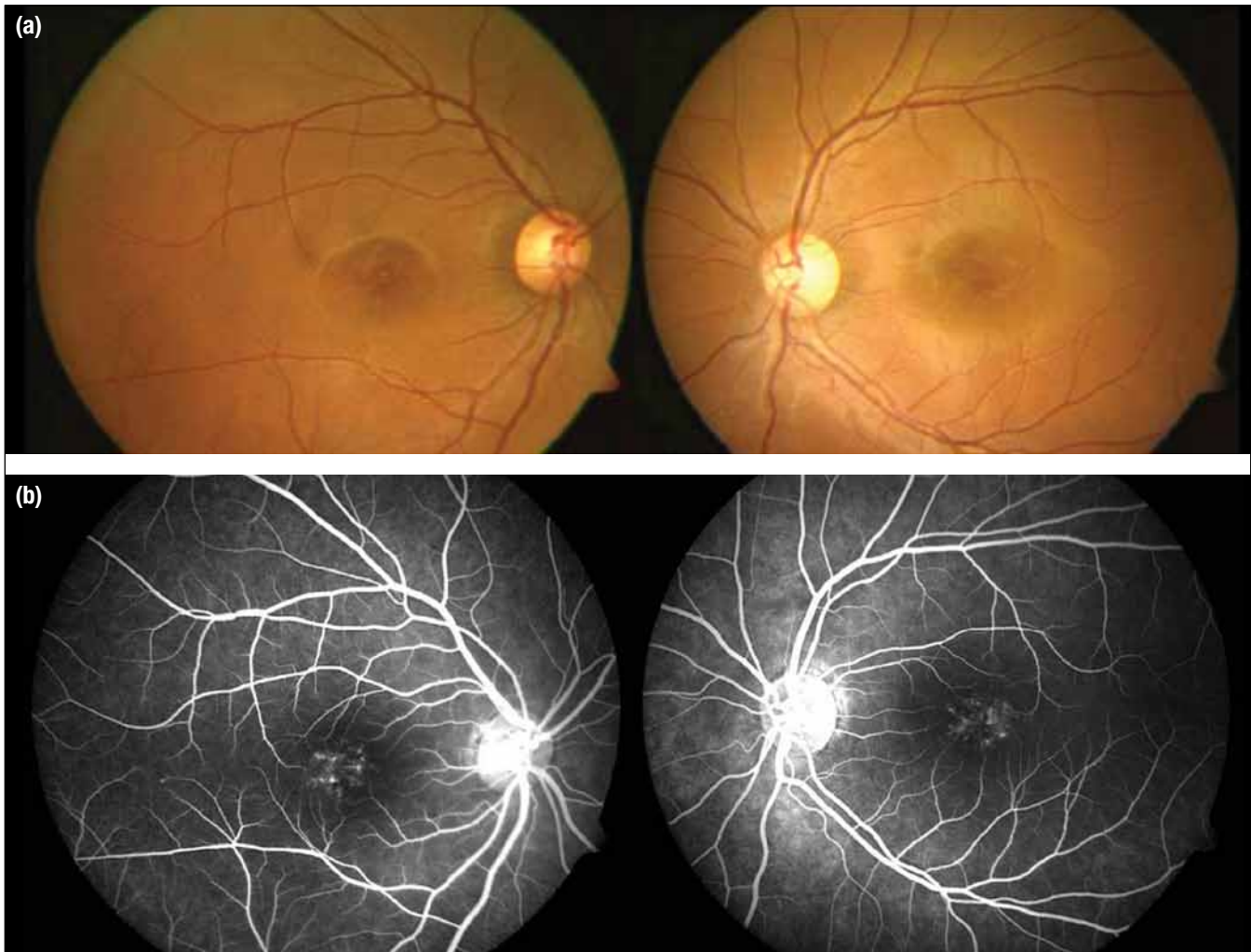
A 20-year-old presented in 2007 with a history of gradual painless decrease in vision for 2 years. She had been taking HQ for rheumatoid arthritis for the previous 3 years at doses of 400 mg daily for the first year followed by 200 mg daily for the next 2 years. Given that her weight was 54 kg, her dose of HQ was 7.5 mg/kg/day in the first year and 3.7 mg/kg/day in the next 2 years. The cumulative dose was 146 g in the first year and 73 g per year for the next 2 years, for a total of 292 g in 3 years.

