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Macular function assessed with mERG before and after panretinal photocoagulation in patients with proliferative diabetic retinopathy

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Abstract

Purpose: To examine macular function and its correlation to macular thickness before and after panretinal photocoagulation for proliferative retinopathy in diabetic patients.

Methods: Ten diabetic patients (aged 57±10 years, diabetes duration 21±10 years) treated with panretinal photocoagulation outside the great vascular arcade underwent multifocal electroretinography (mERG) and optical coherence tomography (OCT) before and six months after treatment. When focal treatment in the macular region was performed prior to panretinal photocoagulation the investigations took place 3 weeks after this treatment but before the panretinal photocoagulation. One eye per patient was examined. Amplitudes and implicit times of the mERG response were analyzed within the four innermost (27˚) of the six concentric rings registered by the mERG, which corresponds to the area measured by the OCT (Ø 3.5 mm).

Results: Visual acuity was similar before and after photocoagulation, 1.0; 0.7-1.0 (md,range) vs. 1.0; 0.6-1.0 (md,range). The mean values of the ring average amplitudes were reduced in the first and second, third and fourth concentric rings from foveola after photocoagulation, p=0.001, p=0.011 and p=0.004, respectively. No change was seen in implicit time after treatment. OCT values were similar before and after photocoagulation. There was no correlation between retinal thickness assessed with OCT and amplitudes measured by the mERG.

Conclusion: In spite of unchanged values of retinal thickness and visual acuity, panretinal photocoagulation seems to cause a functional impairment in the adjacent untreated macula, shown by reduced amplitudes measured by the mERG.

Key words:

Diabetic retinopathy, proliferations, panretinal photocoagulation, mERG, OCT

Introduction

Photocoagulation for diabetic retinopathy is well established according to the results from the Diabetic Retinopathy study Research Group (1) and the Early Treatment Diabetic Retinopathy Study Group (2). Although the treatment is beneficial, reducing the risk of severe visual loss in patients treated with panretinal photocoagulation for proliferative retinopathy by 50% (3), there are side effects. Visual field loss (4), impaired dark adaptation (5,6) and decreased amplitudes in the full-field electroretinogram (ERG) (7), have been reported previously. Further, increased sensitivity to glare (8), prolonged visual recovery time (9) and impaired colour vision (10) have been documented, indicating that photocoagulation treatment not only destroys the retinal areas directly illuminated by the laser beam, but also affects function in the adjacent untreated foveal region.

Most studies of the side effects of panretinal photocoagulation for proliferative retinopathy have focused on subjective parameters such as visual acuity, contrast sensitivity, perimetry, and photostress (11,12). In the cases where objective functions have been studied full-field ERG has been used (13,14). However, full-field ERG cannot be used for evaluation of specifically macular function. Therefore, in the present study we have used multifocal electroretinography (mERG) to evaluate macular function before and after panretinal photocoagulation in patients with proliferative diabetic retinopathy. Furthermore, we have correlated the macular function to the macular thickness measured by optical coherence tomography (OCT).

The aim of the present study was to find out whether macular function was affected by panretinal photocoagulation, and whether the function was correlated to macular thickness assessed by the OCT.

Subjects and Methods

Patients

Ten consecutive diabetic patients (7 male, 3 female, aged 57±10 years, diabetes duration 21±10 years) with proliferative retinopathy, not previously treated with laser photocoagulation, and regularly attending the department of Ophthalmology in Lund, were included. One eye per person was examined.

The patients were treated with panretinal photocoagulation outside the great vascular arcade. The argon laser was operated with a spot size of 320 µm, with powers ranging from 280 to 400 mW, and a constant exposure time of 0.2 sec. Between 1200 and 1800 (mean 1589) burns were applied. The patients were examined with mERG and with OCT before and six months after laser treatment. When focal treatment for leakage from microaneurysms and/or short capillaries in the macular region was performed prior to panretinal photocoagulation (7/10 patients), the mERG examinations took place 3 weeks after this treatment but before the panretinal photocoagulation. The mERG prior to panretinal photocoagulation did not differ between previously macular treated eyes and eyes without such treatment.

Informed consent was obtained from all patients.

