

Electrophysiological assessment of visual function in IDDM patients

Vincenzo Parisi^{a,c,*}, Luigi Uccioli^b, Giovanna Monticone^{b,c}, Leoluca Parisi^d, Gianluca Manni^a, Daniela Ippoliti^c, Guido Menzinger^b, Massimo G. Bucci^{a,e}

^a*Cattedra di Clinica Oculistica, Università di Roma 'Tor Vergata', c/o Complesso Integrato Columbus, via della Pineta Sacchetti 506, 00168 Rome, Italy*

^b*Cattedra di Endocrinologia, Università di Roma 'Tor Vergata', c/o Complesso Integrato Columbus, via della Pineta Sacchetti 506, 00168 Rome, Italy*

^c*Istituto Dermatopatico dell'Immacolata, IRCCS, via Monti di Creta 104, 00167 Rome, Italy*

^d*II Clinica Neurologica, Università di Roma 'La Sapienza', viale dell'Università 30, 00161 Rome, Italy*

^e*Fondazione G.B. Bietti, piazza Sassari 5, 00161 Rome, Italy*

Accepted for publication: 23 January 1997

Abstract

Various electrophysiological tests have been employed to reveal functional abnormalities at different levels of the visual system in insulin-dependent diabetic (IDDM) patients. The aim of our work was to assess, with a comprehensive neurophysiological protocol evaluating the retinal, macular and visual pathways functions, whether and when such electrophysiological abnormalities do appear in IDDM patients free of any fluorangiographic sign of retinopathy with various disease duration. Flash-electroretinogram (ERG), oscillatory potentials (OPs), pattern-electroretinogram (PERG), and visual evoked potentials (VEPs) in basal condition and after photostress were assessed in 12 control subjects (C) and 42 age-matched IDDM patients without clinical retinopathy (DR-) divided, on the basis of the disease duration, into 4 groups (1–5, 6–10, 11–15, 16–20 years). In addition another age-matched group of IDDM patients with a background retinopathy (DR+; $n = 12$; duration of disease 18 ± 49 years) was evaluated. In all IDDM DR- patients PERG and VEP were significantly impaired. In addition, groups 11–15 and 16–20 years displayed impaired OPs. All electrophysiological parameters were further impaired in DR+ patients. In conclusion, retinal, macular and visual pathways functions are differently impaired in IDDM (DR-) patients with different disease duration. Electrophysiological impairment starts in the nervous conduction of the visual pathways with an early involvement, goes on in the innermost retinal layers and in the macula and ends in the middle and outer retinal layers. © 1997 Elsevier Science Ireland Ltd.

Keywords: Electroretinogram; Visual evoked potentials; Photostress; Insulin-dependent diabetes; Diabetic retinopathy; Macular function

1. Introduction

In diabetes mellitus the visual deficits appear to result from both vascular disease and metabolic abnormalities, which can affect the macula, retina, optic nerve and visual pathways.

A functional evaluation of such structures can be assessed by recording electroretinographic signals evoked by flash or patterned stimuli (flash electroretinogram, ERG; oscillatory potentials, OPs; pattern electroretinogram, PERG) and cor-

tical potentials evoked by patterned stimuli (visual evoked potentials, VEPs) in basal condition and after photostress.

In diabetic patients these methods revealed an impaired function of the different retinal layers (Gjotteberg, 1974; Simonsen, 1975; Porciatti and Von Berger, 1983; Arden et al., 1986; Bresnik and Palta, 1987a; Bresnik and Palta, 1987b; Coupland, 1987; Trick et al., 1988; Boschi et al., 1989; Falsini et al., 1989; Trick, 1991), of macula (Ghirlanda et al., 1991; Parisi et al., 1994; Parisi et al., 1995b; Uccioli et al., 1995) and of the visual pathways (Puvanenderan et al., 1983; Cirillo et al., 1984; Collier and Mitchell, 1985; Comi et al., 1986; Comi et al., 1987; Martinelli et al., 1987; Algan et al., 1989; Pozzessere et al., 1989; Lanting et al., 1991; Martinelli et al., 1991; Sartucci et al., 1993; Ziegler et al., 1994). The aim of our work was to assess, with a

* Corresponding author. Cattedra di Clinica Oculistica, Università di Roma 'Tor Vergata', via Santa Maria Goretti 66, 00199 Rome, Italy; tel. and fax: +39 6 3017936; e-mail: vparisi@mbx.vol.it

comprehensive neurophysiological protocol evaluating the retinal, macular and visual pathways functions, whether and when such electrophysiological abnormalities do appear in IDDM patients free of any fluorangiographic sign of retinopathy, with different disease duration.