Her best-corrected visual acuity (BCVA) was 6/18 in both eyes. Her BCVA recorded 4 years previously was 6/6. Anterior segment examination and intraocular pressure were normal. No subepithelial corneal deposits were seen. Colour vision by Ishihara plates and Amsler chart were normal. Fundus examination revealed a few faint yellowish lesions at the level of the retinal pigment epithelium (RPE) in the macula in both eyes. Fundus fluorescein angiography showed window defects corresponding to the RPE lesions (Figure 1). Visual field testing with the Swedish Interactive Thresholding Algorithm fast Humphrey field analyser 30-2 revealed a few paracentral defects. Given the patient's drug history, a diagnosis of retinal toxicity following HQ use was considered.

Full-field ERG (ffERG) and mfERG were recorded using the VERIS™ Science 5.1 system (EDI, Inc, San Mateo, USA) following the guidelines of the International Society for Clinical Electrophysiology of Vision.^{5,6} The stimulus for mfERG consisted of 103 hexagons

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Figure 1. Fundus photographs of the right and the left eyes showing (a) yellowish lesions at the level of the retinal pigment epithelium; and (b) corresponding window defects seen on fundus fluorescein angiography.



viewed at a distance of 53 cm and subtended 35° horizontally and 31° vertically in the visual field. The 103 hexagons appeared to flicker according to a pseudorandom binary m-sequence of black and white hexagonal presentations. A Grass 15LT amplifier (Astro-Med, Inc, West Warwick, USA) with band pass from 10 to 300 Hz and gain of 50,000 was used. The selected pseudorandom binary m-sequence was $2^{15}-1$, the stimulation rate was 75 Hz (interframe base interval, 13.33 ms), and the response signal was sampled at 16 times per frame (interval, 0.83 ms), resulting in a recording time of approximately 7 minutes 17 seconds. The raw waveform was visible throughout the recording and segments were rejected if there were any artefacts due to excessive blinking or poor fixation.⁶ Ambient room lighting was used during mfERG recording. The stimulus pattern comprised a central hexagon corresponding to the fovea and the five concentric rings at different eccentricities corresponding to the paramacular region. Ring 1 (R1) subtended <math><1.6^\circ</math> in diameter, ring 2 (R2) was

1.6° to 6.0°, ring 3 (R3) was 6.0° to 11.4°, ring 4 (R4) was 11.4° to 18.2°, ring 5 (R5) was 18.2° to 26.2°, and ring 6 (R6) was 26.2° to 35.0°.

Both ffERG and mfERG recordings were done using Burien-Allen bipolar contact lens electrodes (Hansen Ophthalmic Laboratories, Iowa City, USA) with the ground electrode placed on the earlobe. Parameters measured were amplitudes and implicit times. The amplitudes were measured in μV for ffERG and nV/deg^2 for mfERG, and implicit times were measured in ms.

The first order kernels of mfERG (N1 and P1 implicit times, amplitudes) were taken for analysis. The mean N1, P1 implicit times and amplitudes for each ring from the mfERG responses of both eyes were calculated and compared with those of age-matched controls ($n = 13$).

ffERG showed normal scotopic and photopic responses (Figure 2), but mfERG revealed a significant decrease in amplitudes and increase in implicit times of N1 and P1 in rings 1 and 2 (Figure 3). The

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Figure 2. Full-field electroretinograms of the right and left eyes showing normal scotopic and photopic responses.

