Original Paper

Ophthalmic Research

Ophthalmic Res 2004;36:106–113
DOI: 10.1159/000076890

Received: August 19, 2003
Accepted after revision: December 15, 2003

# The Multifocal Pattern Electroretinogram in Chloroquine Retinopathy

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**Key Words**
Antimalarial toxicity · Screening · Multifocal pattern electroretinogram · Electrophysiology

**Abstract**
***Purpose:*** Optimal screening for ocular toxicity caused by chloroquine and hydroxychloroquine is still controversial. With the multifocal pattern electroretinogram (mfPERG), a new electrophysiological technique has recently become available to detect early changes of ganglion cells. In this study this new technique is applied to a series of 10 patients seen consecutively receiving long-term chloroquine medication. ***Methods:*** In 10 patients receiving chloroquine medication, clinical examination, Amsler visual field testing and computerized color vision testing were performed. If toxicity was suspected, automated perimetry was carried out. In addition, in all patients conventional pattern electroretinogram (PERG) and mfPERG testing were performed. ***Results:*** On clinical examination 8 patients showed no chloroquine-associated maculopathy, while 2 patients did. Of these 2, only 1 reported abnormalities when viewing the Amsler chart, while automated perimetry showed typical, ring-like paracentral scotomas in both affected patients and color vision was significantly abnormal. In the normal patients, 4 of 8 had a mild color vision disturbance, which correlated to age-related macular changes. The amplitudes of the PERG and the central (approximately 10°) responses of the mfPERG were markedly reduced in chloroquine maculopathy, while the latencies were unchanged. The peripheral rings of mfPERG (ranging to 48°) were not affected by chloroquine toxicity. Both PERG and mfPERG were less affected by age-related macular changes. ***Conclusions:*** The reduction of PERG and central mfPERG responses in chloroquine maculopathy may help with the early detection of toxicity.



## Introduction

Screening strategies for antimalarial retinal toxicity are still controversial, because there is a difficulty in defining the early stages of retinopathy, and in well-monitored patients, the incidence of retinopathy is low. Macular changes and transient defects in visual field testing as well as in color vision testing may be symptoms of a 'prereti-

The authors do not have any commercial interest in any of the materials and methods used in this study.

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nopathy', but are difficult to differentiate from other causes such as age-related changes. While all screening strategies include visual acuity testing and a dilated fundus exam, and many include fundus photographs, other tests like fluorescein angiography [1] or more frequently visual field tests ranging from Amsler grid [2] to automated macular perimetry [3–5] have been used. Also, various color vision tests have been proposed [6] and different electrophysiological tests (electro-oculogram and electroretinogram, ERG) have been evaluated [7–14]. The efficiency of all such ophthalmologic screening procedures is controversial. This is reflected in surveys of current practice patterns showing quite inhomogeneous results [15]. Recently, proposed screening requirements are more and more limited to clinical tests [5, 16] and for hydroxychloroquine no routine ophthalmologic screening is recommended by the Royal College of Ophthalmologists [17]. The recent recommendations of the American Academy of Ophthalmology [5, 16] adopt screening intervals after a baseline exam for both antimalarials because of the anticipated risk to the patient. The proposed routine screening includes an ophthalmologic exam and visual field testing by an Amsler grid or Humphrey 10-2. Optional tests include color testing, fundus photography, fluorescein angiography and multifocal ERG.

While early studies and some recent literature [5, 16] assumed that a binding of chloroquine to melanin caused retinal toxicity [18, 19], there is strong proof that melanin is not at all concerned in ocular toxicity [20]. This is supported by the fact that retinopathy can be reproduced equally both in albino and in pigmented rabbits, rats and cats [21–25]. Several histopathologic investigations report retinal changes, which showed membranous cytoplasmic bodies predominantly in the ganglion cells of the retina in man [26], monkey [27] and rodents [28], whereas the pigment epithelium was affected only in very advanced retinopathy. This mechanism of first impairing ganglion cell function proposes that the strategy for chloroquine retinopathy screening must focus on those cells. Of the electrophysiological tests, therefore, theoretically the pattern ERG (PERG) should be the most effective [29], but has been applied in only a few cases [30]. As retinopathy is known to occur predominantly in the macula, multifocal techniques are very promising [5]. Therefore, the aim of the current study was to investigate if screening for ocular toxicity of antimalarials can be improved by using the PERG and multifocal PERG.