2. Methods and materials

Twelve control subjects and 54 age-matched insulin-dependent diabetic (IDDM) patients were included in the study after informed consent.

The following criteria were required for the control subjects: normal intraocular pressure (<21 mmHg), normal visual acuity (10/10), normal visual field (Goldmann perimetry) and no ocular and/or neurological problems. The criteria required for diabetic patients were: normal intraocular pressure (<21 mmHg), best corrected visual acuity 10/10, and absence of proliferative retinopathy evaluated by fluorescein-angiography. Our IDDM patients without clinical retinopathy (DR–; level 1 according to Klein levels) (Klein et al., 1984) were divided in four groups on the basis of the duration of the disease: 12 with a duration 15 years, 10 with a duration 6–10 years, 10 with 10–15 years, and 10 with 16–20 years. In addition, another group of IDDM patients with a background retinopathy (DR+; Klein level 3–5) ($n = 12$) but not macular disease, was evaluated.

The clinical characteristics of the patients are reported in Table 1.

All subjects underwent electrophysiological evaluations performed in identical experimental conditions. The subjects under examination were seated in a semi-dark room. Prior to each electrophysiological test, all subjects were visually adapted to background of the visual stimuli for 10 min. The luminosity of the background of the flash stimulator (Ganzfield, see below) was about 5 cd/m² and the display for pattern stimulation was surrounded by a uniform field of luminance of 5 cd/m². The pupil diameter of each subject was about 5 mm and mydriatic or miotic drugs were never used. The stimulation was monocular, in the right eye

Table 1
Clinical population profile

Group	N	M/F	Age (years)	Disease duration (years)	HbA1c
Controls	12	7/5	30.0 ± 1.3	–	4.7 ± 0.06
IDDM 1–5y	12	6/6	28.3 ± 2.7	3.3 ± 0.22	6.4 ± 0.6*
DR– 6–10y	10	6/4	25.6 ± 0.7	7.6 ± 0.45	6.8 ± 0.3*
DR– 11–15y	10	5/5	30.4 ± 2.5	13.3 ± 0.3	6.9 ± 0.2*
DR– 16–20y	10	7/3	30.2 ± 1.7	17.8 ± 0.5	7.0 ± 0.4*
DR+16–20y	12	4/6	28.7 ± 1.7	18.0 ± 0.5	6.9 ± 0.3*

IDDM, insulin-dependent diabetic patient; DR–, IDDM without retinopathy; y, years; 1–5, 6–10, 11–15, 16–20, IDDM divided in groups on the basis of disease duration; DR+, IDDM with retinopathy.

* $P < 0.01$ vs. C (ANOVA).

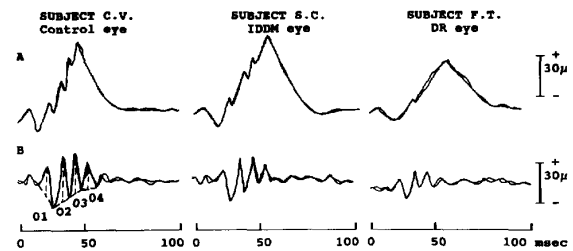


Fig. 1. Flash-ERG (A) and oscillatory potentials (B) layouts of subjects C.V. (control), S.C. (IDDM without retinopathy with 13 years of disease), and F.T. (IDDM with retinopathy: DR eye).

of all patients, after occlusion of the other eye. The following electrophysiological evaluations were performed.

