Doc Ophthalmol
DOI 10.1007/s10633-015-9507-9

ORIGINAL RESEARCH ARTICLE

The value of multifocal electroretinography to predict progressive visual acuity loss in early AMD

L. Ambrosio · G. Ambrosio · G. Nicoletti · G. de Crecchio · B. Falsini

Received: 27 October 2014 / Accepted: 22 June 2015

Abstract
Background To investigate, in a prospective study, the role of multifocal electroretinography (mfERG) for predicting visual acuity decline in early age-related macular degeneration (AMD) with time.
Methods Twenty-six early AMD patients (12 males and 14 females, mean age 66.9 ± 9.8; range 46–82 years) were included in the study. A complete ophthalmic examination and mfERG (Retiscan, Roland Germany, ISCEV standard protocol) were performed at the study entry (baseline), after 20 and 24 months. The first-order kernel mfERG responses were analyzed by ring analysis. The amplitude density (AD) of the first positive peak (P1, nV/deg^2), the P1 amplitude (μV) and P1 implicit time (ms) for Rings 1 (central) to 6 (most peripheral) were evaluated. Data were statistically analyzed by analysis of variance and receiver operating characteristic (ROC) curves.
Results The loss in the mfERG Ring 1 AD from normal control values, recorded at baseline, was correlated with the decrease in ETDRS visual acuity with time ($P = 0.004$). ROC analysis showed that, after 24 months, the average decline in visual acuity was greater (3 letters vs 0.4 letters, $P = 0.0021$) in patients whose Ring 1 P1 AD at baseline was equal to or less than 65.9 nV/deg^2, compared to those with higher AD values. Both P1 amplitude and AD of Ring 1 had an area under the curve of 0.702 (95 % confidence interval 0.50–0.92) with a sensitivity of 64.3 % (35.14–87.24 %) and a specificity of 91.7 % (61.52–99.79 %).
Conclusions The present results indicate that mfERG P1 amplitude and AD of Ring 1 may be highly specific to predict visual acuity decline in early AMD.

Keywords Age-related macular degeneration · Multifocal electroretinography · Progressive retinal degeneration · Visual acuity

Introduction

Age-related macular degeneration (AMD) is a complex, multifactorial and degenerative disease characterized by progressive degeneration of photoreceptors and retinal pigment epithelium (RPE) of the macula. AMD is characterized in the early stage by large soft drusen and hyper/hypopigmentation of the RPE, and a moderate loss of central vision (age-related maculopathy, following the International Classification) [1]. In its late stages, i.e., the geographic atrophy of the RPE or the subretinal neovascular membranes, the disease is associated with more severe central visual

L. Ambrosio (✉) · G. Ambrosio · G. Nicoletti · G. de Crecchio
Department of Neuroscience, University of Naples Federico II, Via Pansini, Naples, Italy
e-mail: lucyambro@yahoo.it

B. Falsini
Department of Ophthalmology, Catholic University, Rome, Italy

Published online: 02 July 2015

impairment and can be considered a leading cause of severe, irreversible vision loss in elderly people of the developed world [2]. Changes in the RPE and photoreceptor cells are early events in AMD and may significantly impact visual function [3, 4]. There is evidence that subclinical visual losses, involving a variety of functions mediated by photoreceptors and/or post-receptoral neurons, can be detected by psychophysical and electrophysiological methods [5, 6].

Clinical diagnostic tests that could be predictive of subsequent development of visual loss have not been consistently employed in the clinical practice. However, a clinical test that shows predictive power for detection of progressive visual acuity decline in early AMD would be particularly relevant to patient management, either for clinical monitoring or for timely intervention, such as nutritional supplementation [7], in order to prevent progression to more advanced disease. Previous studies [8–10] identified psychophysical flicker sensitivity at intermediate temporal frequencies as a potential predictive test for development of visual loss and advanced AMD. However, this test has not been widely implemented in the clinic. Similarly, focal ERG [11–13] that has shown potential as a predictive test is not widely employed. In the present study, we wanted to evaluate whether the multifocal ERG (mfERG), which may be altered in early AMD [14, 15], shows a predictive value for disease progression and subsequent development of visual acuity loss.

Materials and methods

Subjects

Twenty-six patients (12 males and 14 females, mean age 66.9 ± 9.8; range 46–82 years) with a diagnosis of bilateral early AMD, accumulated prospectively over an interval of 6 months at the outpatient service of the institution, were included in the study. Written informed consent was obtained from each study participant after the aims and procedures of the study were fully explained. The research followed the tenets of the Declaration of Helsinki. The study was approved by the Ethics Committee/Institutional Review Board of University of Naples Federico II.