## Methods

*Patients*

A series of 10 consecutive patients presenting at the electrophysiological department of the ophthalmologic department at the Ludwig Maximilians University were included in the study.

On every exam besides full clinical examination, Amsler visual field testing and color vision testing with a computerized color vision test as described below [31–33], applying 6.5° orthotypes, were performed. If chloroquine retinopathy was suspected, automated perimetry (Humphrey 30-2 and/or 10-2; Carl Zeiss Inc., Dublin, Calif., USA) was also performed. The patient characteristics are given in table 1.

As a control group we examined 25 age-matched normal eyes from 25 healthy individuals. Informed consent was obtained from all participants. Average mean and standard deviation (SD) of the healthy subject ages was 61 ± 12 (range 21–72) years. Healthy eyes had no eye disease on ophthalmologic examination and no history of any chronic eye disease or previous ocular surgery. Visual acuity for normal volunteers was 1.0 (20/20) or better with correction.

*PERG and Multifocal PERG Stimulation*

For the PERG a RETIScan System (Roland Consult, Wiesbaden, Germany) was used. The conventional, transient PERG was performed according to the ISCEV Standards [34] applying a 1°25′ checkerboard and 200 averages. For each PERG a positive component at approximately 50 ms (P-50) and a negative component at approximately 95 ms (N-95) was determined. The total amplitude P-50–N-95 was analyzed. Normal values were determined to have a median of 13.7 μV with a 95% interval of 6.7–22.7 μV yielding a lower limit of 6.7 μV.

For the multifocal, transient PERG also a RETIScan System (Roland Consult) was applied, presenting a stimulus pattern of 19 patterned hexagons, each consisting of 6 triangles (which are alternating black and white). No scaling factor was applied, which means that the central hexagon (macula) had the same size (9.6° visual field) as the peripheral hexagons. The stimulus was presented on a 21-inch monitor viewed at 30 cm distance within a central 48° visual field (visual angle of 24°). Mean luminance of the stimulus on the monitor was 180 cd/cm$^2$ and the contrast was approximately 98%. Each hexagon changed at the frequency of 75 Hz with an on/off probability of 0.5. A trace array of all multifocal PERG traces was smoothed and plotted.

*Recording and Response Analysis*

For all recordings gold foil electrodes were used (reference electrodes at the temple, ground electrodes at the forehead) after anesthetizing the conjunctiva with oxybuprocain 0.4% eye drops. Near correction if necessary was applied. For fixation a red target of approximately 1° visual angle was placed in the center of the stimulus. The room illumination was moderate and always the same [35], and no mydriatic eye drops were given.

The pattern changed in accordance of the structure of a corrected m-sequence [36]. Duration of data acquisition was approximately 5 min with a length of 512 divided into 10 sessions of 39 s each. The signals were band-pass-filtered with a high cut at 300 Hz and a low cut at 10 Hz. In case of artifacts due to ocular movement or eyelid movement, the response was eliminated by the computer program. By cross-correlation analysis between stimulation patterns and their responses 19 focal multifocal PERGs were displayed topographi-

**Table 1.** Patient data with results of computer color vision testing, conventional PERG, multifocal PERG (mfPERG) and clinical assessment

