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SHORT COMMUNICATION

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Multifocal ERG in chloroquine retinopathy: regional variance of retinal dysfunction

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Abstract ● Background: A study was carried out to evaluate the regional variance of retinal dysfunction in chloroquine retinopathy.
● Methods: In three patients with different stages of chloroquine retinopathy, ophthalmologic evaluations including recording of full-field electroretinogram (ISCEV standard) and multifocal electroretinogram were performed. ● Results: In one patient with mild chloroquine retinopathy the visual acuity, visual fields and full-field electroretinogram were normal, but retinal dysfunction was indicated by color vision disturbances. The second patient had moderate chloroquine retinopathy with normal visual acuity, visual fields and dark-adapted full-field electroretinogram; light-adapted and flicker full-field electroretinogram responses were, however, borderline and color vision was abnormal. The third patient had severe chloroquine retinopathy with reduced visual acuity, visual field and color vision defects, and a reduced full-field electroretinogram. In the multifocal electroretinogram, recorded with 61 hexagons, amplitudes and implicit times were evaluated in rings surrounding the center. In all three patients severe dysfunction (either amplitudes or implicit times) was found in the parafoveal and perifoveal areas. In the fovea and towards the periphery the function was normal or only moderately reduced.
● Conclusion: Chloroquine retinopathy of different severity presents with characteristic alterations in the multifocal electroretinogram. Regional distribution of cone dysfunction is in agreement with previously reported histologic findings. The multifocal electroretinogram can detect retinal dysfunction in chloroquine retinopathy even when the full-field electroretinogram is normal and retinal alterations are subtle.

Introduction

Chloroquine has a dose-dependent toxic effect on retinal function during long-term administration [5, 6]. Early signs of functional changes can be paracentral visual field defects, color vision deficiencies or reading difficulties. Deterioration of visual acuity and more progressed visual field defects are signs of an advanced retinopathy. Reduced amplitudes in the full-field electroretinogram (ERG) may be present. The retina appears normal in the very early stages. Later, pigmentary changes develop in the macular area. In severe cases, further progression to generalized retinal degeneration may occur even after cessation of medication [3, 4]. The best screening method for chloroquine retinopathy has yet to be defined [2, 3, 5, 6]. Recently, a pathologic multifocal ERG was described [14]. This report demonstrates that chloroquine retinopathy of different severity presents with characteristic alterations in the multifocal ERG.

Table 1 Patient data

	Patient 1	Patient 2	Patient 3
Age at examination (years)	56	57	77
Duration of treatment (years)	1.2	3.4	10
Cumulative dose (g)	110	310	912
Time from end of treatment to first examination	3 weeks	None	11 years
Visual acuity (OD/OS)	20/20 / 20/25	20/20 / 20/20	20/70 / 20/200
Visual field (Goldmann)	Normal	Normal	Paracentral and mid-peripheral scotomas
Color vision (desat. Panel D15)	Medium errors, no axis	Medium errors, no axis	Multiple errors, no axis
ERG (dark adapted)	Normal	Normal	Reduced to 50%
ERG (light adapted, 30-Hz flicker)	Normal	Borderline	Reduced to 40%
Macula	Fine pigment Irregularities	Mild bull's eye Maculopathy	Severe bull's eye Maculopathy
Peripheral retina	Normal	Normal	Attenuated vessels and RPE alterations
Fluorescein angiography	Not performed	Ring-like RPE defekt	Not performed

Patients and methods

The patient data are summarized in Table 1. All patients were females who were taking chloroquine medication for rheumatoid disorders. Patients 1 and 2 were referred to our department because of difficulties with reading or color vision within 4 weeks prior to examination. Patient 3 was referred for evaluation due to progressive visual loss 11 years after cessation of chloroquine medication. In all three patients the family history was normal regarding ocular function and, apart from age, they had no known risk factors for retinal disease. All examinations were performed in conformity with the Declaration of Helsinki after informed consent had been obtained from the patients.

