TEMPORAL ASPECTS OF FULL-FIELD ERG IN PATIENTS WITH DIABETES WITHOUT DIABETIC RETINOPATHY

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ABSTRACT

Aim: To evaluate implicit time changes of full-field ERG in patients with type 2 diabetes without diabetic retinopathy. **Material and Method:** The prospective study included 11 diabetic patients, aged between 50 and 80 years old, without diabetic retinopathy and 14 aged-matched controls. All of the participants underwent full-field ERG and ophthalmologic examination to exclude any ophthalmologic pathology. The ERGs were recorded with Metrovision MonPackOne system, which has the same stimulus parameters as the ISCEV standard. The implicit times were analyzed for "a" and "b" waves in dark-adapted 0.01 ERG, dark-adapted 3 ERG, dark-adapted oscillatory potentials, light-adapted 3.0 ERG, and 30Hz flicker ERG, and compared between diabetic patients and healthy subjects. **Results**: The significantly delayed responses, between diabetic patients and healthy subjects older than 50 years, were the dark-adapted oscillatory potentials N2 (21.91 ± 0.85ms versus 22.45 ± 1.02ms, p=0.044) and P2 (25.49±1.01ms versus 26.13±0.94ms, p=0.027), dark-adapted, scotopic 3 "b" wave (42.89±2.74ms versus 44.99±3.16, p=0.015) and light adapted, photopic 3 "b" wave (31.62±1.62ms versus 32.72±1.36ms, p=0.014). **Conclusion**: The electrophysiological findings from the present study showed that, apart from oscillatory potentials changes, reported in previous studies, there was a significant delay in the cone system "b" wave, which indicates that the functional integrity of the inner retina is compromised before the appearance of clinical changes.

Keywords: ERG, Diabetes Mellitus, ERG implicit time

INTRODUCTION

Diabetes mellitus is one of the most serious global health problems and is associated with increased levels of visual impairment after adjusting for the effects of age, sex, race, educational level, blood pressure, smoking and body mass index [1]. The incidence of type 2 diabetes is increasing worldwide and hence the risk of developing complications [2]. The prevalence of visual impairment in adults with and without diabetes vary from 3.8 to 13% and from 1.4 to 2%, respectively, and the relative risk of blindness is 5.2 times higher in patients with diabetes than in those without diabetes [3].

Diabetic retinopathy (DR), the most common complication in diabetes, is the fifth leading cause of blindness worldwide and the leading cause of visual impairment in adults of working age in industrialized countries [4]. It is not uncommon in clinical practice that DR is already present at the first visit after diagnosis of type 2 diabetes [5].

Classically, DR is described as a microangiopathy, affecting the perycites and endothelial cells [6], caused by the metabolic effects of hyperglycemia. In recent years, more attention has been focused on the neurodegenerative aspects of DR [2]. Barber was the first who observed that one month after inducing diabetes in rats, using streptozotocin there was a high rate of apoptosis in the neuroretina without a significant apoptosis in endothelial cells [7]. Glial cell activation is another phenomenon that occurs in diabetic retina, apart from apoptosis in the neuroretina. In other words, an early event in the pathogenesis of DR which participates in the microcirculatory abnormalities is the retinal neurodegeneration [7].

Since DR constitutes a major cause of visual impairment and blindness in the world, is extremely important to assess the retinal function in patients with diabetes (X). Color vision defects, reduced contrast sensitivity and visual field alterations have been reported in diabetic individuals with minimal or no retinopathy. All these are subjective tests. Thus, it is necessary to evaluate the retinal function in diabetes in an objective way, using electrophysiological tests [5].

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Although, clinical exams focus on the visualization of retinal lesions in diabetic patients, electrophysiological changes have been shown to occur before the onset of clinically visible retinopathy. Hence, an electrophysiological assessment of retinal function could be a valuable monitoring method for retinal health in diabetic patients [8].

Standard full-field ERG is an objective method which reflects the function of the whole retina. In recent years, a big number of studies showed the ERG changes in individuals with diabetic retinopathy, but these studies mainly focused on patients with long duration diabetes [2]. It is already known, that the oscillatory potentials are reduced in amplitude and delayed in diabetic patients without retinopathy, but it is not clearly shown what other components of full-field ERG are modified in this group of patients [8]. As we mentioned above, there can be retinopathic changes in the retina in non-diabetic subjects, especially due to aging. The aim of our study was to evaluate the ERG implicit time changes, in patients with type 2 diabetes, without visible diabetic retinopathy and to eliminate the changes that may be due to aging by comparing them to an aged-match healthy group of subjects.