| Patient No. and eye | Age | Visual acuity | Duration of chloroquine medication | Daily dose mg/kg ideal body weight | Color test threshold, % | | PERG amplitude P-50–N-95 μV | mfPERG amplitude P-50–N-95 nV/deg$^2$ | | | Clinical assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | protan | tritan | | ring 1 | ring 2 | ring 3 | |
| 1 OD | 62 | 0.8 | 4 years | 5 | 17.8 | 38.2 | 1.9 | 7.2 | 7.0 | 3.6 | chloroquine maculopathy |
| 1 OS | | 1.0 | | | 18.4 | 39.0 | 4.8 | 4.3 | 6.0 | 3.7 | chloroquine maculopathy |
| 2 OD | 64 | 0.3 | 20 years | 10 | 40.0 | 70.0 | 4.0 | 2.6 | 2.9 | 2.1 | chloroquine maculopathy |
| 2 OS | | 0.5 | | | 21.0 | 22.0 | 6.0 | 6.7 | 2.5 | 2.7 | chloroquine maculopathy |
| 3 OD | 62 | 0.9 | 6 years | 4 | 2.9 | 8.1 | 15.0 | 8.9 | 9.1 | 4.5 | dry ARM |
| 3 OS | | 0.9 | | | 2.3 | 9.9 | 21.0 | 14.4 | 6.5 | 4.8 | dry ARM |
| 4 OD | 30 | 1.25 | 1 year | 2.8 | 5.2 | 6.0 | 7.7 | 12.6 | 7.6 | 3.4 | normal |
| 4 OS | | 1.25 | | | 5.0 | 3.7 | 7.8 | 20.4 | 7.4 | 6.7 | normal |
| 5 OD | 42 | 1.0 | 3 years | 2.5 | 6.4 | 7.0 | 21.0 | 36.6 | 13.6 | 6.2 | normal |
| 5 OS | | 1.0 | | | 6.4 | 6.2 | 23.0 | 31.8 | 12.6 | 6.7 | normal |
| 6 OD | 25 | 1.0 | 4 years | 3.0 | 4.8 | 5.2 | 13.0 | 20.5 | 7.3 | 4.9 | normal |
| 6 OS | | 1.0 | | | 5.0 | 4.8 | 18.0 | 19.9 | 11.5 | 6.0 | normal |
| 7 OD | 66 | 0.8 | 5 years | 8 | 7.2 | 8.6 | 8.8 | 17.8 | 5.6 | 2.4 | dry ARM |
| 7 OS | | 0.6 | | | 7.8 | 9.1 | 8.3 | 22.4 | 2.8 | 4.9 | dry ARM |
| 8 OD | 76 | 1.0 | 1 year | 2.5 | 9.4 | 10.4 | 9.2 | 11.2 | 4.2 | 2.0 | dry ARM |
| 8 OS | | 1.0 | | | 8.4 | 9.8 | 12.0 | 8.9 | 6.0 | 3.5 | dry ARM |
| 9 OD | 67 | 1.0 | 6 months | 3.0 | 4.8 | 7.2 | 13.0 | 21.7 | 9.9 | 5.1 | normal |
| 9 OS | | 0.8 | | | 7.2 | 9.4 | 10.0 | 13.1 | 8.9 | 3.0 | normal, corneal scar |
| 10 OD | 43 | 1.0 | 20 years | 3.5 | 4.8 | 6.2 | 6.0 | 4.3 | 3.3 | 0.6 | retinal scars, ARM |
| 10 OS | | 1.0 | | | 4.6 | 6.4 | 7.5 | 13.0 | 5.0 | 2.6 | retinal scars, ARM |

Normal values for color testing were less than 8% threshold, for PERG amplitudes more than 6.7 μV. Multifocal PERG normal reference intervals start from 21.7 nV/deg$^2$ for the central ring, from 8.1 nV/deg$^2$ for ring 2 and from 4.1 nV/deg$^2$ for ring 3. ARM = Early forms of age-related maculopathy.

cally. For analysis the 19 hexagons were grouped into one central field and two peripheral rings.

For each multifocal PERG a positive component at approximately 50 ms (P-50) and a negative component at approximately 95 ms (N-95) were determined. The P-50 often rises from a still earlier negative wave at approximately 35 ms (N-35). The positive component is measured from this trough to the following positive peak of P-50. The following negative N-95 component is measured from the peak of P-50 to the following trough at approximately 95 ms. The total amplitude P-50–N-95 was used for analysis and responses were grouped into three regions: a central hexagon (macular hexagon), a middle ring (6 hexagons) and a peripheral ring (remaining 12 hexagons). The responses of the peripheral rings were averaged from the underlying hexagons. Latencies (given in milliseconds) of N-35, P-50 and N-95 were also measured and analyzed for every ring. As they did not show any alterations, data are not shown.

*Color Vision Test*

A computerized color vision test was used. The details of the method are described in detail elsewhere [31–33]. In brief, the system uses a calibrated 21-inch color monitor to present random letters as targets to be identified. The letters are of equal luminance to the background and can only be recognized because their hue differs from the background. Color of the letters is varied along a chosen confusion-confusion axis. A modified binary search is carried out to determine the threshold color contrast along protan and tritan color confusion lines. The resulting threshold should not exceed 8.0% in normal probands and is known to be almost independent of age when applying large 6.5° orthotypes as performed in this study [33]. Thresholds of 8.0% for protan and tritan axis were used according to Berninger et al. [33], where 7.0% was found as an extreme value for protan axis and 7.9% for tritan axis in normals. The threshold represents a deviation of more than 3 SD for protan and 2 SD for tritan from the normal mean.

