Electrophysiological study of age-related macular degeneration

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Purpose
To evaluate the effects of age-related macular degeneration (ARMD) on electrophysiological tests and to correlate between electroretinogram (ERG) and optical coherence tomography.
Patients and methods
Fifty control participants (100 eyes) and 100 patients (100 eyes) with ARMD were examined clinically. ERG, multifocal electroretinogram (MFERG), standard ERG, fluorescein angiography, and optical coherence tomography were performed.
Results
ERG responses were decreased in all types of ARMD, especially in geographic atrophy. The amplitudes of scotopic ERG were slightly decreased, without a change in implicit times. The amplitudes of oscillatory potential were significantly decreased and photopic responses were also decreased in geographic atrophy, choroidal neovascularization, and pigment epithelium detachment. MFERG shows abnormalities not only in the central ring but also in all rings (central, paracentral, and peripheral). There were negative correlations between central macular thickness and the amplitude of MFERG of the central ring and a positive correlation between central macular thickness and latency of MFERG of the central ring in choroidal neovascularizations and pigment epithelium detachment.
Conclusion
Electrophysiological responses indicated a general reduction in retinal function in all parts of the retina (not only in the macula but in every part of the retina) in ARMD.

Keywords:
AMD, electrophysiology, macula

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Introduction

Age-related macular degeneration (ARMD) develops with age, particularly in individuals older than 65 years of age. However, it can develop in individuals in their 40s and 50s. ARMD is more common in women than men, possibly because women live longer than men. Smoking and ultraviolet sunlight increase the risk of ARMD. In elderly, ARMD is the leading cause of legal blindness in western nations [1,2].

There are two main types of ARMD: wet and dry ARMD. The dry type is marked by the occurrence of a well-defined progressive lesion or atrophy in the macula. The wet type is characterized by the occurrence of abnormal choroidal neovascularization (CNV) under the retina and macula, causing bleeding and leaking of fluid. This leads to bulging and lifting of the macula and distortion of central vision [3,4].

The exact causes of ARMD are still unknown. Electrophysiological tests are used to describe the site of retinal dysfunction [5,6].

Full-field electroretinogram (ERG) and electrooculogram (EOG) measures are summed responses from different cells of larger areas of the retina, whereas multifocal electroretinogram (MFERG) is a map function with high resolution within the central 30°. It can measure local cone-mediated and rod-mediated functional impairment at early and late stages of ARMD [7].

EOG is superior to ERG in the fact that its electrodes do not need to come in direct contact with the eye [8].

The aims of the study are to investigate the electrodiagnostic, tomographic, and angiographic findings in ARMD and to correlate visual acuity, central macular thickness (CMT), and MFERG.

Patients and methods

This study was carried out on patients attending the OutPatient Clinic of Mansoura Ophthalmic Center during the period from May 2013 to February 2014. The study included 200 eyes of 150 patients (100 eyes

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of 100 patients with ARMD and 100 eyes of 50 control participants).

All procedures were carried out in accordance with the tenets of the Declaration of Helsinki (1989) of the World Medical Association. The study was approved by the Ethics Committee of the Mansoura University Hospital trust. Each patient signed a written consent statement before participating in the study.

ARMD was diagnosed when the following criteria were fulfilled: age older than 55 years, visual acuity up to 0.5, and fundus examination with a picture of drusen, geographic atrophy (GA), CNV, and pigment epithelium detachment (PED).

Patients who had ocular diseases such as myopia more than 3 D and diabetes, which may influence the ERG, EOG, and optical coherence tomography (OCT), were excluded from the study.

All participants underwent a complete ophthalmologic examination including visual acuity [BCVA; logarithm of the minimum angle of resolution (log MAR)], automated autorefractometry (using Topcon autorefractor), ocular tension tonometry using a Goldman Tonometer, and slit-lamp examination. Indirect and direct posterior segment examinations were performed using a 90 D lens and a Goldmann 3-mirror lens. Fluorescein angiography was performed using (2000, TRC, 50IX; Topcon Corporation, Tokyo, Japan). OCT, EOG, and ERG were performed.