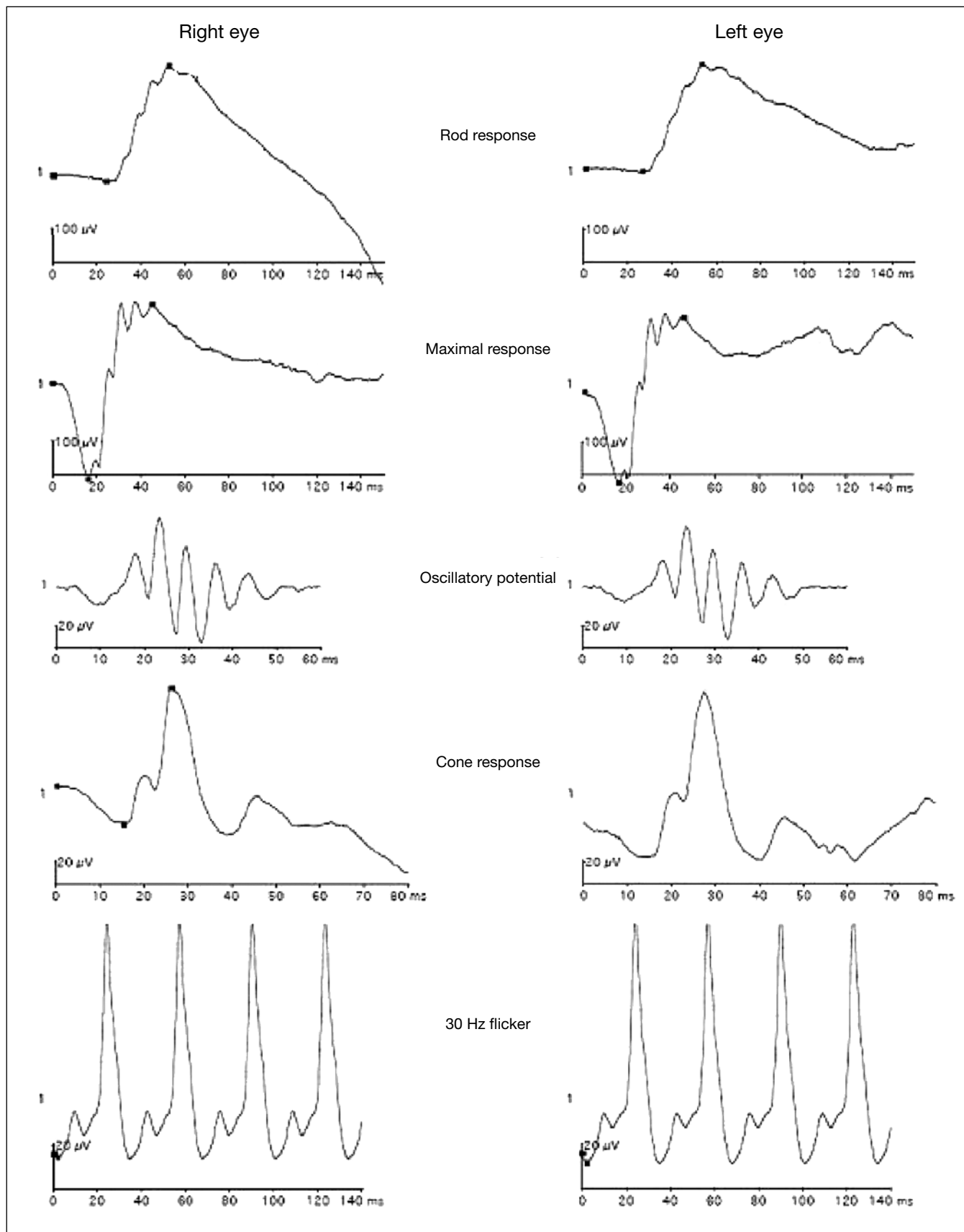