*Statistics*

All data were collected and analyzed using SPSS 11.0 for Windows (SPSS Inc., Chicago, Ill., USA). In all cases nonparametrical tests were used and always only the right eye of each patient (and controls) included.

## Results

The patient details are given in table 1. Mean patient age was 54 ± 17 years (range 25–76 years) and did not differ from normal controls. In table 1 all results of test-

ing: color vision, PERG, and multifocal PERG, are listed. The results were analyzed for significant differences in color vision thresholds, the amplitudes of the PERG, differences in amplitudes from negative N-95 to positive P-50 in multifocal PERG and for differences in the latencies.

*Color Vision Testing*

Regarding color vision, patients with chloroquine maculopathy showed a marked increase in thresholds for protan ($p = 0.06$) and tritan color axis ($p = 0.06$; Mann-Whitney U test) within the shown patient group. All toxic maculopathies were by far exceeding the normal thresholds of 8%. Eyes with a maculopathy due to early age-related changes (ARM) showed also some abnormal color test results as compared to the normal control group. For the protan axis only 1 patient with ARM (patient 8 in table 1) exceeded the threshold of normals, while most patients with ARM showed slightly abnormal values for the tritan axis.

*PERG Testing*

In the 2 patients with chloroquine maculopathy, the amplitudes of conventional PERG testing (table 1) were outside the lower reference limit for healthy individuals of 6.7 μV. In contrast, nearly all other patients including those with early ARM did exceed this minimal amplitude. Even when comparing within all 8 patients on chloroquine to those 2 with chloroquine maculopathy (table 1), a significant reduction in PERG amplitudes at $p = 0.04$ was obtained.

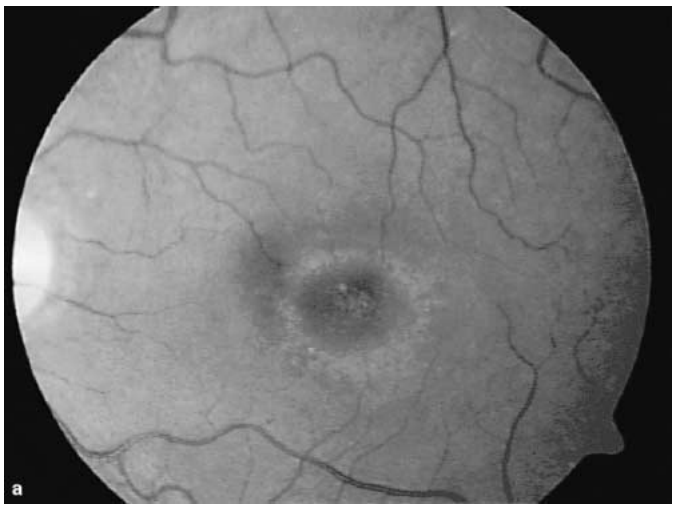
*Multifocal PERG Testing*

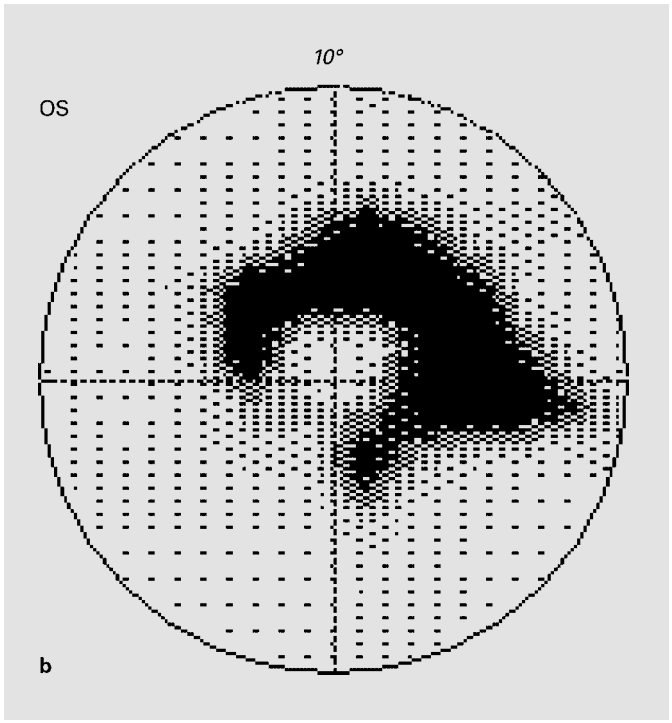
On multifocal PERG testing the multifocal PERG P-50–N-95 amplitudes of the normal age-matched control group were $37.37 \pm 7.83$ nV/deg$^2$ for the central ring, $15.82 \pm 3.87$ nV/deg$^2$ for ring 2 and $9.50 \pm 2.69$ nV/deg$^2$ for ring 3 (each representing mean ± SD). This calculated 2 SD lower reference limits of 21.7 nV/deg$^2$ for the central ring, 8.1 nV/deg$^2$ for ring 2 and 4.1 nV/deg$^2$ for ring 3. For all cases with established maculopathy a clear reduction throughout all rings was observed with the central ring showing the by far largest reduction of amplitudes (table 1). The patients with ARM also exhibited some degree of central reduction as did other pathologies such as corneal or central retinal scars. However, those changes were less pronounced than in chloroquine maculopathy. Throughout all patients with any maculopathy the peripheral ring 3 was affected least.