Full-field ERGs were recorded according to the ISCEV Standard [9] as described in detail previously [8]. Multifocal ERGs were recorded and analyzed with the VERIS Clinic II System (Tomey, Erlangen, Germany) [12]. Recording was performed with maximally dilated pupils following the full-field ERG using a Jet contact lens electrode. Refractive errors were corrected. For stimulation a black and white pattern of 61 hexagons was presented on a monitor (200 cd/m^2 for white, 99.3% contrast). Duration of data acquisition was 4 min divided into eight sessions of 30 s. The response (first-order kernel) elicited by the central hexagon (ring 1) and summated responses elicited by concentric rings of hexagons surrounding the center (rings 2–5) were evaluated (Fig. 1). Based on manually controlled cursor placement, amplitudes and implicit times were determined for the first negative and positive component of each trace. Amplitudes were expressed relative to their respective area (nV/deg^2). The normal ranges for these amplitudes and implicit times were defined by calculation of the median and the 95% confidence intervals in one eye of 15 age-similar probands. Multifocal ERG stimuli location and anatomical areas (according to Polyak [10, 15]) correspond roughly as follows: ring 1 to the fovea, ring 2 to the parafovea, ring 3 to the perifovea, ring 4 to the near periphery and ring 5 to the central part of the middle periphery.

Results

Results of clinical and functional evaluation are given in detail in Table 1. Patient 1 had an early chloroquine retinopathy. In patient 2 a more advanced retinopathy was present, and severe chloroquine retinopathy was evident in patient 3.

In the multifocal ERG, the most severe functional alterations were seen in rings 2 and 3 (Figs. 1, 2). In ring 2, amplitudes of the positive component were markedly abnormal in both eyes of the three patients. In ring 3, amplitudes were in the lower normal range in both eyes of patient 1 and the right eye of patient 2. Amplitudes were subnormal in the left eye of patient 2 and severely reduced in patient 3. In rings 1, 4 and 5, amplitudes in both eyes of patient 1 and 2 were within the normal range except for the left eye of patient 2 in ring 1. Patient 3 showed reduced amplitudes in both eyes in rings 1 and 4 and in the right eye in ring 5. The implicit times were delayed in five of six eyes for the negative component and in all eyes for the positive component in ring 2. In ring 3, implicit times were delayed in all eyes for the negative component and in four of six eyes for the positive component. In rings 1, 4 and 5, patients 1 and 2 showed normal or slightly delayed implicit times for both components in both eyes. In patient 3, the implicit times of rings 4 and 5 were delayed for both components in both eyes.

Discussion

The multifocal ERG allows the determination of local cone and bipolar cell activity at the posterior pole and thus provides a means to analyze regional variances in retinal dysfunction [7]. In chloroquine retinopathy, severe functional changes in the macular area were present in the multifocal ERG despite a normal or almost normal full-field ERG. The results of the multifocal ERG indicated a severe dysfunction of the outer retina in the parafovea and perifovea. In the fovea and towards the periphery, the outer retina was less affected. This