MATERIAL AND METHOD

Subjects

Full-field ERGs were recorded for 28 eyes from 14 healthy subjects aged 50 to 80 years old (63.00 ± 11.62) who had no history of ophthalmologic disease, normal findings on eye examination, normal visual acuity, clear optic media, no history of diabetes mellitus or other vascular or neurologic disease which could influence the ERG. The ERGs were also recorded for 22 eyes of 11 diabetic patients without diabetic retinopathy, aged between 50 and 80 years old (63.18 ± 7.09). All these patients were seen by an ophthalmologist and recruited from the Diabetic Eye Department. The inclusion criteria for these patients were: clinical diagnosis of type 2 diabetes mellitus for less than ten years, no other vascular or neurologic diseases, no history of ophthalmological disease, normal findings on eye examination without any lesion of diabetic retinopathy on photo fundus, normal visual acuity, clear optic media.

The study was performed according to the tenets of the Declaration of Helsinki and was approved by the University Ethics Committee. All the subjects were fully informed about the possible consequences of the research protocol, and they sign their approval for participation.

Recording protocol

The ERGs were recorded at Ophthalmological Research Centre “Ocularius”, Craiova, under an agreement with the University of Medicine and Pharmacy of Craiova. We used the MonPackOne System (Metrovision, Perenchies, France), which has stimulus parametres according to the ISCEV standards. Recording electrodes were HK loop type ("Hawlina- Konec loop") and the reference and ground ones were Ag-AgCl cup type.

The research methodology consisted, for each subject, in:

A. Usual eye examination: visual acuity, biomicroscopy, intraocular pressure, fundus examination, refraction, color vision,
B. ERG recording according to ISCEV protocol:
    1. fully dilatated pupils using 1% tropicamide and 2.5% phenylephrine eye drops;
    2. skin cleansing with an abrasive paste and medicinal alcohol;
    3. 4% xiline in the lower conjunctival bag;
    4. electrods’ placement: the active electrodes were placed on the free edge of the lower eyelid for each eye; the reference electrodes were placed near each orbital rim, with the ground electrode placed on the vertex, using a conductive paste;
    5. dark adaptation for 20 minutes;
    6. dark adapted ERG recording:
        – rod response: the stimulus is a dim blue flash of 0.01 cd.s.m^{-2} , with an interval of 2 seconds between flashes;
        – combined rod-cone response: the stimulus is a white flash of 3.0 cd.s.m^{-2} , with an interval of 10 seconds between flashes;
        – oscillatory potentials: the stimulus is a white flash of 2.0 cd.s.m^{-2} , with an interval of 165 seconds between flashes.
    7. light adaptation for 10 minutes;
    8. light-adapted ERG recording:
        – single flash cone response: a 3.0 cd.s.m^{-2} stimulus, with an interval of 0.5 seconds between flashes and a background luminance of 30cd.m^{-2}
        – 30 Hz flicker: 30 stimuli of 3.0 cd.s.m^{-2} per second.

Statistical analysis

The analysis of the results of ERG recordings was performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT add-on for MS Excel (Addinsoft SARL, Paris, France). We used the Anderson-Darling test to assess data normality. Because most of the data of diabetic patients did not follow a Gauss distribution, we had to use nonparametric tests (i.e. Mann-Whitney test) to compare data between the two groups.

RESULTS

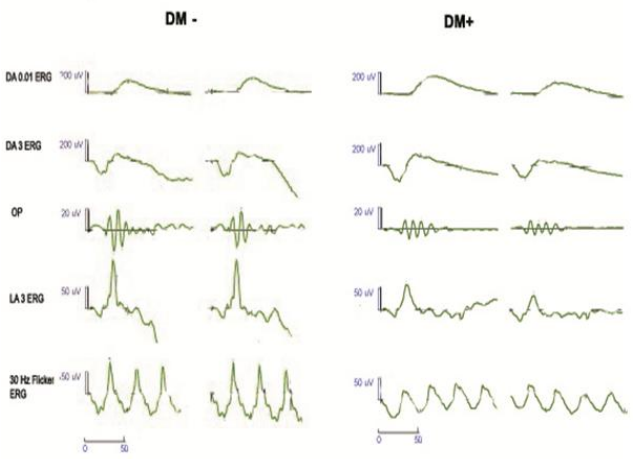

Fig. 1. Sample ERG recording for subjects without Diabetes Mellitus (DM-) and subjects with Diabetes Mellitus (DM+)

We computed mean values and standard deviations for the implicit times of all parameters described for the ERG responses, recorded according to the ISCEV standard procedure (Figure 1).