When comparing the multifocal PERG amplitudes within all patients taking chloroquine (all patients from table 1), the 2 maculopathy cases exhibited the largest difference for the central ring ($p = 0.07$), less pronounced in ring 2 ($p = 0.19$), while for the peripheral ring 3 no difference was found ($p = 0.60$). When those 4 patients with ARM changes were excluded from analysis, similar results were obtained. When comparing within table 1 only those eyes with age-related changes to those 2 with chloroquine-induced maculopathy, overall the largest statistical differences were obtained for color vision testing ($p = 0.06$), the conventional PERG ($p = 0.06$) and ring 1 of multifocal PERG ($p = 0.17$). One case example with established maculopathy will be described here briefly to illustrate the typical changes.

*Case Example*

The 62-year-old woman (table 1, patient 1) was first seen 2 years ago with a developing bilateral bull's-eye maculopathy, the right eye more than the left eye (fig. 1a). She had suffered from rheumatoid arthritis for 24 years and taken a 250-mg chloroquine tablet daily for the last 4 years (cumulative dose 365 g). The recommended daily dose for this patient, based on her ideal body weight for her height (158 cm), would be only 175 mg/day, so the actual dosage was high. The patient's general ophthalmologist was following her with automated 30° visual fields, where in both eyes central absolute scotomas developed within the last 6 months before presentation to our department (fig. 1b). These visual field changes had occurred at first without any and later on with subtle fundus changes (fig. 1a) alarming him of retinopathy. Best-corrected visual acuity at first presentation was on the right 0.8 (20/25) and on the left 1.0 (20/20). The patient showed a marked cornea verticillata and on funduscopy early bull's-eye maculopathy (fig. 1a). The patient herself had recognized a slightly blurred vision for some months, but could not localize any defect on Amsler grid testing. Conventional multifocal ERG was completely normal, indicating no photoreceptor dysfunction. However, the PERG (fig. 1c, table 1) and central multifocal PERG amplitudes (fig. 1d, table 1) were markedly reduced. The color vision test was highly pathologic. It yielded for protan axis OD 17.8% and OS 18.4% (normal <8%), and for tritan axis OD 38.2% and OS 39.0% (normal <8%). The patient discontinued chloroquine and has had stable visual acuity for 2 years now with constantly improving color vision and PERGs.