Each patient underwent standard general and ophthalmic examination (including detailed family history, anterior segment biomicroscopy, corrected ETDRS visual acuity, direct and indirect ophthalmoscopy, intraocular pressure measurement). Clinical diagnosis of early AMD was established by direct and indirect ophthalmoscopy, when any of the following primary lesions in the macular area (i.e., the area within an eccentricity of approximately two disk diameters from the fovea) of one or both eyes was identified: soft, distinct or indistinct drusen, areas of hypopigmentation associated with drusen, or areas of hypopigmentation of the RPE, without any visibility of choroidal vessels, associated with drusen. All patients met the following inclusion criteria: best corrected visual acuity of 0.7 or better, central fixation (assessed by direct ophthalmoscopy), normal color vision with Farnsworth D-15 testing, clear optical media, no signs of other retinal or optic nerve disease, and no concomitant ophthalmic or systemic diseases (e.g., ocular hypertension or glaucoma, diabetes, systemic hypertension). Eight patients had moderate systemic hypertension in hemodynamic equilibrium with an associated absence of retinopathy. No other systemic diseases were present. None of the subjects or patients were taking medication (e.g., chloroquine) known to affect macular function.

In all patients, clinical examinations were performed at the study entry (baseline) at 20 and 24 months. These examinations included visual acuity testing with a calibrated standard Snellen and ETDRS chart from 1-m fundus examination by direct and indirect ophthalmoscopy, with additional testing of optical coherence tomography, microperimetry and multifocal electroretinography (mfERG). Clinical and mfERG examinations were performed on the same day, with ophthalmoscopy always done after mfERG recordings.

The eye with the best visual acuity underwent the full protocol examinations ("study eye"). If both eyes had equal acuity, one eye was randomly selected.

Twenty control subjects, with an age and sex distribution comparable to that of the patients, were also tested.

Fundus grading

AMD lesions of the studied eyes were graded on stereoscopic fundus photographs of the central 30° of the posterior pole (centered of the fovea). A macular grading scale based on the International Classification

and Grading System [1] was used by a single grader who evaluated the photographs while masked as to subject characteristics and mfERG results. The presence of basic AMD lesions was noted within each of the nine subfields delimited by a scoring grid. Fluorescein angiography was also performed according to standard techniques in all study eyes at the time of the diagnosis, to confirm the presence of early AMD lesions and exclude geographic atrophy or RPE detachment. According to results of grading, all study eyes were diagnosed as having early AMD with one or more large drusen (≥63 μm) and/or focal hypo–hyperpigmentation of RPE within the macular region. The average number of drusen was 9 ± 2 (range 4–22). Focal RPE abnormalities extending for at least 10 % of one of the middle subfield areas in the macular region were present in 6 out of 26 patients.

Clinical examination was completed by optical coherence tomography and microperimetry to accurately evaluate the disease stage at baseline.

Electrophysiological methods

Multifocal electroretinography (Retiscan, Roland Germany) was performed according to ISCEV standard to evaluate retinal function [16]. The mfERG measures neuroretinal function (post-receptoral responses, cone-mediated ON and OFF bipolar cells and inner retinal cell contributions) in localized retinal areas. It is useful for documenting central retinal diseases, such as AMD.

In all subjects, the mfERG testing protocol was started after pre-adaptation period of 20 min. To the stimulus mean luminance. Pupils were pharmacologically (tropicamide 1 %) dilated to 8–9 mm. The cornea was anesthetized with 0.4 % oxybuprocaine.

The mfERGs were recorded monocularly, patching contralateral eye, by means of ERG Jet contact electrode using methylcellulose. A small gold skin ground electrode was placed at the center of the forehead after preparing the skin with abrasive gel and filling the electrode cup with electrolyte electrode gel. Meanwhile, one skin electrode was placed at outer canthus, and it was used as a reference. The contralateral eye was occluded to help suppress blinking. Interelectrode resistance was less than 3 kΩ.

Subjects fixated (from a distance of 30 cm) at the center of the stimulation field with the aid of a small fixation mark.

The multifocal stimulus, consisting of 103 scaled hexagons, was displayed on a high-resolution, black and white monitor (size 30 cm width and 30 cm height) with a frame rate of 75 Hz.

In its conventional, fast-flicker application, the mfERG derives electrical responses from a large number of small retinal areas (usually 61 or 103 areas). The array of hexagons subtends 20° of the visual field. It uses black and white hexagonal stimuli presented on a CRT monitor that follow a pseudorandom stimulation sequence. Each hexagon is independently alternated between black (1 cd/m^2) and white (200 cd/m^2) according to a binary m-sequence. This results in a contrast of 99 %. The luminance of the monitor screen is 100 cd/m^2. The luminance of the central fixation cross (used as target) is also 100 cd/m^2. Total recording time is divided into 12 segments of about 40 s each. Between segments, the subject is allowed to rest for a few seconds. Focusing lenses were used when necessary (≥3 diopters). At every mfERG examination, each patient positively should report that he/she could clearly perceive the cross-fixation target. The eye's position was monitored by a video system in the screen of the computer. The mfERG allows comparison of many local waveform responses from the central retina.