2.1. Flash ERG

The bioelectrical signal was recorded by means of platinum hook electrodes inserted in the external corner of the inferior eyelid (active electrode). Local anesthesia was provided by application of novesine 0.4%. A silver/silver chloride electrode was positioned and fixed with collodion in Fpz (International System 10–20 of EEG recording) (reference electrode). The ground electrode was in the left arm. The interelectrode resistance was maintained lower than 5 kΩ.

2.2. ERG recordings

The visual stimulus was BM 6000 Ganzfield (Biomedica Mangoni, Pisa, Italy) at 0.1 J of intensity. A single flash was presented at the temporal frequency of 1 Hz.

The signal was amplified (gain 5000), filtered (band pass 1–100 Hz and averaged with automatic rejection of artifacts (40 events for every trial) by BM 6000. The analysis time was 150 ms.

The typical ERG is a biphasic signal characterized by a certain number of waves, two of which (a- and b-waves) have mean latency of 16 and 40 ms in normal subjects. Examples of recordings of ERG are shown in Fig. 1.

2.3. OP recordings

The visual stimulus was BM 6000 Ganzfield at 1 J of intensity. A single flash was presented at the temporal frequency of 0.1 Hz. The signal was amplified (gain 5000), filtered (band pass 100–5000 Hz) and averaged with automatic rejection of artifacts by BM 6000 (20 events for every trial). The analysis time was 150 ms.

OPs are characterized by a certain number of waves: OP1, OP2, OP3, OP4. Examples of recordings of OPs are shown in Fig. 1.

2.4. PERG recording

The visual stimuli were checkerboard patterns (contrast

expressed as ' $L_{max} - L_{min}/L_{max} + L_{min} \times 100$ ' was 95%, mean luminance 100 cd/m^2) generated on a TV monitor and reversed in contrast at the rate of 2 reversals/s. At the viewing distance of 114 cm the check edges subtended 15 min of visual arc and the screen of the monitor subtended 12.5° (Celesia et al., 1993).

The bioelectrical signal was recorded by means of platinum hook electrodes inserted in the external corner of the inferior eyelid. Electroretinograms were derived bipolarly between the tested (active electrode) and the patched (reference electrode) eye using the method previously described (Fiorentini et al., 1981). Local anesthesia was provided by application of novesine 0.4%. The ground electrode was in Fpz (Marmor et al., 1996). The interelectrode resistance was maintained lower than $3 \text{ k}\Omega$. The signal was amplified (gain 50 000), filtered (band pass 1–30 Hz) and averaged with automatic rejection of artifacts (200 events for every trial) by BM 6000. The analysis time was 250 ms.

The transient PERG response is characterized by a number of waves with 3 subsequent peaks, of negative, positive, and negative polarity, respectively. In normal subjects and in the condition of our experiment, these peaks have the following mean latencies: 35, 50 and 95 ms.

In the recording session PERGs were recorded at least twice and the resulting waveforms were superimposed to check the repeatability of the results.

Examples of recording of PERG are shown in Fig. 2.

2.5. VEP recording

VEPs were recorded according to a previously described method (Bucci et al., 1991; Parisi and Bucci, 1992).

The visual stimuli were checkerboard patterns (contrast 70%, mean luminance 110 cd/m^2) generated on a television monitor and reversed in contrast at the rate of 2 reversals/s. At the viewing distance of 114 cm the individual check edges subtended 15 min of visual arc (Ristanovic and Haidukovic, 1981; Tomoda et al., 1990) and the screen of the monitor subtended 18° .

Cup-shaped electrodes of silver/silver chloride were fixed with collodion in Oz position (active electrode), and in Fpz position (reference electrode) with the ground in the left arm.

The interelectrode resistance was kept below $3 \text{ k}\Omega$. The bioelectric signal was amplified (gain 20 000), filtered (bandpass 1–100 Hz) and averaged, with automatic rejection of the artifacts, over a number of stimulus periods using a BM 6000.