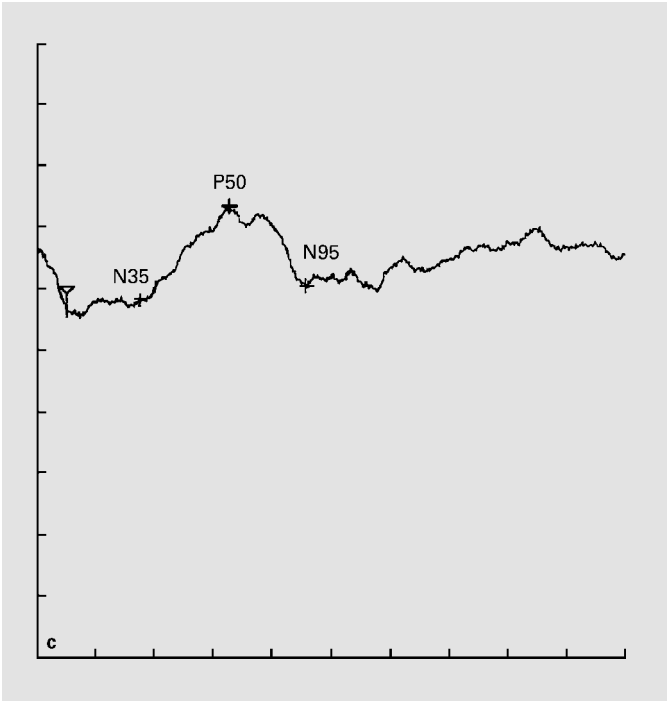
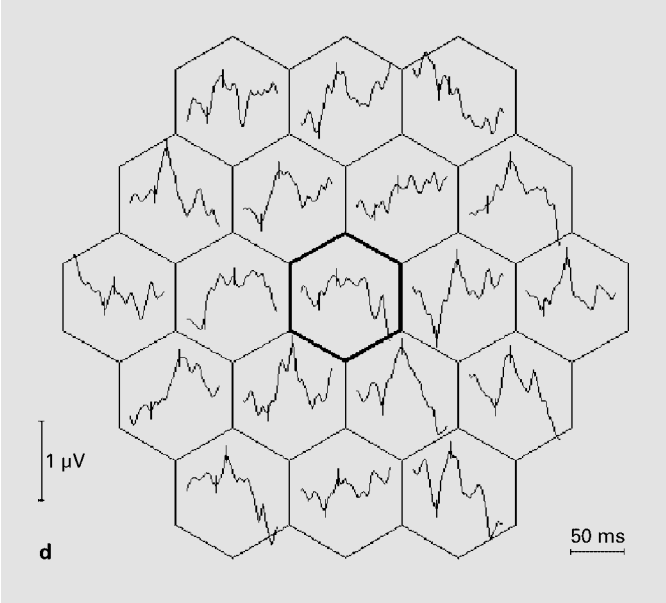



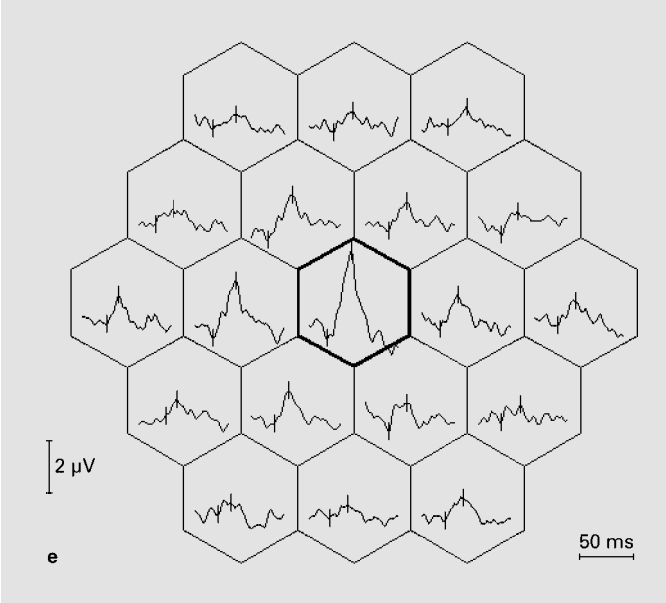

**Fig. 1. a** Fundus picture of the left eye of patient 1 with chloroquine maculopathy. Visual acuity was 1.0. The other eye showed similar changes. **b** Central 10° visual field (Humphrey 10-2) of the left eye of the same patient shows a typical paracentral scotoma. The defects correlate well with the fundus picture in **a**. **c** Conventional PERG shows markedly reduced amplitudes with a mean P-50–N-95 of 4.8 μV. The scale is 20 ms/Div and 5 μV/Div. **d** Multifocal PERG by monitor stimulation on a RETIScan System (Roland Consult) shows reduced central responses. In addition the curve form in the central hexagon changed in a way so that N-95 could hardly be determined. Each hexagon corresponds to 9.6° of visual field. The markers in the traces represent N-35 and P-50. **e** The multifocal PERG trace of a 60-year-old normal patient is plotted for comparison.