Ophthalmologic examination and grading of retinopathy

Best corrected visual acuity was tested before and six months after treatment, using a Snellen chart. The degree of retinopathy was based on fundus examination after dilation of the pupil by biomicroscopy or using fundus photography. Photography visualized three fields per eye (45°), nasally, temporally and the macular region (Nikon NFC 50).

Only patients with proliferative retinopathy and without visually disturbing cataract were included.

Multifocal ERG and Optical coherence tomography (OCT)

Multifocal ERGs were recorded using the Visual Evoked Response Imaging System (VERIS)

(EDI. San Mateo, CA), developed by Sutter et al. (15,16), and according to the ISCEV guidelines with a slight modification (17). The stimulus matrix consisted of 103 hexagonal elements that were displayed on a screen in an IR camera, and driven at 75 Hz frame rate. The sizes of the hexagons were scaled with eccentricity to elicit approximately equal amplitude responses at all locations. At a viewing distance of 27 cm the radius of the stimulus array subtended approximately 23 degrees. The luminance of each hexagon was independently alternated between black and white according to a pseudorandom binary m-sequence at 75 Hz. The maximum luminance was 138.0 cd/m^2 and the minimum luminance was 3.5 cd/m^2 resulting in a mean luminance of approximately 70.8 cd/m^2, which also was the level of the background luminance. Pupils were maximally dilated with tropicamide and phenylephrine hydrochloride. A gold ground electrode was attached to the forehead. Retinal activity was recorded with a Gold bipolar contact lens which was placed on the anesthesized (oxibuprocain) cornea. The contralateral eye was occluded with an eye patch. A small black fixation object was placed at the center of the stimulus matrix (18). Fixation was monitored with an eye camera. The surrounding illumination was comfortably moderate.

For the first order maximal amplitude, was defined as peak to through of the first positive spike (P1) representing the averaged ring amplitude, and the implicit time as the time from stimulus to peak of this spike (17).

The first and second order components of the mERG were analyzed regarding amplitudes and implicit time, before and after laser treatment. For comparison with the results from the OCT (diameter of measured area = 3.5mm) we analyzed the summed response from the first and second ring, the third and the fourth of the fourth innermost of the six concentric rings measured by the mERG. (13.5º eccentricity from fovea) corresponding to the OCT measured area (Figure 1).

For the first order component maximal amplitude was defined as peak to through of the positive spike representing the averaged ring amplitudes, and the implicit time as the time from stimulus to peak of this spike. Amplitudes and implicit times were analyzed within the four innermost (27˚) of the six concentric rings registered by the mERG, which correspond to the area measured by the OCT (Ø 3.5 mm).

For the second order component maximal amplitude was defined as peak to through of the first positive spike representing the averaged amplitudes, and the implicit time as the time from stimulus to the through of this first positive spike. Amplitudes and implicit times were analyzed within the four innermost (27˚) of the six concentric rings registered by the mERG, which correspond to the area measured by the OCT (Ø 3.5 mm).

A commercially available OCT unit (Carl Zeiss Ophthalmic Systems, model 3000, Humphrey Division, Dublin, California, USA) was used to perform 6 radial linear scans of 3.5 mm length through the center of fixation, rotated at 30˚. Retinal thickness was computed automatically, using OCT retinal mapping software. The principles of the optical coherence tomography technique is based on low-coherence interferometry that provides optical cross-sectional images of the eye (19,20,21).

To compare the areas from OCT to the measurements from the mERG, the average thickness values from each of the three concentric rings from the OCT were used.

Analytical techniques

Glycemic control was assessed by glycated hemoglobin (HbA_{1c}). HbA_{1c} levels were analysed by ion-exchange chromatography using commercially available microcolumns (Bio-Rad, Richmond, CA) or by fast liquid chromatography (Kontron Instruments, Milan, Italy). Normal value for both methods is <5.3%.

Statistical analyses

Values were given as mean ± S.D. Visual acuity was given as median and range. Students`s

paired samples *t*-test was used for comparison of amplitude values and implicit times. Repeated measure analysis for variance was used as complement to take in account for multiple testing. Correlation between variables were tested with Spearman`s rank test. The statistical analyses were performed with SPSS 11.0 for Windows.