The signal was amplified (gain 100.000) and filtered (band pass 1–100 Hz). After automatic rejection of artifacts, the first-order kernel response, K1, was examined. The average responses P1 amplitude density (RAD, expressed in nV/deg^2), P1 amplitude (μV) and P1 implicit times (ms) were analyzed. These parameters were obtained from six concentric annular retinal regions (rings) centered on the fovea. Therefore, the P1 RADs derived from 0 to 2.5° (Ring 1, R1), from 2.5 to 5° (Ring 2, R2), from 5 to 10° (Ring 3, R3), from 10 to 15° (Ring 4, R4), from 15 to 20° (Ring 5, R5) and from 20 to 25° (Ring 6, R6) were analyzed and taken as the main mfERG measures.

Typically, the mfERG response measures include the peak through response density (amplitude per unit retinal area in nV/deg^2), the P1 amplitude (μV) and the implicit time (time from the onset of the stimulus to the first positive peak, P1, in ms).

Statistical analysis

For each patient included in the study, one eye, typically the eye with the best visual acuity, was

Table 1 Clinical results: baseline, 12- and 24-month follow-ups

VA	Baseline		12-month follow-up		24-month follow-up		Δ (24-month follow-up – baseline)		*P* 24-month follow-up versus baseline (Wilcoxon)
	Median (25–75 % percentiles)	Range	Median (25–75 % percentiles)	Range	Median (25–75 % percentiles)	Range	Median (25–75 % percentiles)	Range	
Decimals	0.8 (0.6–1)	0.6–1	0.8 (0.6–0.85)	0.6–1	0.8 (0.6–0.85)	0.5–1	0 (0–0)	−0.4 to 0	0.0545
ETDRS	65 (60.75–70)	60–70	64 (60–67.25)	56–70	64 (60–67.25)	55–70	−1 (−2 to 0)	−8 to 2	0.0027**
logMAR	0.10 (0.18–0.00)	0.18–0.00	0.10 (0.18–0.10)	0.18–0.00	0.10 (0.18–0.10)	0.3–0.00	0 (0–0)	0 to 0.2	0.0477*

	Baseline		12-month follow-up		24-month follow-up		Δ (24-month follow-up versus baseline)	*P* 24-month follow-up versus baseline (paired *T* test)
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	
MP[§] (dB)	−8.03 ± 4.1	−17.4 to −0.3	−7.89 ± 4.3	−17.8 to −1.8	−7.76 ± 4.2	−18.8 to −2.1	0.26 ± 2	0.512
OCT[#] (μm)	223.38 ± 27.7	170–267	222.50 ± 27.2	172–265	221.23 ± 26.8	175–266	−2.15 ± 20.5	0.569

* $P < 0.05$; ** $P < 0.005$

[§] Microperimetry (MP): dB loss from the normal value

[#] Optical coherence tomography (OCT): foveal thickness (normal range 229 ± 20.46 μm)

selected and designated as the study eye. The data from the study eyes were included in the statistical analysis. Main outcome variables were mfERG P1 amplitude density and visual acuity.

Data are expressed as mean ± standard deviation or as median and percentiles, for data having normal and non-normal distribution, respectively. Correlation analysis was performed using the Spearman's ρ test. Comparisons were performed using the paired t test or the Wilcoxon test, as indicated. A $P < 0.05$ was considered statistically significant. The data were analyzed using the software package SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

Receiver operating characteristic (ROC) curves were calculated using Sygmastat for each mfERG parameters (P1 amplitude density, AD, P1 amplitude and P1 implicit time) for Rings 1–6. The optimal cutoff for P1 amplitude and response AD was established by Youden's index. The area under the curve (AUC) was used to assess diagnostic accuracy.

Results

Clinical results (VA, OCT, MP) are summarized in Table 1 as median and percentiles or as means (±SD), respectively. The electrophysiological results (mean ± SD) for Rings 1–6 at baseline and at two follow-up time points are summarized in Table 2. There was a significant reduction in ETDRS visual acuity at the end of follow-up (after 24 months), compared to baseline ($P = 0.0027$). mfERG AD in Ring 1 also tended to decrease on average at the end of follow-up. However, this difference did not reach statistical significance.

Early AMD patients compared to normal subjects at study entry showed statistically significant differences in clinical and electrophysiological assessment. Concentric ring analysis of mfERG demonstrated a significant reduction in amplitude density in AMD patients compared to the control group. The magnitude of differences in amplitude density between the two groups was higher for the Rings 1–3 ($P < 0.001$). In early AMD subjects, the implicit times in Rings 1, 2 and 3 were slower compared to controls, even if not significantly.