Optical coherence tomography

OCT was performed by (3 dimensional OCT-1000; Topcon, USA). OCT measurements were performed using a fiber optical Michelson interferometer with a short coherence length super-luminescent diode source.

OCT was performed with a 512×128 scan pattern. Macular area was automatically measured with 1 mm radius around the fovea.

Electrophysiological tests

An EOG and an ERG (full field ERG and MFERG) were recorded using the Roland Consult, Brandenburg, and Germany system.

During electrophysiological tests, monitoring of the fixation is allowed through fundus viewing. Electrophysiological tests were performed in accordance with the International Society for Clinical Electrophysiology of Vision.

Pupils were fully dilated (≥7 mm). After administration of a topical corneal anesthesia (benoxinate hydrochloride 4%), a Dawson, Trick, and Litzkow electrode (positive electrode) was placed in contact with the corneal limbus, a ground electrode was installed on the forehead, and a negative electrode was applied near the orbital rim temporarily. Before placing the electrodes, the skin was cleaned with cleaning rub cream. The electrodes should be installed under dim red light and after dark adaptation for 20 min. The recording was monocular and the contra-lateral eye was occluded with light pressure to suppress blinking.

Full-field electroretinogram

The patient was placed in a comfortable position, with the head in front of the stimulator and the eyes fixated on a red light point in the Ganzfeld globe; then, the test was started and recorded in five steps: scotopic rod response, scotopic combined response, oscillatory potential, light adaptation for 10 min, and photopic cone response and flicker response recording.

Multifocal electroretinogram

Participants were positioned 30 cm from the stimulus monitor. The stimulus was presented on a 32×22 cm monitor driven at a 75 Hz frame rate and included an array of 61 hexagonal elements across a field (44° horizontally×40° vertically). The luminance of white hexagons was 185–200 cd/m^2 and that of dark hexagons was 1–2 cd/m^2, resulting in local contrasts of 98–99%. Each hexagon was modulated between light and dark according to a binary m-sequence. At any time, ~50% of the stimulus elements displayed were white and 50% were black. The patients fixated at a spot in the center of the stimulus during 8-min recording sessions. Each session was continued for 30 s, followed by brief rest periods to improve fixation stability. Signals were amplified (gain, 10^6) and band pass filtered (10–300 Hz). Two recordings were obtained from each eye. Recording segments with two amplifier artifacts were discarded.

The results of two recordings were averaged to improve the signal to noise ratio. Amplitude was measured as the voltage difference between first trough and the first peak of a scaled template wave.

Implicit time was calculated to the first prominent response peak of the wave. The P component of the first order kernel of the MFERG was analyzed using software. These arrays were divided into five-concentric rings centered on the fovea.

Electrooculogram

The test participants had to be in normal indoor lighting for 60 min before the test without exposure to any strong light.

After dark adaptation for 15 min and pupil dilation, the electrodes were placed close to canthi of each eye. Each eye required two electrodes after cleaning the skin with alcohol. The ground electrodes were placed on the forehead.

The patients placed their chin on a Ganzfeld stimulator and moved their eyes with fixation light (which consists of two red fixation lights 15° left and right of a central light). The fixation lights had to be as dim as possible in the dark. After the dark phase, stable white light was switched on. A period of 15 min is required for light adaptation before the light phase is started. The luminance of light should be calibrated regularly. When the light-adapting background is on, the fixation lights should be bright.

Before recording the participant was taught how to fixate on the two alternate fixation lights with stable pacing. Both in the dark phase and in the light phase, when the lights change, eyes move in single sweep to next one every 1-s for 10 times in 1 min, the left time for rest.

In each saccade, there may be an overshoot (which appears when eyes exceed the fixation lights and then go back to a stable position). The amplitude of saccades is measured automatically. The light peak amplitudes (from light peak to baseline). The dark trough amplitudes (from dark peak to baseline) and Arden ratio (ratio of amplitude of light peak to amplitude of baseline).

Statistical analysis

Electrooculogram

The dark trough, light peak, and Arden ratio values were determined from each recording.

Full field electroretinogram

Amplitudes and implicit times of the rods and cones responses were determined. Also, the amplitude of the oscillatory potential component and the mean peak-to-peak amplitude of flicker ERG were measured.