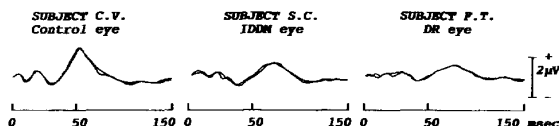


Fig. 2. Pattern-ERG layouts of subjects C.V. (control), S.C. (IDDM without retinopathy: DR-) and F.T. (IDDM with retinopathy: DR eye).

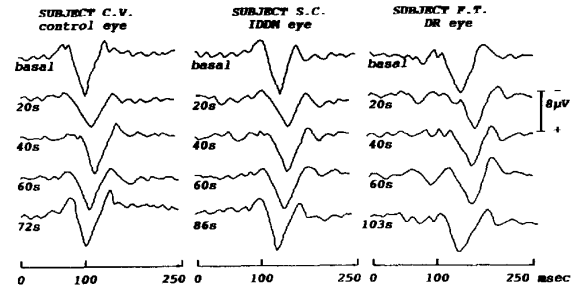


Fig. 3. VEP layout of subjects C.V. (control), S.C. (IDDM without retinopathy: DR-), and F.T. (IDDM with retinopathy: DR eye) in basal condition and 20, 40 and 60 s after photostress. At 20, 40 and 60 s after photostress we observed an increase in latency and a decrease in amplitude. The recovery time (VEPs superimposable on the basal waveform) was at 72 s in the control eye, at 86 s in the IDDM DR- eye and at 103 s in IDDM DR+ eye.

The recording session began with a preliminary experiment in which at least two VEPs were recorded, averaging over 100 stimulus periods and excluding artifacts. The analysis time was 500 ms.

The transient response was characterized by several waves with 3 peaks, that in normal subjects appeared after 75–100 and 145 ms. These peaks had negative (N75), positive (PICO) and negative (N145) polarity, respectively.

After this preliminary trial, a control VEP was recorded, reducing the average to 40 events per trial (with no more than two sweeps discarded because of artifacts). This VEP record was defined as 'basal' on the computer and it was kept on the display monitor.

Photostress was then induced for 30 s by means of a circular diffusing surface (the bulb of a 200 W lamp) that was centrally fixated by the subject from a distance of 20 cm and produced a central scotoma of 6° diameter. The pupil diameter reduced to about 2 mm both in controls (C) and IDDM (C, $2.33 \pm 0.14 \text{ mm}$; IDDM, $2.22 \pm 0.06 \text{ mm}$; $P = 0.434$).

Immediately after the end of photostress, fixation was shifted to the pattern stimulus and recording of VEPs started. Recordings were taken for successive 20 s periods (averaging 40 stimuli every 20 s) and displayed successively on the monitor until the VEP obtained was superimposable on the basal recording. The time taken for VEP to become superimposable was considered as the recovery time after photostress (RT).

Examples of recordings of VEPs in basal condition and after photostress are shown in Fig. 3.

We accepted PERGs and VEPs signals with signal-to-noise ratio >2 . The noise was measured by recording the bioelectrical signals while the monitor was screened by cardboard, and it was $<0.1 \mu\text{V}$ (mean $0.085 \pm 0.005 \mu\text{V}$) in all subjects tested.

For all electrophysiological records the peak latency and the peak amplitude of each wave were measured directly

Table 2

Mean \pm SEM of flash-ERG parameters

Group	N	a-wave latency (ms)	b-wave latency (ms)	b-wave amplitude (μ V)	OPs amplitude (μ V)
Controls	12	16.0 \pm 0.4	40.7 \pm 1.4	74.5 \pm 3.2	118.5 \pm 1.8
IDDM 1–5y	12	16.7 \pm 0.8 [†]	41.2 \pm 2.3 [†]	73.7 \pm 4.2 [†]	117.6 \pm 1.6 [†]
DR– 6–10y	10	16.9 \pm 1.1 [†]	40.3 \pm 2.7 [†]	70.9 \pm 3.8 [†]	116.9 \pm 1.2 [†]
DR– 11–15y	10	16.7 \pm 0.9 [†]	40.4 \pm 2.5 [†]	71.3 \pm 3.3 [†]	88.9 \pm 1.8 ^{†,*}
DR– 16–20y	10	16.6 \pm 1.7 [†]	42.2 \pm 2.1 [†]	70.1 \pm 3.5 [†]	75.6 \pm 2.1 ^{†,*}
DR+16–20y	12	21.7 \pm 3.6*	52.3 \pm 6.7*	42.8 \pm 6.5*	44.6 \pm 1.9*