The baseline mfERG, OCT and MP results were evaluated to determine whether these tests had a predictive value on the development of visual acuity

Table 2 Electrophysiological results (mean ± SD) for Rings 1–6: baseline, 12- and 24-month follow-ups

	Baseline			12-month follow-up			24-month follow-up			Normal data		
	mfERG AD P1 (nV/deg^2)	mfERG amplitude P1 (μV)	mfERG implicit time P1 (ms)	mfERG AD P1 (nV/deg^2)	mfERG amplitude P1 (μV)	mfERG implicit time P1 (ms)	mfERG AD P1 (nV/deg^2)	mfERG amplitude P1 (μV)	mfERG implicit time P1 (ms)	mfERG AD P1 (nV/deg^2)	mfERG amplitude P1 (μV)	mfERG implicit time P1 (ms)
Ring 1	86.89 ± 39.9	0.83 ± 0.39	39.41 ± 4.05	86.12 ± 46.39	0.84 ± 0.45	38.89 ± 4.98	80.47 ± 37.1	0.85 ± 0.33	40.38 ± 3.87	145 ± 28.68	1.47 ± 0.23	32.18 ± 3.42
Ring 2	56.15 ± 15.77	0.74 ± 0.211	37.26 ± 2.75	49.08 ± 15.42	0.65 ± 0.2	38.62 ± 3.4	52.89 ± 15.85	0.7 ± 0.21	37.32 ± 1.93	98 ± 8.86	1.31 ± 0.11	33.26 ± 2.75
Ring 3	41.59 ± 9.78	0.76 ± 0.18	36.04 ± 2.17	36.85 ± 11.73	0.67 ± 0.21	35.67 ± 1.65	38.19 ± 10.1	0.69 ± 0.18	35.81 ± 1.81	75 ± 5.36	1.39 ± 0.11	33.04 ± 2.17
Ring 4	31.14 ± 6.4	0.76 ± 0.16	35.08 ± 1.38	30.51 ± 9.1	0.75 ± 0.22	35.34 ± 1.1	28.64 ± 6.98	0.7 ± 0.17	35.45 ± 1.45	56 ± 5.31	1.41 ± 0.15	34.08 ± 1.38
Ring 5	25.73 ± 6.17	0.81 ± 0.19	34.88 ± 1.29	14.37 ± 14.34	0.81 ± 0.26	35.68 ± 2	23.86 ± 6.08	0.75 ± 0.19	35.08 ± 1.13	45 ± 4.12	1.45 ± 0.13	34.05 ± 1.29
Ring 6	20.84 ± 5.6	0.87 ± 0.23	34.89 ± 1.35	11.52 ± 11.62	0.86 ± 0.29	35.12 ± 1.42	19.65 ± 5.1	0.82 ± 0.21	35.34 ± 1.8	36 ± 2.82	1.52 ± 0.12	34.67 ± 1.35

loss at the end of follow-up. Neither OCT nor MP showed a significant predictive value ($P = 0.693$; $P = 0.107$), whereas baseline mfERG amplitude and mfERG response density tended to be associated with subsequent changes in visual acuity ($P = 0.004$). Figure 1 AB shows a representative example of this association. In A, the OCT images and the baseline mfERG response density plots, as well as the ring averaged responses, are reported for a patient with mildly or severely reduced central response amplitudes, respectively. The first patient (patient A) showed normal foveal thickness (214 µm) with a very small RPE interdigitation in the foveola area. The mfERG AD in Ring 1 was 92 nV/deg^2, and the P1 amplitude in Ring 1 was 0.9 µV. Patient B showed a normal foveal thickness as well (208 µm), but mild changes in the inner segment ellipsoid (ISe) band correlated with a smaller mfERG amplitude (AD P1 Ring1 57.1 nV/deg^2; amplitude P1 Ring 1 0.56 µV). Patient B showed a VA decrease over time. In Fig. 1b, visual acuities of both patients are plotted as a function of time. It can be seen that, while the acuity of the