Results

Clinical Findings

In all patients the proliferations had regressed after photocoagulation and no patient was in need of any re-treatment at follow up 6 months later.

Visual acuity was similar before and after photocoagulation: 1,0;0,7-1,0 (md, range) vs. 1,0; 0,6-1,0 (md, range). Visual acuity showed no correlation with either amplitudes or implicit time assessed with the mERG, nor with retinal thickness measured by the OCT at follow up, (Table 1).

Multifocal ERG and OCT

Analysis of the first order component of the mERG showed that the mean values of the ring average amplitudes were reduced in the first and second summed response, the third and the fourth concentric ring from the fovea after photocoagulation, p=0.001, p=0,011 and p=0.004 (paired samples *t*-test), respectively. Repeated measure analysis of variance showed significant difference; p=0.001 for the time factor before and after photocoagulation and p=0.001 for the different areas measured No change in implicit time was seen after photocoagulation (Table 2). Analysis of the second order component of the mERG showed no reduction of amplitudes in the first and second summed response, and in the third concentric ring from the fovea, whereas amplitudes were reduced in the fourth concentric ring after photocoagulation, p=0.010. Implicit time was prolonged only in the fourth concentric ring after photocoagulation, p=0.047 (Table 3).

No difference was seen neither in amplitudes nor in implicit times between patients (n=7) focally treated in the macular region prior to panretinal photocoagulation and patients not receiving such treatment (n=3).

OCT

The average OCT values from the inner, middle and outer concentric rings were similar before and after photocoagulation (270±65µm vs. 231±49µm; p=0.238, 266±46µm vs. 259±58µm; p=0.77, 268±43µm vs. 264±51µm; p=0.88 respectively, (paired samples *t*-test)). Repeated measure analysis of variance showed no significant difference; p=0.51 for the time factor before and after photocoagulation and p=0.086 for the different areas measured. There was no correlation between retinal thickness assessed with the OCT and the amplitudes measured by the mERG, (Table 4).

Discussion

It is known that panretinal photocoagulation may cause transient (22) or persistent visual disturbance due to increased leakage in the macular region (23). However, also patients without macular edema may show a decline in color contrast vision and contrast sensitivity after scatter treatment indicating that foveal function is affected. In clinical trials different attempts to modify the laser treatment have been performed with the intention to decrease the negative influence on the foveal region. Various spot locations in the diabetic retina have been compared (12,13), as has modification of the spot size and the intensity of the laser beam (24). Studies so far have used subjective parameters to evaluate macular function after panretinal photocoagulation. As an objective index of retinal function full field electroretinogram (ERG) has been performed (13,14), however giving a mass response from the entire retina and not

specifying macular function.

In the present study we have objectively demonstrated that the foveal function was affected after photocoagulation. Using multifocal electroretinography (mERG), we have shown reduced amplitudes after treatment in ring 1+2 (summed response) 3 and 4 from the fovea. No difference was seen between patients treated in the macular region prior to the panretinal photocoagulation and patients not treated focally. Furthermore, all the investigations took place three weeks after the focal laser treatment but before the panretinal photocoagulation, thus indicating that the reductions of the amplitudes were caused by the panretinal photocoagulation and not by focal laser burns. A later effect of the perifoveal burns that did not show any influence on the first mfERG taken seems not plausible. These findings are inconsistent with the results from a previous study where central visual fields with the Humphrey analyzer were measured and the retinal sensitivity was unchanged 3 months after panretinal photocoagulation (25). However, another study using the same perimeter program did show a reduction in central retinal sensitivity after scatter treatment for proliferative retinopathy (26). The inconsistent findings in studies evaluating subjective parameters indicate the need of mERG as an objective method for detection of macular dysfunction.

Implicit time in the mERG response was unchanged after the panretinal photocoagulation. This is in agreement with a recent study where oscillatory potentials of multifocal electroretinogram were tested before and after panretinal photocoagulation for preproliferative diabetic retinopathy, and where only the amplitudes were altered, whereas the implicit time was unchanged (27). However, our results partly contradict a study with mERG on retinal function after focal treatment for macular edema (28), where the timing was more affected than the amplitudes. In the referred study the mERG was assessed directly from a localized photocoagulated area, whereas in the present study we tested non photocoagulated adjacent areas. However, also in our study, the implicit time was prolonged in the fourth ring, which

represents an area closest to photocoagulated retina.