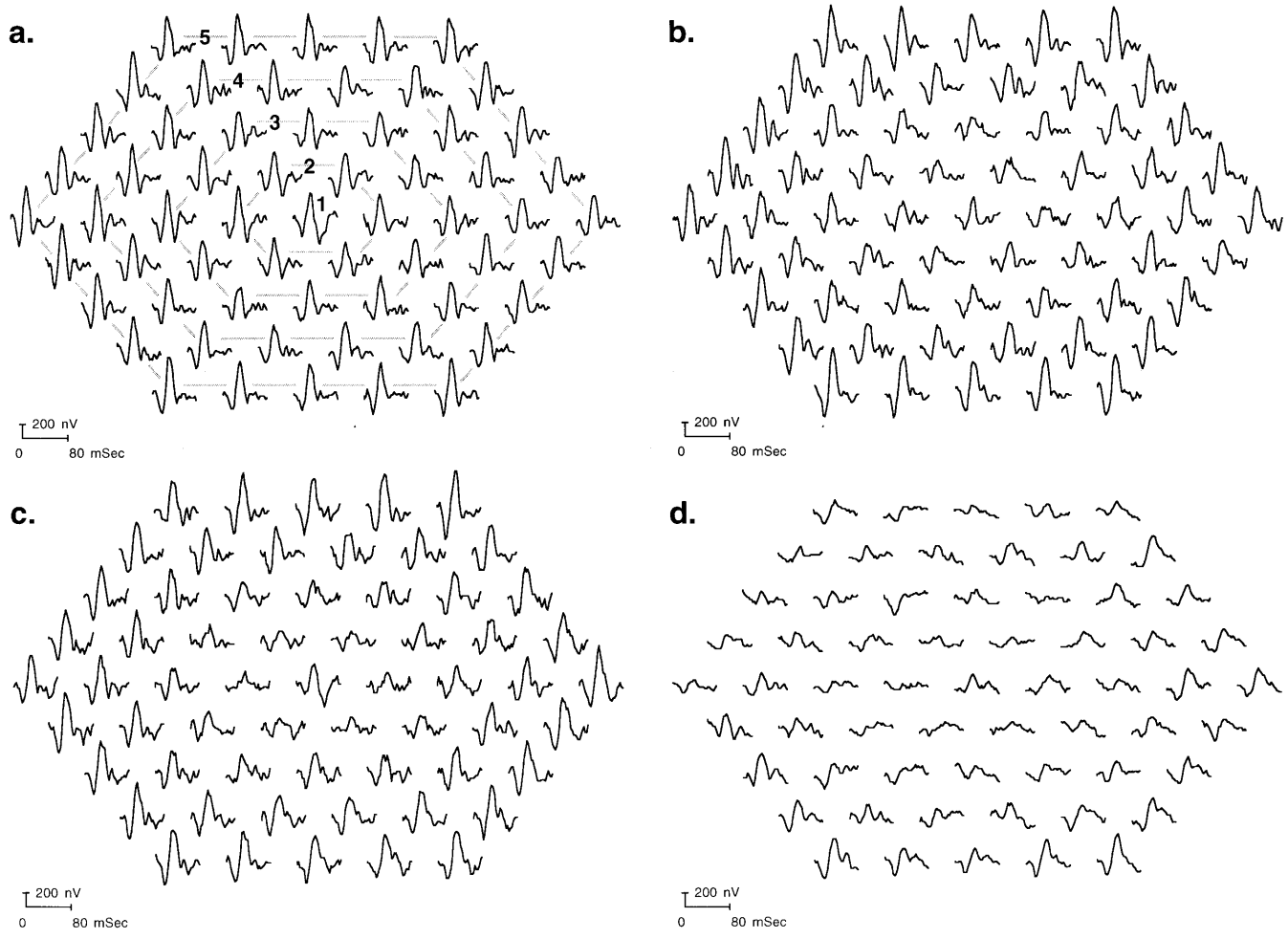

Fig. 1a–d Multifocal ERG trace array: recordings from **a** a normal subject, **b** patient 1, **c** patient 2 and **d** patient 3. In the recording from the normal subject, rings 1–5 are indicated. In all three patients the amplitudes in ring 2 and 3 are predominantly reduced

distribution of pathologic alterations was evident in early stages and remained in severe chloroquine retinopathy.