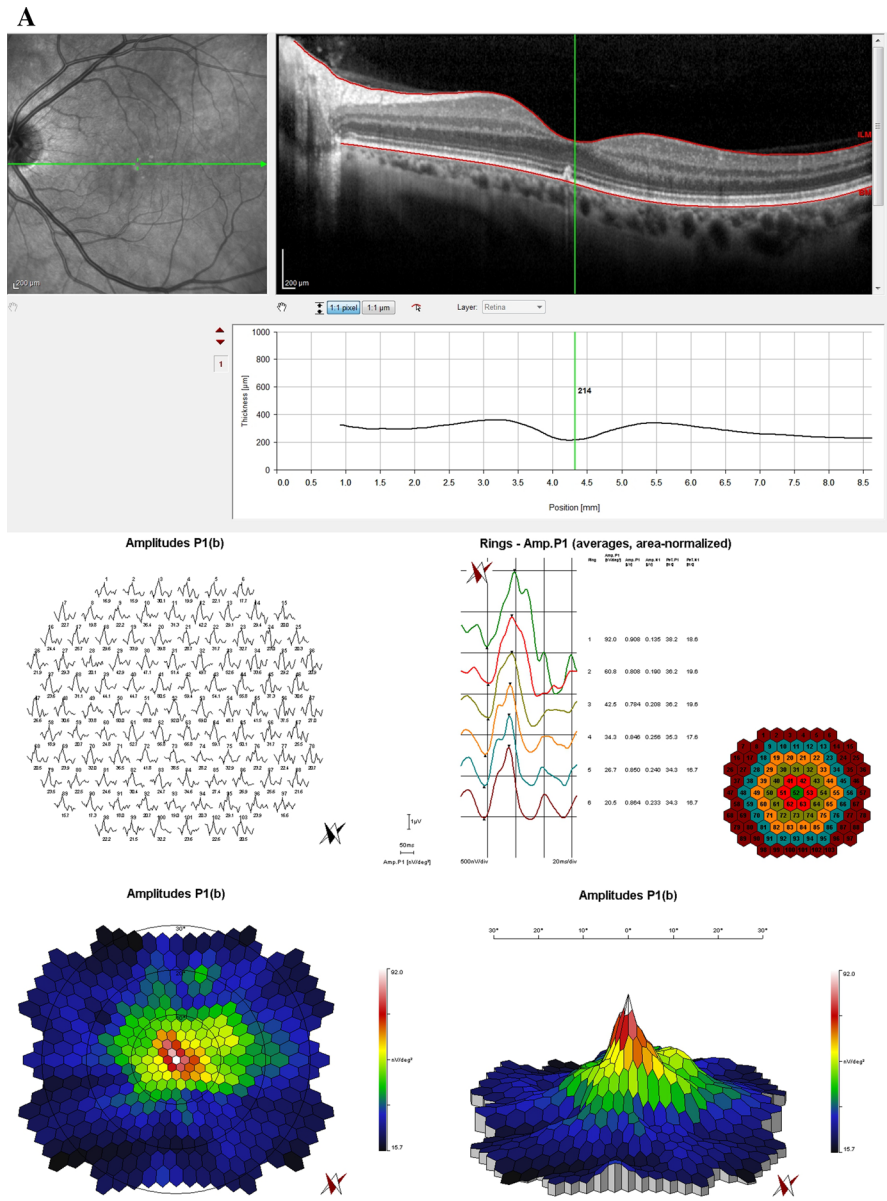
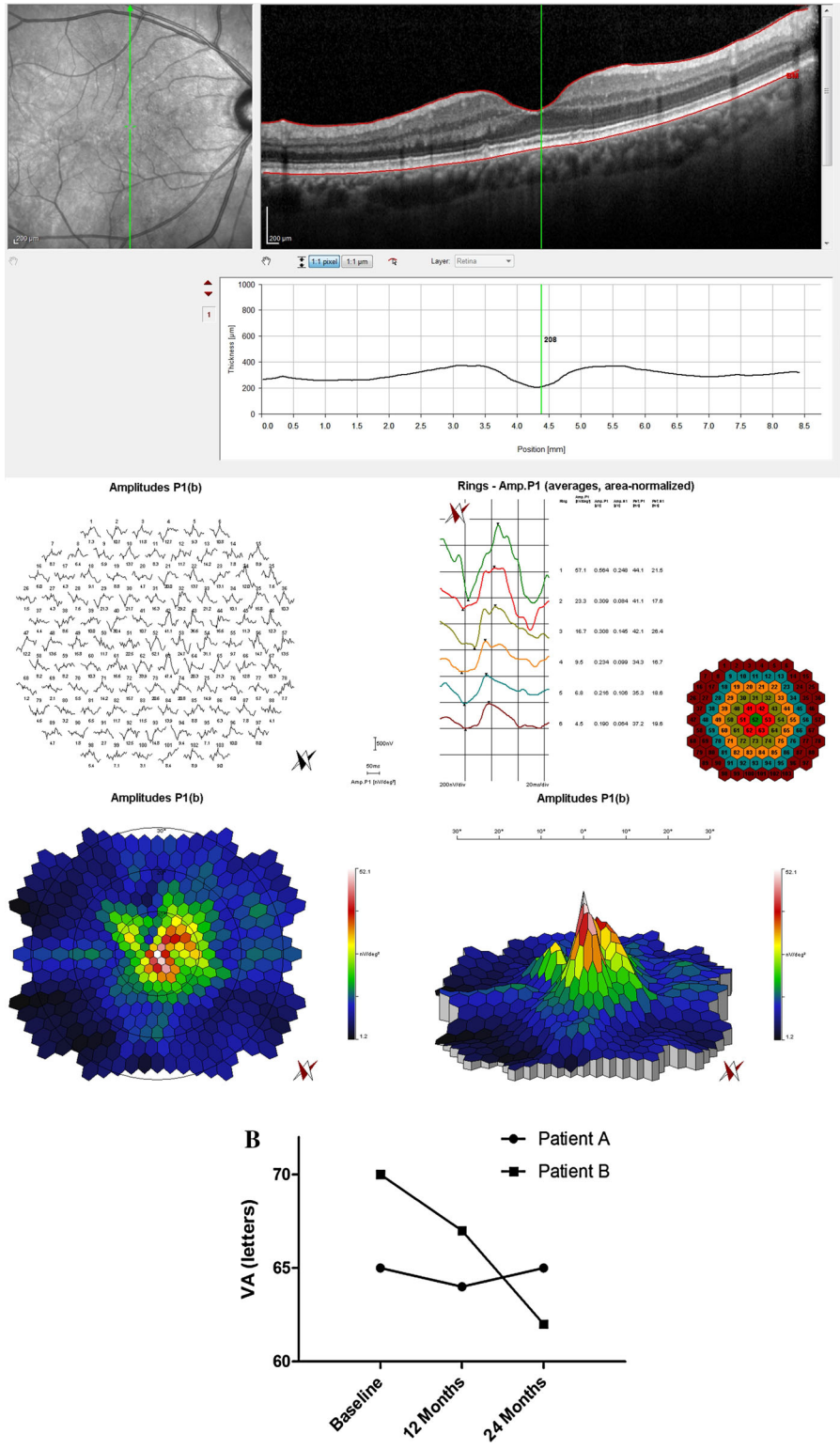