Multifocal electroretinogram

The amplitude and implicit time of the P wave over the rings were determined.

Optical coherence tomography

CMT was determined.

Data from ARMD patients and normal controls were analyzed using statistical package for the social sciences (SPSS; IBM Corporation, New York, USA). Qualitative data were presented as number. The χ^2-test of significance was used for comparison. Quantitative data were represented as mean±SD. Kruskal–Wallis, Mann–Whitney, and Kolmogorov–Smirnov tests were used for comparison. Spearman's correlation coefficient was used to calculate the correlation between CMT and ERG values.

Differences were considered statistically significant when P value of less than 0.05.

Results

Fifty normal individuals (100 eyes) and 100 patients (100 eyes) with ARMD were included in the study. The mean age of the control group and was 55±12.5 years and that of the ARMD group was 54±14.9 years.

Visual acuity

The mean best-corrected visual acuity in ARMD was 0.49±0.5 and that in the control group was 0.98±0.22.

Fluorescein angiography

Drusen was found in 30 eyes, geographic atrophy (GA) was found in 30 eyes, PED was found in 10 eyes, and CNV was found in 30 eyes (15 eyes had well-defined CNVs and 15 eyes had occult CNVs).

Electrophysiology

Electrooculogram

The value of the EOG dark trough was 510±30 μv in the control group versus in 227.5±30 μv in the ARMD group, light peak was 450±59 μv in the ARMD group versus 998±50 μv in the control group, and the Arden ratio was 1.5±0.4 μv in the ARMD group versus 2.5± 0.59 μv in the control group. The values were significantly lower in the ARMD group than in the control group (Table 1 and Fig. 1).

In drusen, light peak values were normal (Fig. 2), but the values in eyes with geographic atrophy were subnormal. Thus, in drusen light rise was greater than in geographic atrophy.

The lowest values of dark trough were found in geographic atrophy, whereas the highest values were found in PED.

In drusen, the elevation of light rise in eyes was significantly greater than in other groups (Table 1).

Full field electroretinogram

In drusen, light peak values were normal (Fig. 2), but the values in eyes with geographic atrophy weresubnormald.

The a-wave of the combined flashed response in ARMD was not significantly different. However, the amplitudes of the scotopic b-wave and the b-wave of the combined responses were significantly reduced in GA, CNVs, and PED, whereas the implicit times of the b-waves were within normal. Also, the amplitudes of the oscillatory potentials were decreased in ARMD (GA, CNVs, PED). The amplitudes of photopic a-wave and b-waves were significantly lower in the ARMD group (GA, CNVs, PED), whereas the implicit time of the a-wave was significantly prolonged and the implicit time of the b-wave was normal. The amplitude of the flicker ERG was also reduced (Table 2).

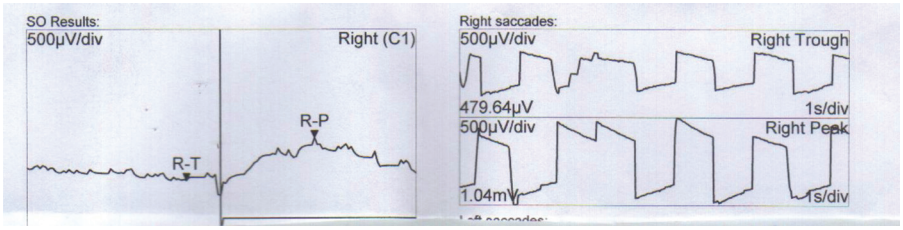
Multifocal electroretinogram

The MFERG recordings showed a marked reduction in the site of GA, CNVs, and PED (as shown by fundus photography and fluorescein angiography) and a slight reduction in the surrounding rings. The trace array and response density maps were subnormal, especially in the site of the lesion and within the lower normal level in drusen (Table 3 and Fig 3).