IDDM, insulin-dependent diabetic patient; DR–, IDDM without retinopathy; y, years; 1–5, 6–10, 11–15 and 16–20, IDDM divided in groups on the basis of disease duration; DR+, IDDM with retinopathy; OPs, oscillatory potentials; addition of O1 + O2 + O3 + O4 amplitudes.

* $P < 0.01$ vs. C (ANOVA).

[†] $P < 0.01$ vs. DR+ (ANOVA).

from the displayed recordings with a pair of cursors. In the analysis of OPs results, we considered the addition of the single amplitude of each OP (OP1 + OP2 + OP3 + OP4).

2.6. Statistical analysis

Results are expressed as mean \pm SE. Differences between groups were statistically evaluated with analysis of variance (ANOVA) and with linear regression and were considered significant with $P < 0.05$.

3. Results

3.1. ERG and OPs in normal subjects and in IDDM patients (Table 2)

In control subjects the ERG parameters were within our normal limits (Parisi et al., 1995a). In groups 1–5 and 6–10 years IDDM (DR–) patients the parameters of the ERG were within normal limits and without significant differences from the parameters of the control subjects. In groups 11–15 and 16–20 years IDDM (DR–), a significant decreased amplitude of OPs ($P < 0.01$) was observed. In DR+ IDDM patients delayed 'a' and 'b' waves peak latency and reduced b-wave and OPs amplitudes ($P < 0.01$ vs. DR and C) were recorded.

3.2. PERG in normal subjects and IDDM patients (Table 3)

In control subjects, the PERG parameters (N35 and P50 latencies and P50-N95 amplitude) were within our normal limits (Parisi et al., 1995a) expressed as mean values \pm 3 SD for N35 and P50 latencies and mean values \pm 1 SD for P50-N95 amplitude.

N35 and P50 latencies were significantly delayed and P50-N95 amplitude was significantly reduced in all diabetic groups compared to C; DR+ showed a further impairment of both parameters. No correlation between PERG parameters and the duration of disease was found.

3.3. Basal VEPs

The mean basal data for all groups of patients are shown in Figs. 4 and 5.

In C, the VEP parameters (P100 latency and N75-P100 amplitude) were within our normal limits (Parisi et al., 1995a) expressed as mean value \pm 3 SD for P100 latency (93.15 \pm 3.43 ms) and mean value \pm 1 SD for N75-P100 amplitude (9.5 \pm 2.18 μ V).

P100 latency was significantly higher and N75-P100 amplitude was significantly lower in all diabetic groups than in C; both parameters were further impaired in DR+. No correlation between basal P100 latency and N75-P100 amplitude disease was found.

Table 3

Mean \pm SEM of pattern-ERG parameters

Group	N	N35 latency (ms)	P50 latency (ms)	P50-N95 amplitude (μ V)
Controls	12	34.8 \pm 0.55	54.5 \pm 1.34	1.84 \pm 0.12
IDDM 1–5y	12	39.7 \pm 0.58 ^{†,*}	59.8 \pm 0.47 ^{†,*}	0.92 \pm 0.07 ^{†,*}
DR– 6–10y	10	41.2 \pm 0.82 ^{†,*}	60.3 \pm 0.64 ^{†,*}	0.87 \pm 0.12 ^{†,*}
DR– 11–15y	10	41.6 \pm 0.79 ^{†,*}	61.1 \pm 0.65 ^{†,*}	0.82 \pm 0.09 ^{†,*}
DR– 16–20y	10	42.0 \pm 0.92 ^{†,*}	61.9 \pm 0.82 ^{†,*}	0.83 \pm 0.07 ^{†,*}
DR+16–20y	12	48.7 \pm 0.46*	68.2 \pm 1.01*	0.53 \pm 0.05*

IDDM, insulin-dependent diabetic patient; DR–, IDDM without retinopathy; y, years; 1–5, 6–10, 11–15 and 16–20, IDDM divided in groups on the basis of disease duration; DR+, IDDM with retinopathy.