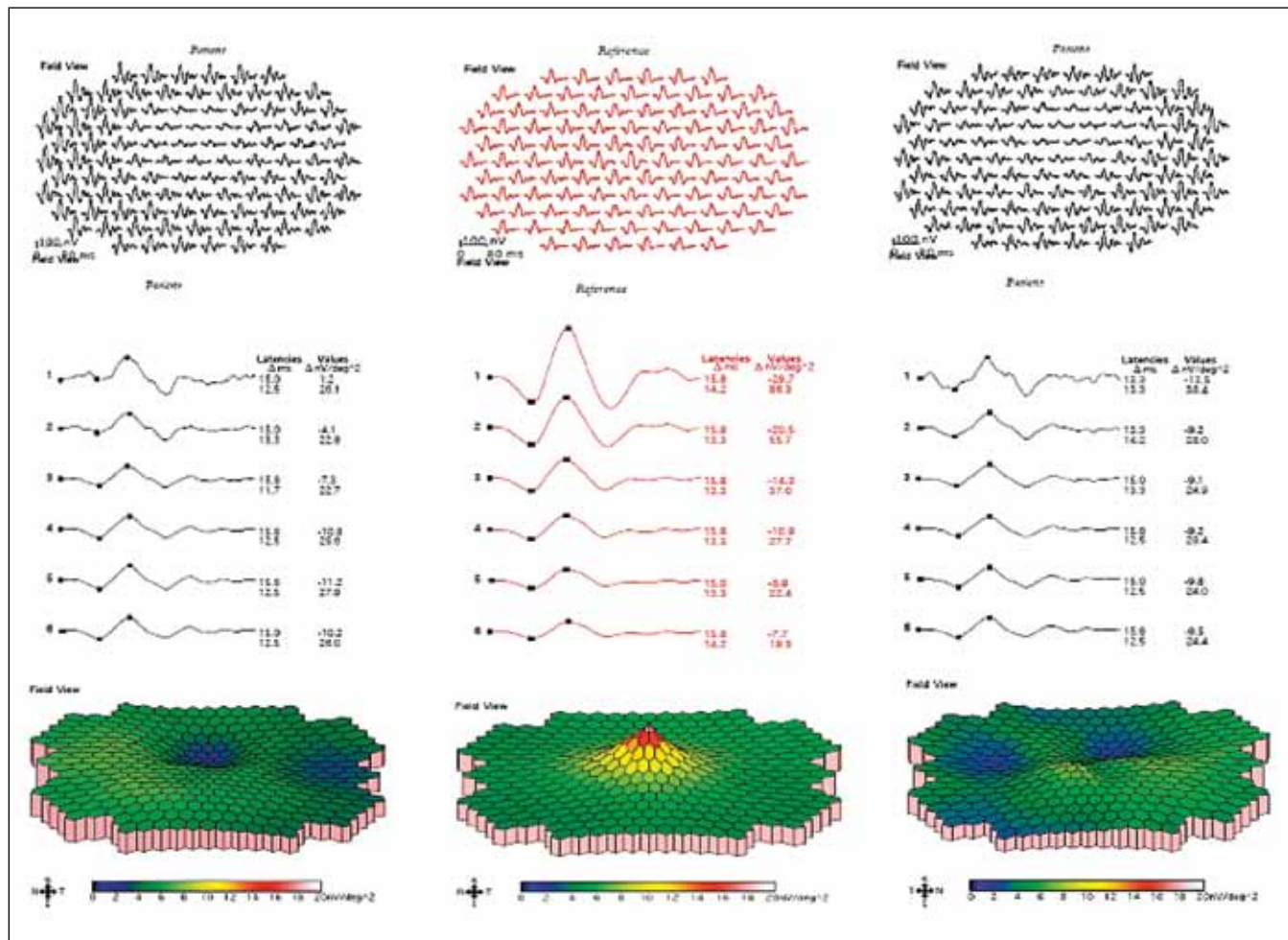