Optical coherence tomography

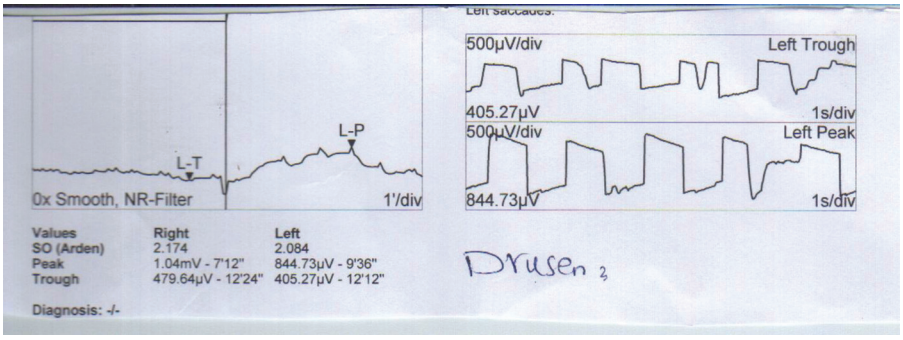
The mean CMT in drusen showed almost normal values (CMT=180±14), whereas CMT were 335±90

Figure 1



EOG among groups. (left) EOG in a normal control participant with normal dark trough and light peak. (top right) EOG in drusen with low normal dark trough and light peak. (bottom right) EOG in geographic atrophy with a marked reduction in dark trough and mild reduction in the light peak. EOG, electrooculogram.

Figure 2



A case of drusen with normal ERG and EOG.

Table 1 Electrooculogram changes among groups

Groups	Light peak (µv)	Dark trough (µv)	Arden ratio
Control	998±50	510±30	2.5±0.59
ARMD			
Drusen	750±45	400±40	2.4±0.4
Geographic atrophy	150±60	50±20	2.9±0.9
CNVs	405±30	210±42	1.5±0.3
PED	480±30	450±44	0.9±0.4
P	0.001	0.005	0.008

ARMD, age-related macular degeneration; CNV, choroidal neovascularization; PED, pigment epithelium detachment.

Table 2 Full-field electroretinogram changes among groups

ERG parameters	Control	Drusen	Geographic atrophy	CNVs	PED
Scotopic					
b-wave					
Amplitude (0.001)	85±13 nv	72±10 nv	40±5.5	38.8±7.6	39±8.5
Implicit time (*P*=0.1)	60±10	65±6.6	75±9.9	92±9.1	90±8.3
Combined					
a-wave					
Amplitude (*P*=0.22)	110±9.9	100±5.2	90±12.1	88±10.9	85±9.8
Implicit time (*P*=0.4)	20±4.9	21±4.6	22±3.8	23±3.3	23±4.1
b-wave					
Amplitude (*P*=0.005)	230±30 nv	200±20	120±20.3	120±15.5	122±17.6
Implicit time (*P*=0.31)	40±8	36±6.3	46±12.1	44±5.6	45±6.1
Oscillatory potential (*P*=0.007)					
Implicit time	23±2 ms	25±3 ms	15±3.8	14±4.2	14.4±3.9
Amplitude	27±3 nv	24±2 nv	30±4.6	32±5.4	33±5.2
Photopic					
a-wave (0.0009)					
Amplitude	45±5.8	43±5 nv	25±6.8	21.2±5.8	22±6.1
Implicit time	15±3.3	16±4.1	30±5.7	31.4±4.9	32±5.1
b-wave					
Amplitude (*P*=0.001)	50±9 nv	49±5.4	26±7.7	25.2±8.9	24±7.7
Implicit time (*P*=0.8)	30±5.3	33±3.1	35±4.9	39±5.1	38±4.6
30 Hz flicker					
Implicit time	50±5 ms	51±4.7 ms	60±3.4	70±5.3	69.8±4.9
Amplitude	55±6 nv	50±10 nv	40±9.8	30±8.9	29±8.5

CNV, choroidal neovascularization; ERG, electroretinogram; PED, pigment epithelium detachment.