The distribution of functional loss is in accordance with previously reported histologic data. In advanced chloroquine retinopathy normal numbers of bipolar and ganglion cells but severe loss of rod and cone outer and inner segments were described [1, 11, 13]. In the fovea, however, cones remained present despite severe loss of parafoveal cones. There are no obvious reasons why the parafovea and perifovea are more susceptible to chloroquine than the fovea. Histologic data revealed that rods are earlier affected than cones [11]. One might speculate that due to the primary loss of rods, the fovea would show less dysfunction than the parafovea. Although one would also expect a similar dysfunction in the more peripheral areas of the retina, the contrary was found in this study. A certain genetic disposition of the paracentral cones to damage by chloroquine is unlikely because more severe changes in the perifovea were seen in all retinal neurons in the rhesus monkey [11].

From the present results it is impossible to determine whether amplitude reduction or implicit time delay occurs earlier in chloroquine retinopathy. The regional distribution of pathologic changes was similar for the two parameters. The delay of implicit times of both the negative and positive components of the multifocal ERG may indicate either a primary disorder of the cones or a further defect in the bipolar cells.

The multifocal ERG may be a helpful technique in cases of suspected chloroquine retinopathy with inconclusive findings. Further detailed evaluation is necessary to define whether the multifocal ERG might be superior to other screening methods such as central visual field testing or color vision [3, 5].

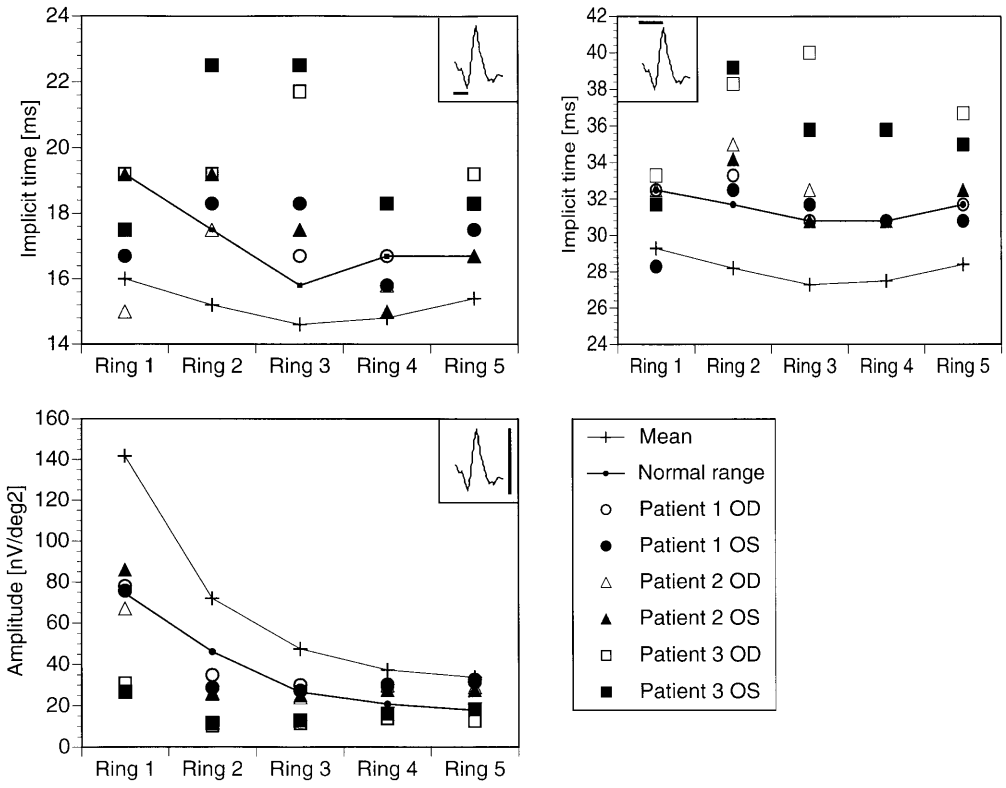

Fig. 2 Multifocal ERG: Distribution of amplitudes and implicit times for rings 1–5 in patients 1–3. *Top left* Implicit times of the negative component, *top right* implicit times of the positive component, *bottom* amplitudes of the positive component

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