Table I. Comparison of mean implicit times between subjects without Diabetes Mellitus (DM-) and subjects with Diabetes Mellitus (DM+)

Parameter	DM-	DM+	p Mann-Whitney	Significance
Scotopic 0.01 ERG a	29.62 ± 2.29	30.31 ± 2.57	0.320	- NS
Scotopic 0.01 ERG b	61.27 ± 2.99	62.90 ± 2.99	0.061	- NS
Scotopic 3.0 ERG a	21.03 ± 2.43	21.40 ± 2.12	0.573	- NS
Scotopic 3.0 ERG b	42.89 ± 2.74	44.99 ± 3.16	0.015	- S
Photopic 3.0 ERG a	15.87 ± 1.10	15.82 ± 0.46	0.833	- NS
Photopic 3.0 ERG b	31.62 ± 1.62	32.72 ± 1.36	0.014	- S
Photopic 3.0 Flicker a	18.38 ± 2.07	18.70 ± 2.04	0.586	- NS
Photopic 3.0 Flicker b	30.69 ± 2.57	31.37 ± 2.18	0.324	- NS
Oscillatory potentials N2	21.91 ± 0.85	22.45 ± 1.02	0.044	- S
Oscillatory potentials P2	25.49 ± 1.01	26.13 ± 0.94	0.027	- S
Oscillatory potentials N3	29.01 ± 1.37	29.64 ± 1.04	0.081	- NS
Oscillatory potentials P3	32.72 ± 1.78	33.32 ± 1.26	0.189	- NS

The significantly delayed responses, between diabetic patients and healthy subjects older than 50 years, were the dark-adapted oscillatory potentials N2 (21.91±0.85ms versus 22.45±1.02ms, p=0.044, Figure 2) and P2 (25.49±1.01ms versus 26.13±0.94ms, p=0.027, Figure 3), dark-adapted, scotopic 3 "b" wave (42.89±2.74ms versus 44.99±3.16, p=0.015, Figure 4) and light adapted, photopic 3 "b" wave (31.62±1.62ms versus 32.72±1.36ms, p=0.014, Figure 5). Other ERG parameters showed a delay for DM+ patients, but the statistical significance was slightly above 0.05, so further studies on larger patients group should be conducted.

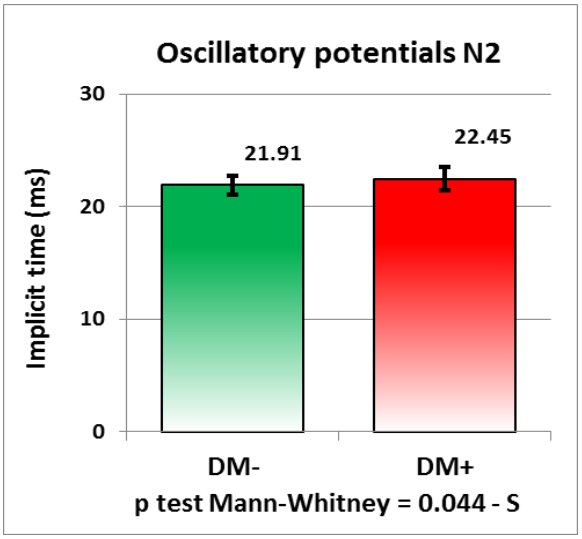

Fig. 2. Comparison of mean values of implicit times for dark-adapted oscillatory potentials N2 wave between DM- and DM+ subjects