Table 3 Multifocal electroretinogram amplitudes and latencies over rings

Groups	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5
Amplitude					
Control (*P*=0.002)	65±10	53±6	44±7	35±5	30±4.00
ARMD (*P*=0.001)					
Drusen	64±9.00	54±6.00	42±8.00	33±5.00	30±5.00
Geographic atrophy	33±5.00	31±3.00	30±2.00	22±4.00	20±3.00
PED	30±6.00	19±5.00	18±4.00	17±3.00	16±5.00
CNVs	25±5.0	15±7.0	16±6.0	11±5.00	10±6.00
Latencies					
Control (*P*=0.001)	35±0.9	36±1	37±0.5	40±0.9	40±0.8
ARMD (*P*=0.000)					
Drusen	36±0.7	35±1	37±0.9	39±0.8	40±1
Geographic atrophy	50±3	49±1	52±1.0	55±1.2	55±1.0
PED	52±4	53±2	54±2.1	54±1	54±1.0
CNVs	55±3	52±2	53±1.5	56±3	56±2

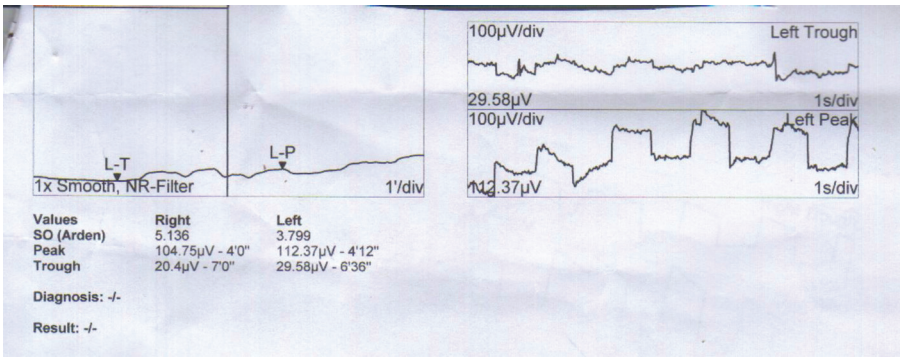
ARMD, age-related macular degeneration; CNV, choroidal neovascularization; PED, pigment epithelium detachment.

in CNVs and 301±100 in PED. There were negative correlations between CMT and the amplitude of MFERG of the central ring and a positive correlation between CMT and the latency of MFERG of the central ring in CNVs and PED. The increase in CMT is accompanied by an increase in implicit times and a decrease in the amplitude of MFERG. There were correlations between the amplitudes of MFERG and the sizes of GA, CNVs, and PED (*P*=0.002, *R*=0.55). There were no significant correlation between CMT and MFERG in drusen (*P*=0.5). There were significant correlations between the size of the lesion and amplitudes over the affected area (Tables 4 and 5).

Discussion

Electrophysiological tests showed complicated interactions between choroids, RPE, and receptor layer on the one hand and on the postsynaptic layers on the other [9].

Figure 3



MFERG in ARMD. (a) MFERG in normal with normal peak and trough. (b) MFERG in drusen with low normal peak and trough. (c) MFERG in geographic atrophy with an irregular curve in the first center that affected the ring, and subnormal peak and trough in the surrounding unaffected rings. ARMD, age-related macular degeneration; MFERG, multifocal electroretinogram.

Table 4 Central macular thickness among groups

Groups	CMT
Control (*P*=0.001)	170±9
ARMD (*P*=0.000)	
Drusen	180±14
Geographic atrophy	250±50
PED	301±100
CNVs	335±90

ARMD, age-related macular degeneration; CMT, central macular thickness; CNV, choroidal neovascularization; PED, pigment epithelium detachment.

Table 5 Correlation between central macular thickness and visual acuity and multifocal electroretinogram

Groups	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5
Amplitude					
CMT					
P	0.000	0.001	0.001	0.009	0.00
R	–0.55	–0.5	–0.5	–0.4	–0.4
Implicit time					
P	0.001	0.002	0.005	0.05	0.06
R	0.5	0.5	0.51	0.4	0.4
Amplitude					
Visual acuity					
P	0.000	0.001	0.002	0.005	0.003
R	0.65	0.55	0.52	–0.42	–0.42
Implicit time					
P	0.01	0.02	0.08	0.05	0.06
R	–0.45	–0.445	–0.451	–0.44	–0.34

CMT, central macular thickness.

Full-field ERG is a general response from the retina, whereas MFERG yields a series of localized waves from a single recording and enables the assessment of spatial information across the macula [10].

EOG provides additional information on the function of retinal pigment epithelium. The disadvantage is the high interindividual and intraindividual variability in the results [11].