Fig. 1 **a** OCT images and mfERG baseline responses (ring analysis) recorded from an early AMD patient with mildly abnormal mfERG (*patient A* AD P1 Ring 1 92 nV/deg^2; amplitude P1 Ring 1 0.9 µV) and from a patient showing a more severely abnormal mfERG (*patient B* AD P1 Ring 1 57.1 nV/deg^2; amplitude P1 Ring 1 0.56 µV). **b** The *letter* acuities of both patients are plotted as a function of follow-up time

Fig. 1 continued



patient with mild central response amplitude reduction at baseline remained stable over the follow-up period, the acuity of the patient with more severely reduced amplitude showed a progressive decline over the follow-up.

Figure 2a, b shows the changes in visual acuity recorded at the end of follow-up, minus the values recorded at baseline, plotted as a function of baseline central mfERG P1 amplitudes of Ring 1. In Fig. 2b, the same changes are plotted as a function of baseline central mfERG P1 amplitude densities of Ring 1. It can be seen that changes in visual acuity were positively correlated with mfERG amplitudes recorded at baseline, indicating that the worser the amplitude at baseline, the greater the likelihood of visual acuity reduction at the end of follow-up.

The optimal cutoff for central mfERG amplitude density to predict visual acuity deterioration was determined as 65.9 nV/deg^2 (Youden's Index = -Sens−Spec−1). This cutoff provided a sensitivity of 64.3 % (35.14–87.24 %) and a specificity of 91.7 % (61.52–99.79 %). Figure 3 depicts the ROC curves that were calculated for baseline central mfERG P1 amplitude, response AD and P1 implicit time. The best discrimination and predictive values for detecting visual acuity deterioration at the end of clinical follow-up were provided by central response amplitude and by central response AD, with an identical AUC of 0.702 (95 % confidence interval for response amplitude: 0.503–0.918; for response AD: 0.502–0.917).

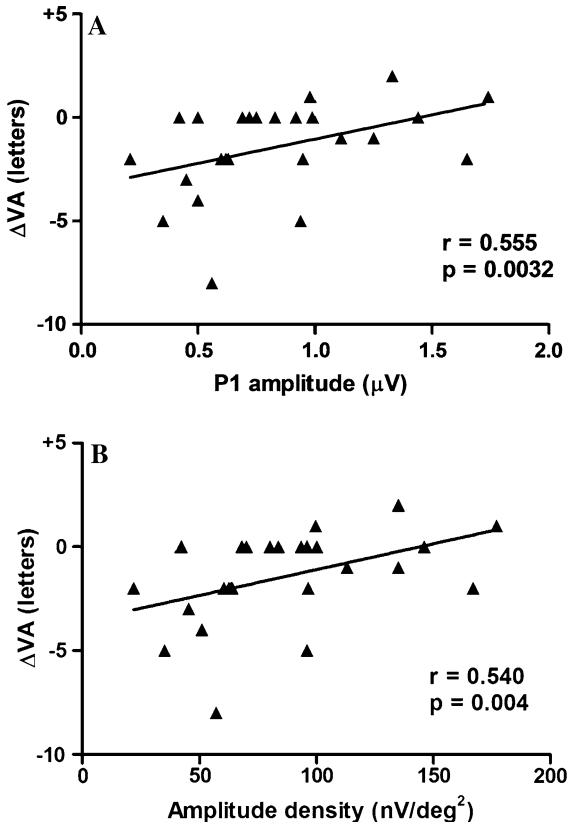


Fig. 2 **a** Changes in visual acuity seen at the end of follow-up compared to baseline, *plotted* as a function of baseline central mfERG P1 amplitudes of Ring 1. **b** The same changes are shown as a function of baseline central mfERG P1 amplitude densities of Ring 1

In Fig. 4a, b, the individual values of visual acuity (A) recorded at baseline and at two follow-up time points are plotted for patients with central mfERG P1 amplitude above or below the optimal cutoff established by ROC analysis. In Fig. 4b, box plots of changes in visual acuity observed in patients with mfERG amplitudes below or above the optimal cutoff are compared. It can be noted in Fig. 4a that visual acuity (no. of letters seen) tended to decrease in most patients whose amplitude was below the cutoff value, but it remained stable in patients with amplitudes above the cutoff. In Fig. 4b, it is shown that there was a significant difference in visual acuity changes between patients with mfERG amplitudes above or below the cutoff value, indicating that a worse baseline amplitude was more likely associated with a deterioration of visual acuity, compared to a better baseline amplitude. Such a difference was specific for the central responses and was not found for the responses derived from the other rings. In addition, implicit time of the P1 component was not correlated with the corresponding changes in visual acuity at the end of follow-up.