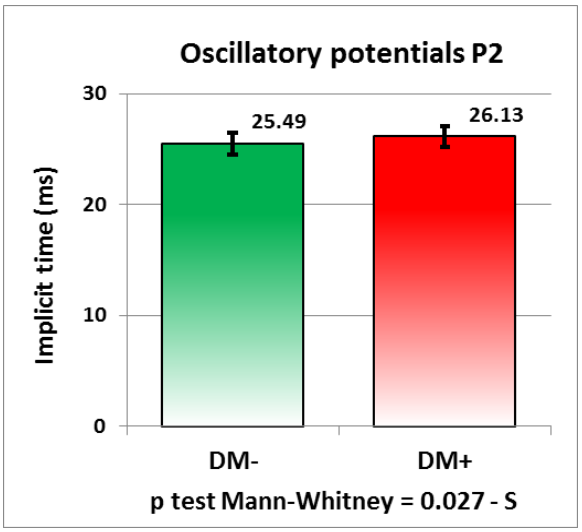

Fig. 3. Comparison of mean values of implicit times for dark-adapted oscillatory potentials P2 wave between DM- and DM+ subjects

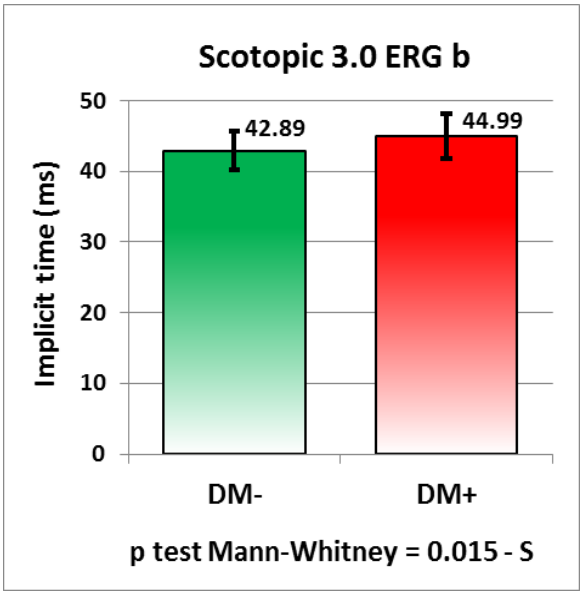

Fig. 4. Comparison of mean values of implicit times for dark-adapted (scotopic) 3 "b" wave between DM- and DM+ subjects

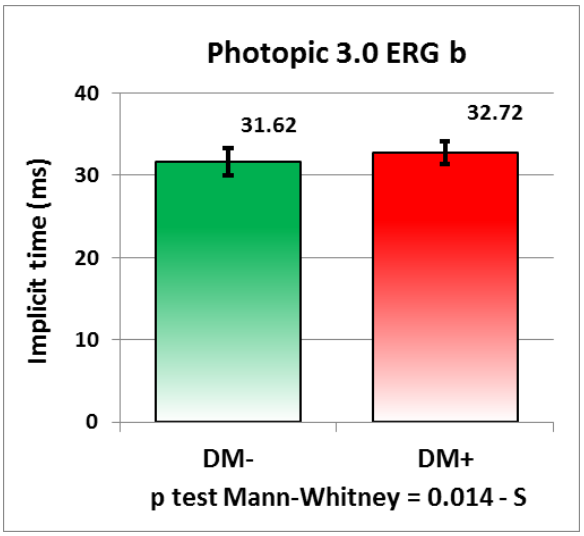

Fig. 5. Comparison of mean values of implicit times for light-adapted (photopic) 3 "b" wave between DM- and DM+ subjects

DISCUSSIONS

As we stated before, diabetes is a disease with both neurologic and vascular components. Recent studies showed that neurodegeneration is an early event in the pathophysiology of diabetic retinopathy and is already present before any vascular abnormalities can be seen in ophthalmoscopic examination [7]. The results of the present study strengthen these findings, showing ERG abnormalities in patients with diabetes and normal ophthalmologic examination.

The full-field ERG is an objective method which reflects the electrical answer from the whole retina [5] and thus a specific tool for assessing the functional response of this tissue. As symptoms do not appear in the first stages of diabetic retinopathy, early diagnosis is a challenging step in the prevention of complications.

Oscillatory potentials deterioration was one of the earliest functional retinal abnormalities reported in the literature [1, 9] in patients with diabetes but without diabetic retinopathy. Our study is in consent with these reports, showing a delayed OP2, which probably indicates early damage of the neuronal synaptic activity of the amacrine and horizontal cells.