## Discussion

*Toxicity*

While early studies assumed a binding of chloroquine to melanin to cause retinal toxicity [18, 19], it is nowadays known that melanin is not the primary mechanism of ocular toxicity [20–25]. Histopathologic investigations showed membranous cytoplasmic bodies predominantly in the ganglion cells of the retina in both man [26], monkey [27] and rodents [28], whereas the pigment epithelium showed only changes in very advanced retinopathy. In this study it is shown on a small group of patients receiving long-term chloroquine medication that both full-field PERG and central multifocal PERG responses are reduced in retinal chloroquine toxicity. Additionally, the tritan color axis is earlier affected than the protan system [37], which may support the theory that ganglion cells in the macula are the primary site of chloroquine toxicity,




which mainly generate the PERG responses [34]. However, other more distal effects such as luminance-dependent influences from photoreceptors or even pigment epithelium damage may still contribute to the decrease of the PERG responses. While the changes more altering the response at N-95 than at P-50 (fig. 1d) hint towards a ganglion cell affection, the other causes mentioned cannot be completely excluded from this limited patient series.

Regarding the underlying mechanism, lipid complex accumulation causes ganglion cells to develop complex-containing lysosomes, Müller and bipolar cells being first affected [22]. As far as is known, chloroquine forms complexes with gangliosides, inhibiting further degradation [38] and finally leading to an accumulation of lipid complexes in the neuroretina [39, 40]. Ultimately this may cause irreversible damage to rods and cones even after cessation of the drug [41, 42]. This explains why the multifocal ERG is suitable for detecting more advanced chloroquine retinopathy [43, 44]. However, changes in rods and cones occur in more advanced toxicity, thus limiting all tests on this system [37].

*Color Vision*

Defects in color vision are known to occur with antimalarial treatment that causes retinal toxic changes [45] and may precede visible fundus changes [46]. However, changes may be subtle and frequently are not detected by conventional color testing [47–52]. It is known that the earliest changes resulting from retinal toxicity occur with blue-yellow (i.e. tritan) colors, while protan defects occur in more advanced cases [53, 54]. This explains why every color test is not equally applicable. We have previously shown that the computerized, quantitative color test used in this study has a high sensitivity and specificity for chloroquine-induced maculopathy [37]. Additionally, it has the advantage that it can be performed fast and easily (less than 5 min for both eyes). When using large optotypes, there is only a trivial disturbance in color perception due to age [33].

*Visual Field Testing*

Visual field testing is frequently performed for monitoring [15] since it was first proposed by Hart et al. [3] in 1984. Definite maculopathy is defined by Easterbrook [52, 55] as reproducible bilateral field defects, while early maculopathy does not show visual field defects [56]. The use of Amsler grid for testing is inexpensive and fast and therefore is frequently recommended [2, 5, 15, 16, 57]. However, it is very dependent on the compliance of the patient and nonspecific as approximately 6% of the normal population has defects [50]. Amsler grid testing may still give hints and allow a less frequent use of automated static perimetry [16].

Although routinely many centers use static 10-2 automated perimetry, only few reports exist regarding its suitability for screening. Easterbrook [58] found 91% sensitivity and 58% specificity for a red perimetry, which is in the range of color vision tests. Interestingly, in our case

series, early visual field changes (see case report) showed an arcuate scotoma similar to that seen in glaucoma. This further supports the theory that ganglion cells are first affected, as it is known that maximal ganglion cell densities are reached in a horizontally oriented, elliptical ring 0.4–2.0 mm from the foveal center [59]. This is also the area where first changes are seen in chloroquine retinopathy, leaving the foveal center unchanged (fig. 1), although in the foveal center the highest melanin contents of the overall low melanized macula are found [60, 61]. In more advanced, later forms only the typical ring-like scotoma is found at the area of highest ganglion cell density corresponding to secondary changes of the retinal pigment epithelium. As changes of ganglion cells can be well measured by the PERG [62], it is reasonable to apply this test to detect early chloroquine retinopathy, representing a 'ganglion cellopathy' in early stages. In this study we could show in a first case series that in chloroquine retinopathy usually both full-field PERG and central multifocal PERG responses are reduced, but no changes are found in patients without retinal toxicity.

## Conclusions

The reduction of PERG and central multifocal PERG responses in chloroquine maculopathy may help with the early detection of toxicity.

## Acknowledgments

The authors thank Christel Hörmann for expert technical assistance regarding electrophysiological examination and Doris Oepke regarding visual field testing.

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