Minor differences regarding luminance, contrast scattering light could certainly also influence the measurements.

It has been speculated that the laser effects not only destroy the retinal tissue directly illuminated by the laser beam, but also reduce the signal transmission in adjacent retina (7). This has also been observed in a study on scatter laser treatment in rats, where only one half of the retina was treated. An increased inflammatory response was seen also in the nonphotocoagulated half of the retina (29).

Visual acuity was unchanged after laser treatment in all patients and no patient developed macular edema due to treatment, confirmed by the OCT. In the present study no difference in retinal thickness assessed with the OCT technique was seen six months after laser treatment This differs from another recent report which showed that 60% of eyes treated with panretinal photocoagulation increased in foveal thickness, detectable by a scanning retinal thickness analyzer, after panretinal photocoagulation (30).

In summary the results from the present study demonstrate that panretinal photocoagulation in patients with proliferative diabetic retinopathy, reduces macular function in adjacent untreated central parts of the macula. The mERG seems to be a sensitive method for evaluating macular function for this specific purpose.

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Legends to Figure and Tables

Figure 1. The three concentric white rings represents the area analyzed with the OCT (diameter of measured area = 3.5mm), which correspond to the summed response from the first and second ring, the third and the fourth of the fourth innermost of the six concentric rings of hexagons measured by the mERG. (13.5º eccentricity from fovea).

Table 1. Correlation coefficient r for Visual Acuity before and after photocoagulation and mERG amplitudes of First Order Retinal Responses Densities of ring 1+2, Implicit Time of ring 1+2 and Retinal Thickness for the most inner circle measured with OCT.

Table 2. First Order Retinal Responses Densities and Implicit Time of Ring 1+2 (summed response), 3 and 4 of mERG before and 6 months after photocoagulation.

Table 3. Second Order Retinal Responses Densities and Implicit Time of Ring 1+2 (summed response), 3 and 4 of mERG before and 6 months after photocoagulation.

Table 4. Correlation coefficient r between the corresponding fields assessed by mERG (First Order Retinal Responses Densities) and retinal thickness assessed with OCT.

Table 1.

Visual Acuity

	Before Photocoagulation	After Photocoagulation
mERG Area 1+2	0.478	0.484
implicit time	-0.18	0.484
OCT Central	-0.355	0.465

Correlation coefficient r for Visual Acuity before and after photocoagulation and mERG amplitudes, implicit time and retinal thickness for the central circle measured with OCT. No value showed to be significant on the level $p<0.05$.

Table 2

	Amplitudes (nV/deg^2)		Implicit Time (ms)	
	Before Photocoagulation	6 Months After Photocoagulation	Before Photocoagulation	6 Months After Photocoagulation
Area 1+2	17.4±7.1	12.2±5.6 *	29.0±1.4	29.4±1.8
Area 3	11.7±4.7	8.3±3.8 **	27.8±1.7	28.7±1.5
Area 4	10.0±2.9	7.5±3.0 ***	27.6±1.5	28.0±1.3

All values are given as mean ± SD.

* = $p<0.05$, **=$p<0.01$,***=$p<0.001$ (paired samples *t*-test).

Table 3

	Amplitudes (nV/deg^2)		Implicit Time (ms)	
	Before Photocoagulation	6 Months After Photocoagulation	Before Photocoagulation	6 Months After Photocoagulation
Area 1+2	2.2±0.7	2.9±1.4	24.0±3.3	24.6±2.6
Area 3	2.3±1.3	2.2±1.3	24.4±2.6	23.3±2.0
Area 4	2.6±1.2	2.1±1.2 *	22.5±1.2	23.4±1.5 *