Figure 3. Multifocal electroretinogram trace array and 3-dimensional chart showing a significant decrease in the central ring responses.



responses in the peripheral rings were comparable with those of age-matched controls (Figure 4).

Discussion

Retinal toxicity due to HQ has decreased as the dose of HQ prescribed for arthritis has been optimised over the years. Sight-threatening retinopathy in these patients occurs less frequently at the currently recommended dose of 400 mg daily.² In 2002, the American Academy of Ophthalmology recommended that patients taking HQ with normal baseline investigations do not require special ophthalmological monitoring for 5 years provided that the daily dose of HQ is less than 6.5 mg/kg body weight and the cumulative dose does not exceed 200 g.⁷ However, retinopathy has been noticed at drug doses that are considered 'safe' (<6.5 mg/kg body weight).⁸ For this patient, the cumulative dose was more than 200 g and the dose per year was more than the recommended dose. The patient did not have any high risk factors such as kidney or liver disease or high body fat.⁷ Although she had experienced a decrease in vision over 2 years, she had no history of prior screening for HQ toxicity.

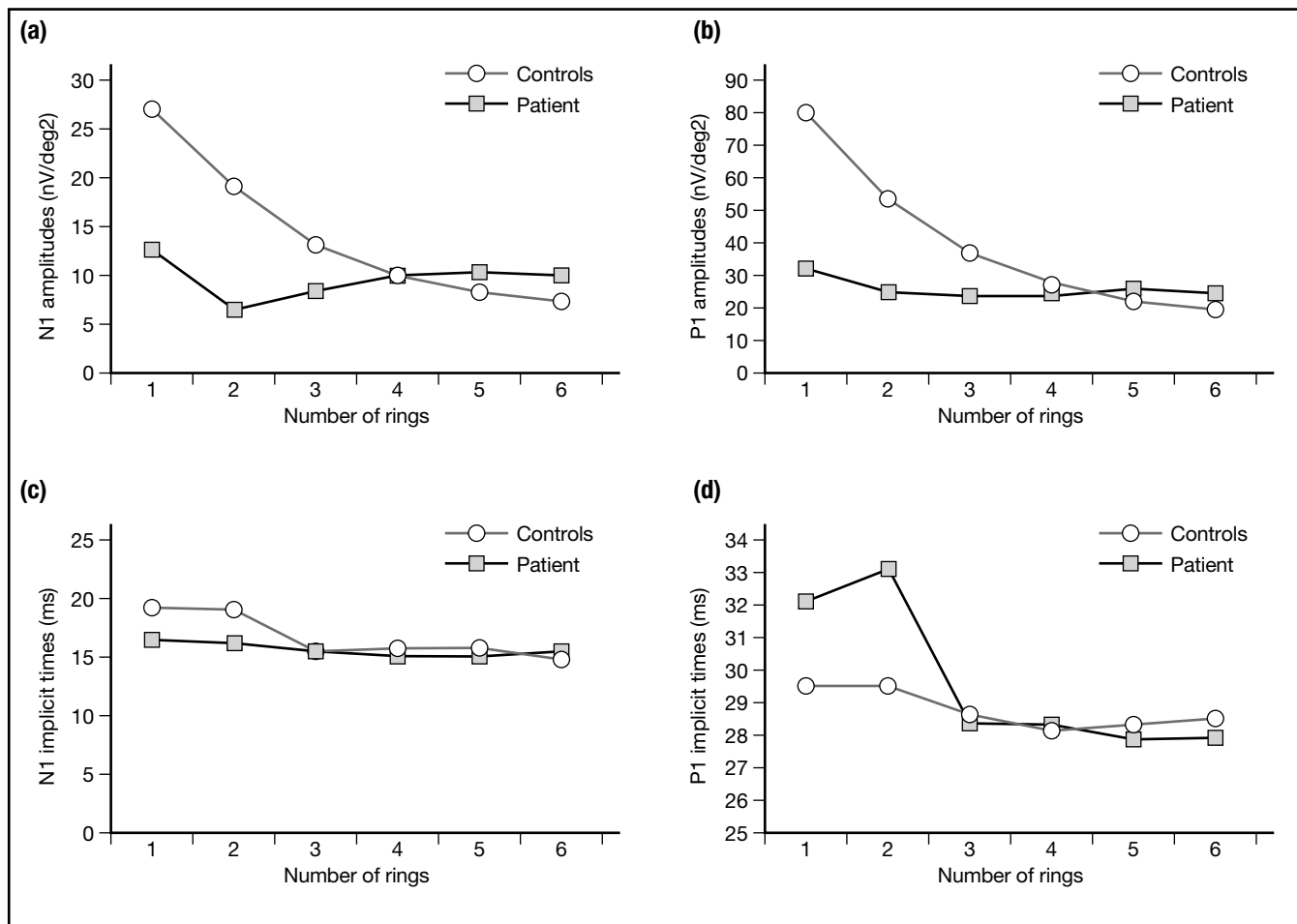
Therefore, awareness of the treating physician is needed to optimise the drug dose while considering the risks and benefits of HQ. Asian patients, especially women, often weigh less than western women, and this must be considered when adjusting the dose.