Discussion

AMD is an important cause of irreversible central vision loss in subjects aged over 55 years [17]. In AMD eyes, excessive accumulation of under gradable products of photoreceptors metabolism as a result of cell damage was demonstrated. These ultrastructural changes of photoreceptors are related to impairment of macular photoreceptor functions [18]. It has been suggested that the measurement of retinal function using mfERG would be useful in the assessment in

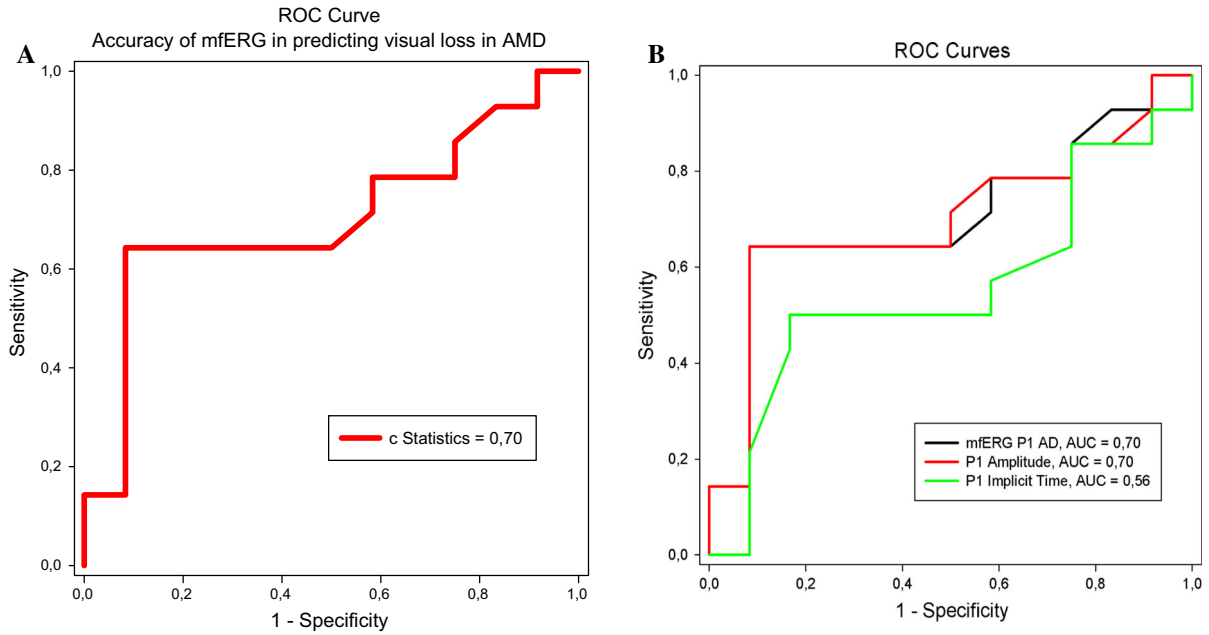


Fig. 3 Receiver operating characteristic (ROC) curves evaluating diagnostic accuracy for central P1 mfERG amplitudes, response densities and implicit time, for predicting progressive loss of visual acuity at the end of follow-up. *Optimal cutoff* (Youden's Index = Sens−Spec−1) for mfERG < 65.9 nV/deg^2: sensitivity = 64.3 %; specificity = 91.7 %

early stages of AMD [19]. It is known that the mfERG amplitude is largest in the fovea, where cone photoreceptors and bipolar cells are densest [16]. Moreover, the best corrected visual acuity is more highly correlated with foveal integrity. The present prospective study was conducted in order to determine whether functional testing of early AMD could predict visual acuity deterioration in patients who were observed for a period of 24 months. Although our baseline results did not show a significant correlation between mfERG (amplitude and/or response density) and visual acuity, they showed that central mfERG amplitude demonstrated a clinical value in predicting visual loss over time, with a high specificity. Along with previous studies [20–23], our results have shown that the mfERG amplitude was decreased in all rings in early AMD subjects, even if it was lower in the foveal area. Li et al. [24] noted a significant reduction in the P1 amplitude, as well as a significant delay in the N1 latency of foveal responses from early AMD eyes. Other evidence showed that the P1 implicit time was not significantly affected in early AMD (Table 3). Takiura et al. [25] showed that the amplitude decrease represented photoreceptor loss, whereas the delay in implicit time reflected disorders in the inner retina. These results suggest that the photoreceptors are affected at early stages of AMD, whereas the inner retina is likely to be affected at later stages of AMD [25]. Fiegl et al. [26] compared two different mfERG protocols (conventional fast-flicker mfERG and global-flash mfERG) in early AMD. They suggested that the global-flash mfERG detects reduced adaptation responses earlier than the conventional mfERG. They supported the finding that the damage in early AMD, which is responsible for complex adaptation responses as evoked by the global-flash mfERG, targets the postreceptoral site first.