In this study, normal EOG (normal light rise values, dark trough values, and Arden ratio), normal full-field ERG, and normal MFERG in drusen were found, but values were considered the lower limit of normal in drusen. These results of ERG suggest that the retinal pigment epithelial electrophysiologic function is well maintained in drusen despite the widespread physical abnormalities of the retina pigment epithelium.

Also, in this study, in drusen, implicit times were shorter than other subgroups. The reason for this is that the features of photoreceptors in drusen were slightly different from other types of ARMD. In drusen, phototransduction may yield faster ion exchange, initiating faster synaptic transmission to bipolar cells.

Similarly, Gupta and Marmar [12] found that there were no significant differences between the normal participants and patients with drusen.

Also, Fishman *et al.* [13] and Rover and Bach [14] reported that EOG was close to normal. Normal EOG was presented in all cases of drusen, which means that the disease did not affect the retinal pigment epithelium [13,14].

In contrast, Walter *et al.* [15] found that dark trough was reduced in eyes with drusen.

In this study, in geographic atrophy, there were reductions in full-field ERG and MFERG parameters. The lowest dark trough was found in these cases.

Similarly, Walter *et al.* [15] and Friedman [16] reported that there was a decrease in the values of full-field ERG and EOG in cases of geographic atrophy.

In contrast, Marcus *et al.* [17] found a reduction in light rise in only one of 12 patients with ARMD.

In this study, reductions in EOG, full-field ERG, and MFERG values were found. The reduction in MFERG was found not only in the ring of the site of the lesion but also in the surrounding rings in cases of PED.

The cause of global retinal dysfunction in ARMD may be vascular [18–20].

The same as Walter *et al.* [15] found a reduction in EOG and full-field ERG in PED.

In this study, in cases of CNVs, there were reductions in all values of EOG, full-field ERG, and MFERG. In MFERG, there were marked reductions in amplitude and prolongation in implicit times in the affected ring and a mild reduction in the surrounding rings.

Also, Schouten *et al.* [21], Matuci *et al.* [22], Oh *et al.* [23], and Park *et al.* [24] observed reductions in response densities to less than normal values and prolongation of implicit time. The number and function of photoreceptor cell are responsible for p amplitude reductions [25], whereas the bipolar cell response of the outer retina may be responsible for P implicit time delay [26].

Hood believed that the implicit time is affected more than the amplitude because of damage of photoreceptors and the outer plexiform layer [27].

Maturi and Yu [28] reported that the origin of MFERG is the cells of the outer retina rather than cells from the inner retina.

Similarly, Li *et al.* [25] observed a reduction in retinal function in early ARMD, subclinical AMD, and in fellow eye with a normal fundus appearance. Indicating generalized retinal function disorder of both eyes and areas beyond the sites of visible lesions in the affected eye [25].

However, Jurklies, *et al.* [29] found a reduction in MFERG response densities in the site of CNVs. The amplitudes in the ring 3–5 were within the low normal range (<2 SDs below the mean value) [29].

In this study, for ERG, there were significant differences between ARMD patients (except drusen) and controls. Both scotopic and photopic responses were reduced and prolonged, indicating that in ARMD, not only cones but also the rod system were impaired. The oscillatory potentials were affected severely.

In this study, there were highly significant positive correlations between the MFERG amplitude over CNVs, PED, and GA and visual acuity, whereas there was a statistically insignificant correlation between the visual acuity of the patients and the size of CNVs, PED, and GA, indicating that the size of the lesion does not have an effect on retinal function.

Similarly, Jurklies *et al.* [29] and Park *et al.* [24] found a strong correlation between MFERG response and visual acuity and a weak correlation between MFERG response and lesion size.

In summary, in ARMD not only local responses but also general responses were impaired, indicating that in these patients, a larger retinal area was affected than one may suspect from the fundus appearance. MFERG enables topographic mapping and an objective assessment of retinal function within as well as outside the fovea. It enables estimation of the extent of retinal dysfunction within the central 30° of the retina. MFERG is used to determine the local electrophysiological response of the central retina, whereas full-field ERG provides information on general retinal function.

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Conflicts of interest
There are no conflicts of interest.

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