Various screening tests have been proposed to detect retinal lesions due to HQ, including visual acuity testing, automated perimetry, Amsler chart, colour vision, indirect ophthalmoscopy, ERG, and electrooculogram. For this patient, fundus examination, colour vision, and Amsler chart did not reveal the typical features of bull's eye maculopathy, and mfERG was non-committal. However, mfERG recordings revealed a decrease in central retinal responses, as seen by Maturi et al⁹ and Lai et al.¹⁰ The pattern of a central depression with normal peripheral responses is one of the typical presentations of HQ toxicity. Automated perimetry also showed paracentral defects. However, perimetry is a subjective evaluation, while mfERG is an objective technique for detecting the topography of the toxicity.^{11,12}

Although mfERG is a useful method for early detection of retinal toxicity, its application may be limited because of inadequate

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Figure 4. Multifocal electroretinogram graphs depicting (a) N1 amplitude; (b) P1 amplitude; (c) N1 implicit times; and (d) P1 implicit times compared with age-matched controls.



access to this technology in many ophthalmic centres, especially in developing nations in Asia. Incorporation of an appropriate ophthalmic screening programme for the management of patients with HQ toxicity needs to be considered to prevent permanent visual loss. Base-line mfERG should be done before administering HQ. mfERG and mfERG compliment each other, and mfERG can detect macular toxicity even when other investigations are normal.

References

- van Jaarsveld CH, Jahangier ZN, Jacobs JW, et al. Toxicity of anti-rheumatic drugs in a randomized clinical trial of early rheumatoid arthritis. *Rheumatology (Oxford)*. 2000;39:1374-82.
- Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. *Am J Med*. 1983;75:25-34.
- Sassani JW, Brucker AJ, Cobbs W, Campbell C. Progressive chloroquine retinopathy. *Ann Ophthalmol*. 1983;15:19-22.
- Yam JC, Kwok AK. Ocular toxicity of hydroxychloroquine. *Hong Kong Med J*. 2006;12:294-304.
- Marmor MF, Fulton AB, Holder GE, Miyake Y, Brigell M, Bach M;

- International Society for Clinical Electrophysiology of Vision. ISCEV Standard for full-field clinical electroretinography (2008 update). *Doc Ophthalmol*. 2009;118:69-77.
- Hood DC. Assessing retinal function with the multifocal technique. *Prog Retin Eye Res*. 2000;19: 607-46.
- Marmor MF, Carr RE, Easterbrook M, Farjo AA, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2002;109:1377-82.
- Bienfang D, Coblyn JS, Liang MG, Corzillius M. Hydroxychloroquine retinopathy despite regular ophthalmologic evaluation: a consecutive series. *J Rheumatol*. 2000;27:2703-6.
- Maturi RK, Yu M, Weleber RG. Multifocal electroretinographic evaluation of long-term hydroxychloroquine users. *Arch Ophthalmol*. 2004;122:973-81.
- Lai TY, Chan WM, Li H, Lai RY, Lam DS. Multifocal electroretinographic changes in patients receiving hydroxychloroquine therapy. *Am J Ophthalmol*. 2005;140:794-807.
- Marmor MF. The dilemma of hydroxychloroquine screening: new information from the multifocal ERG. *Am J Ophthalmol*. 2005;140: 894-5.
- Gilbert ME, Savino PJ. Missing the bull's eye. *Surv Ophthalmol*. 2007;52:440-2.