* $P < 0.01$ vs. C (ANOVA).

[†] $P < 0.01$ vs. DR+ (ANOVA).

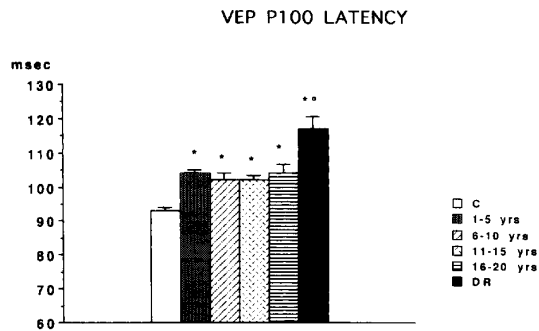


Fig. 4. Histograms of mean values of VEP P100 latency in the basal condition. Error bars represent one standard error of the mean. C, control eyes; 1–5 years, 6–10 years, 11–15 years and 16–20 years, IDDM without retinopathy divided in groups on the basis of disease duration; DR, IDDM with retinopathy. ANOVA: * $P < 0.01$ vs. C; °DR vs. 1–5, 6–10, 11–15, 16–20 years.

3.4. VEPs after photostress: controls

The standard responses of P100 latency after photostress are shown in Figs. 6 and 7.

At 20 s after photostress, an increase in P100 latency and a decrease in N75-P100 amplitude were observed. At 40 and 60 s after photostress the P100 latencies were shorter than the 20 s value, but still longer than in the basal P100 latency. The N75-P100 amplitude increased from the value observed at 20 s, but without reaching the basal value. The RT was 72.8 ± 0.8 s.

3.5. VEPs after photostress in IDDM patients.

In IDDM patients the response to photostress followed a pattern similar to that described in control subjects.

The mean increments in P100 latency observed at 20, 40 and 60 s after photostress were higher, although not significantly, in groups 1–5, 6–10, and 11–15 years than in C. This increment was significantly higher in 16–20 years and DR groups. The value of DR + group was significantly

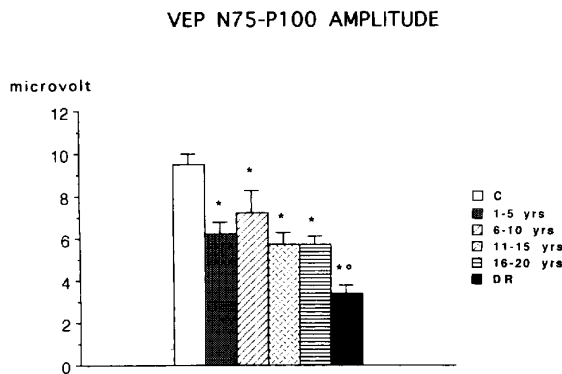


Fig. 5. Histograms of mean values of VEP N75-P100 amplitude in the basal condition. Error bars represent one standard error of the mean. ANOVA: * $P < 0.01$ vs. C; °DR vs. 1–5, 6–10, 11–15, 16–20 years.

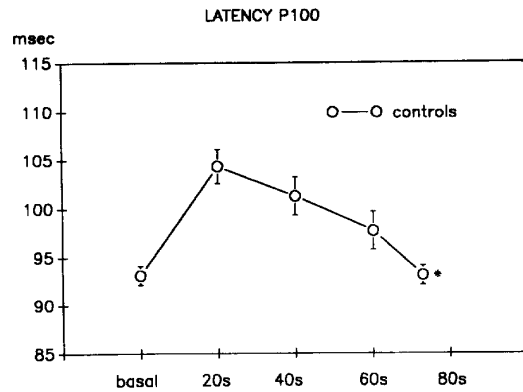


Fig. 6. Graphic representation of mean values of VEP P100. latency in the basal condition and 20, 40, 60, and 80 s after photostress. Error bars represent one standard error of the mean. The recovery time after photostress (*) is 72.8 s.

higher than 1–5, 6–10 and 11–15 years groups (Table 4).