Previous studies [8–10] demonstrated that the psychophysical flicker sensitivity recorded at intermediate temporal frequencies may predict severe subsequent visual loss in AMD patients. However, the characteristics of the study cohort differ from those of the group tested in the current study, since most patients had more severe funduscopic abnormalities at baseline compared to our patients.

Although mfERG amplitude and visual acuity can be correlated in AMD, it has been shown in previous studies that macular electrophysiology as assessed by fERG [11] may detect macular/foveal dysfunction before the onset of visual acuity loss.

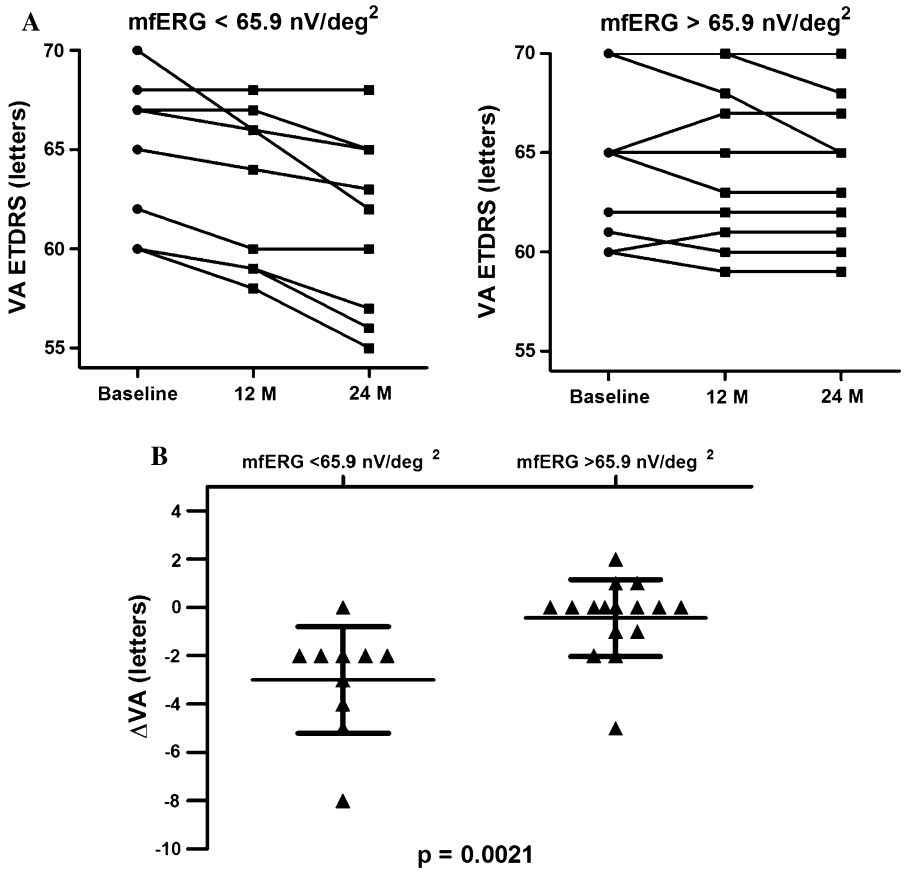


Fig. 4 **a** Visual acuities of individual patients with central mfERG amplitudes above or below the optimal cutoff, recorded at baseline, and after 12- and 24-month follow-ups. **b** *Box plots* of changes in visual acuity observed in patients with mfERG amplitudes below or above the optimal cutoff

Table 3 Results of recent studies on early AMD which showed clinical characteristics comparable with our subjects

	P1 amplitude	P1 implicit time
Yavas et al. [23] Ring 1	*	°
Ma et al. [21] Rings 1–3	*	°
Gin et al. [19] Ring 1	*	*
Parisi et al. [14] Ring 1, 2	*	°

* Affected, ° Not affected

Our findings confirm these previous observations. The potentially different sensitivity of mfERG and visual acuity can be ascribed to the different nature of the two measurements: mfERG is a more direct assessment of macular function, while acuity, as other psychophysical measures, reflects the response contribution of both retinal and post-retinal pathways. The mfERG [14, 15, 19] and the fERG [11, 27] have shown high sensitivity, but relatively low specificity, in detecting central retinal dysfunction in patients with early AMD. This study shows that mfERG may be highly specific in predicting visual loss over time.

Large clinical trials evaluating the progression of early AMD and the protective effect of antioxidant supplementation have focused mainly on disease progression. In this context, the use of an outcome measure, obtained from mfERG, and able to predict subsequent functional deterioration, would be of potential value for the design of future clinical trials in which supplementation would be administered to patients according to different risk levels. Future studies should be able to address this point by using a larger population and a longer follow-up compared to those employed in the current pilot study.

Compliance with Ethical Standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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