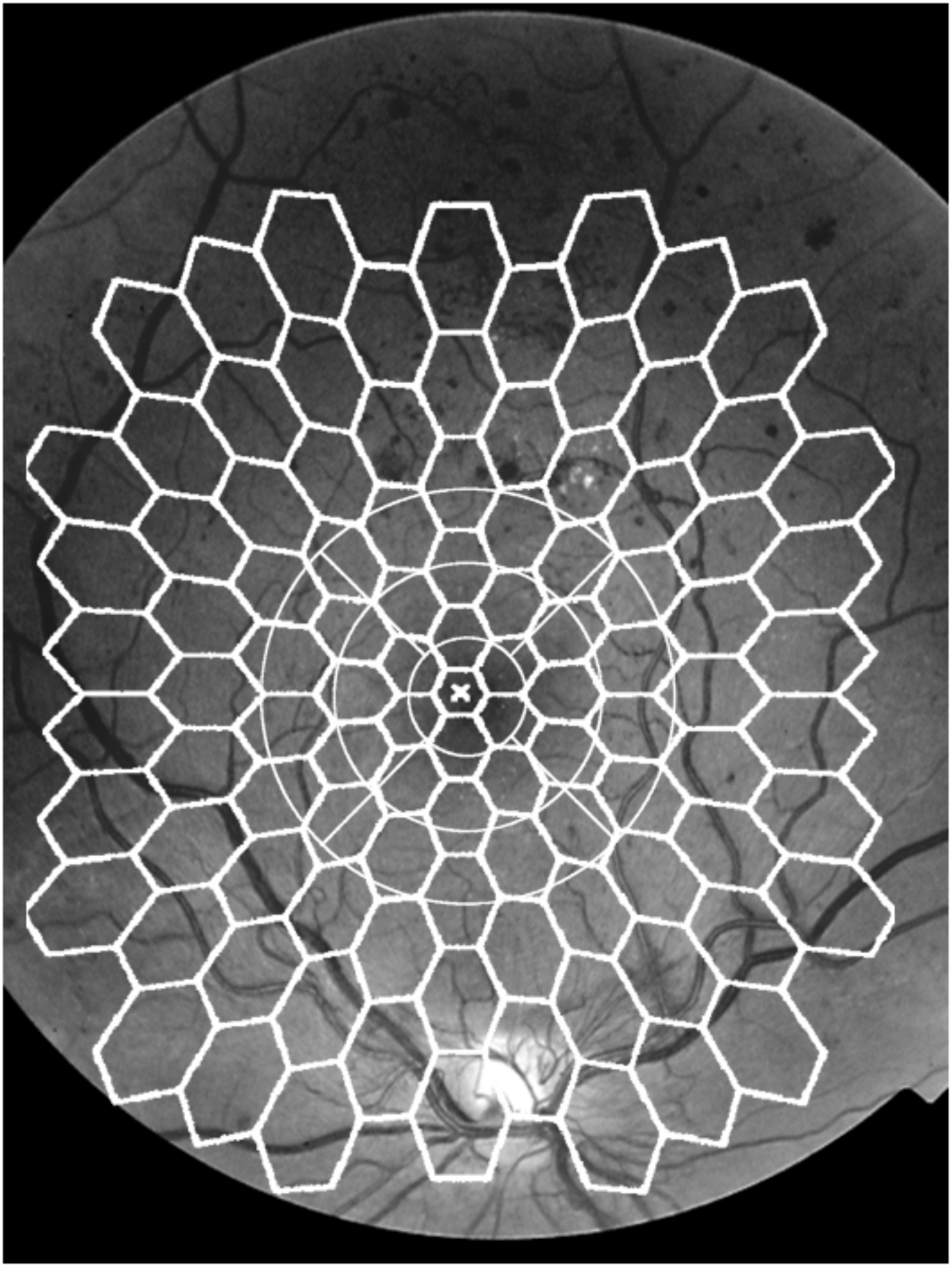
All values are given as mean ± SD.