The "a" wave of both rod and cone systems had a slightly higher, but statistically insignificant implicit time ($p>0.05$), compared to age-matched controls. This finding is not in consent with a previous study that showed a delayed "a" wave [2], reflecting that the photoreceptors are more affected by age than diabetes, at least at the onset of the disease as yet there are no changes of diabetic retinopathy.

In our study, the averaged "b" wave implicit time was delayed for both rod and cone systems in diabetic patients compared to the aged-matched controls. These changes in the "b" wave implicit time are consistent with damage in the inner retinal layers in the early stages of disease. Holopigian et al showed in their study [10], that apart from oscillatory potentials, "b" wave is also a sensitive indicator of retinal damage in patients with diabetes and no visible diabetic retinopathy.

CONCLUSIONS

By eliminating age influence on ERG responses, because the most affected parameters in the diabetic patients without diabetic retinopathy are the scotopic oscillatory potentials, "b" wave in scotopic 3.0 and photopic 3.0 ERG, we can conclude that the retinal dysfunction in Diabetes Mellitus appears first in the inner retinal layers. Therefore, the aforementioned parameters could be used to assess the evolution in the initial stages of DM, before clinical ophthalmological symptoms appear.

The electrophysiological findings from the present study showed that, apart from oscillatory potentials changes, reported in previous studies, there was a significant delay in the cone system b wave, which indicates that the functional integrity of the inner retina is compromised before the appearance of clinical changes.

ACKNOWLEDGMENT

Dragoş O. Alexandru received financial support for this paper under the frame of European Social Fund, Human Resources Development Operational Programme 2007–2013, project no. POSDRU/159/1.5/S/133377.

Andreea C. Corici received financial support for this paper under the frame of European Social Fund, Human

Resources Development Operational Programme 2007–2013, project no. POSDRU/159/1.5/S/136893.

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ASPECTE TEMPORALE ALE ERG FULL-FIELD LA PACIENTII CU DIABET FĂRĂ RETINOPATIE DIABETICA

REZUMAT

Scop: Evaluarea modificărilor latentei undelor ERG full-field la pacienții cu diabet zaharat tip 2, fără retinopatie diabetica. Material și metodă: Studiul prospectiv a inclus 11 pacienți cu diabet zaharat, cu vârste cuprinse între 50 și 80 de ani, fără retinopatie diabetica si 14 subiecți cu vârste similar, folosiți ca lot martor. Tuturor participanților li s-a efectuat ERG full-field și examinare oftalmologică pentru a exclude orice patologie oftalmologică asociată. Electroretinogramele au fost înregistrate cu sistemul Metrovision MonPackOne, care are parametrii de stimulare in conformitate cu standardul ISCEV. A fost analizata latenta pentru undele "a" și "b", pentru ERG 0,01 cu adaptare la întuneric, ERG 3 cu adaptare la întuneric, potențialele oscilatorii cu adaptare la întuneric, și ERG 3.0, 30Hz flicker cu adaptare la lumină, care au fost comparaţi între pacienții diabetici și subiecții sănătoși. Rezultate: Răspunsurile întârziate semnificativ, la compararea lotului de pacienți diabetici cu lotulde subiecți sănătoși cu vârstă peste 50 de ani, au fost potențiale oscilatorii cu adaptare la întuneric N2 (21.91 ± 0.85ms versus 22.45 ± 1.02ms, p = 0,044) și P2 (25.49 ± 1.01ms față 26.13 ± 0.94ms, p = 0,027), unda "b" pentru ERG 3, cu adaptare la întuneric (42.89 ± 2.74ms versus 44.99 ± 3.16, p = 0,015) și unda "b" pentru ERG 3, cu adaptare la lumina (31,62 ± 1.62ms versus 32.72 ± 1.36ms, p = 0,014). Concluzie: Rezultatele electrofiziologice din prezentul studiu au arătat că, în afară de modificările potențialelor oscilatorii, raportate în studiile anterioare, a existat o întârziere semnificativă pentru unda "b", ceea ce indică faptul că integritatea funcțională a starturilor interne ale retinei este compromisă înainte apariția modificărilor clinice.

Cuvinte cheie: ERG, diabet zaharat, latenta