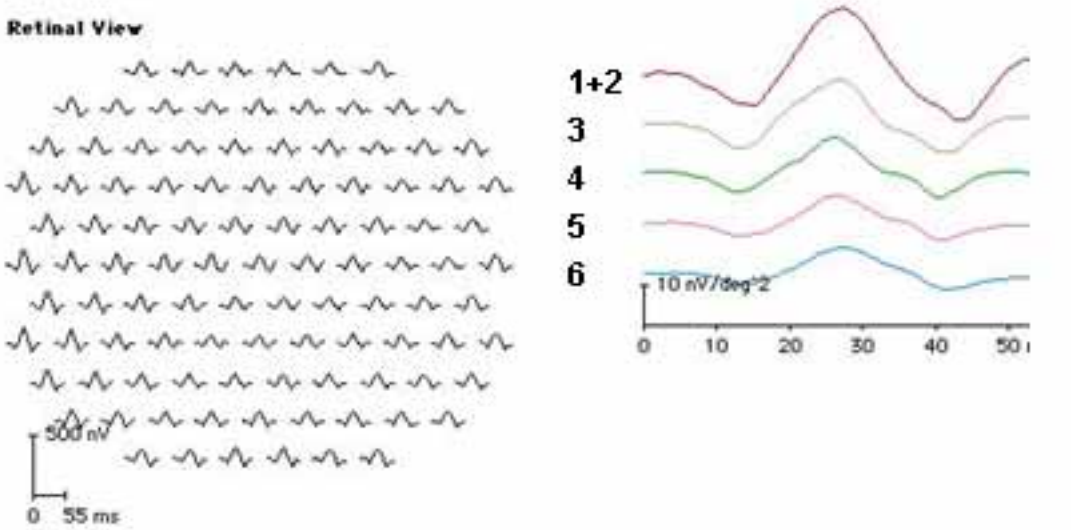
* = p<0.05, **=p<0.01,***=p<0.001

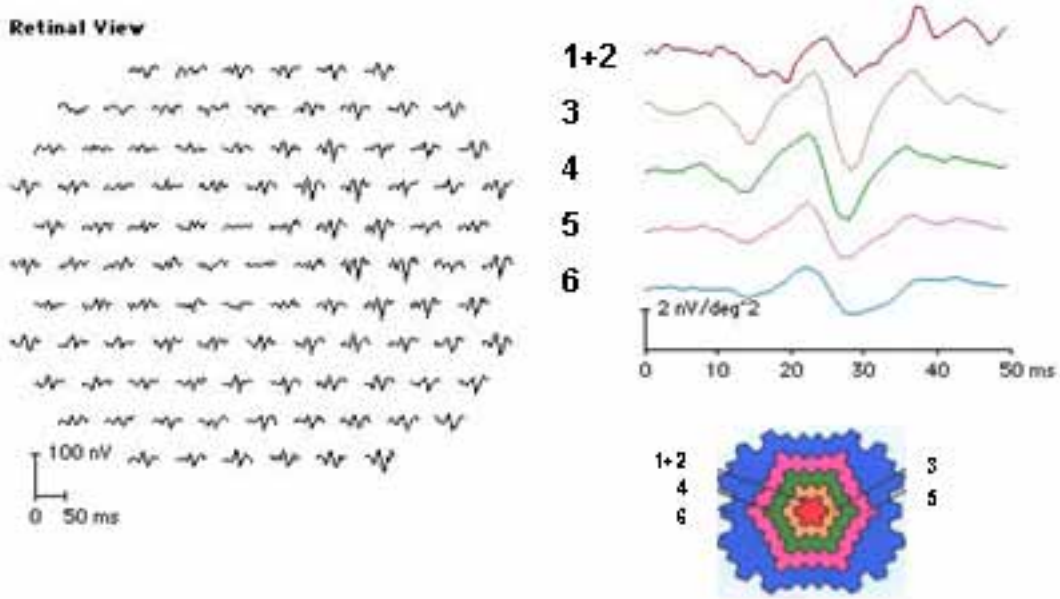
Table 4.

	Before Photocoagulation			Six months after Photocoagulation		
(µm)	OCTcentr	OCT inner	OCT outer	OCTcentral	OCT inner	OCT outer
Amplitudes (nV/deg^2)						
Area 1+2	-0.37			0.515		
Area 3		0.091			0.224	
Area 4			0.115			-0.036

Correlation coefficient r between the corresponding fields assessed by mERG and OCT. No value showed to be significant on the level $p<0.05$.




Retinal View
1+2
3
4
5
6
10 nV/deg^2
0
10
20
30
40
50
500 nV
0
55 ms


Retinal View
1+2
3
4
5
6
2 nV/deg^2
0
10
20
30
40
50 ms
100 nV
0
50 ms

1+2
4
6
3
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