The mean percentage decrement of amplitude observed after photostress was higher in all diabetic groups than in C, and no differences were found between all diabetic groups (Table 4).

Recovery time (RT) was significantly longer in all IDDM than in C, and in DR + than in other IDDM groups (Fig. 8).

No correlations between duration of disease and mean increment of P100 latency, mean percentage decrease in amplitude and RT were found.

4. Discussion

4.1. Flash-ERG and OPs

Flash-ERG has been utilized to assess the bioelectrical activity of the outer retinal layers, and the OPs to evaluate

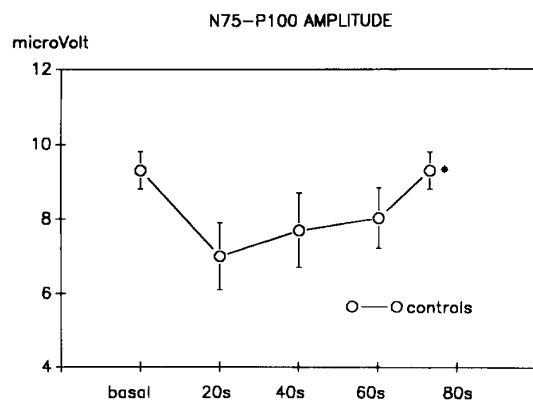


Fig. 7. Graphic representation of mean values of VEP N75-P100 amplitude in the basal condition and 20, 40, 60, and 80 s after photostress. Error bars represent one standard error of the mean. The recovery time after photostress (*) is 72.8 s.

Table 4

Mean \pm SEM of increase in P100 latency and percentage decrease in N75-P100 amplitude observed at 20, 40 and 60 s after photostress

Group	N	Mean increase in P100 latency (ms)	Mean decrease in N75-P100 amplitude (%)
Controls	12	7.4 \pm 0.5	14.9 \pm 1.4
IDDM 1–5y	12	10.5 \pm 1.1 [†]	24.4 \pm 2.3*
DR– 6–10y	10	10.4 \pm 0.9 [†]	24.3 \pm 1.7*
DR– 11–15y	10	10.5 \pm 1.8 [†]	26.4 \pm 1.3*
DR– 16–20y	10	12.8 \pm 1.2*	26.6 \pm 1.9*
DR+16–20y	12	14.7 \pm 1.4*	28.8 \pm 3.2*

IDDM, insulin-dependent diabetic patient; DR–, IDDM without retinopathy; y, years; 1–5, 6–10, 11–15 and 16–20, IDDM divided in groups on the basis of disease duration; DR+, IDDM with retinopathy.

* $P < 0.01$ vs. C (ANOVA).

[†] $P < 0.01$ vs. DR+ (ANOVA).

the activity of the middle retinal layers (Algere, 1968; Ogden, 1973; Armington, 1974; Wachtmeister and Dowling, 1978; Maffei and Fiorentini, 1981; Maffei and Fiorentini, 1982; Heynen et al., 1985). Some authors have revealed abnormalities of flash-ERG and in particular of OPs in IDDM patients with early retinopathy (Gjotteberg, 1974; Simonsen, 1975; Bresnik and Palta, 1987a; Bresnik and Palta, 1987b).

In our previous experience flash-ERG and OPs parameters did not differ between controls and newly diagnosed IDDM patients. Our data suggested that in newly diagnosed IDDM the outer and the middle retinal layers are not functionally impaired (Uccioli et al., 1995). The functional impairment of these retinal layers appears in patients free of any clinical and fluoroangiographic sign of retinopathy, but with a duration of disease greater than 10 years. A further impairment is observed in patients with background retinopathy.

Our data confirm that electrophysiological changes may be present also in the absence of clinical retinopathy (Bresnik and Palta, 1987a; Bresnik and Palta, 1987b; Shirao et al., 1991), although a further impairment is observed with the appearance of clinical retinopathy.

4.2. PERG

PERG reflects the bioelectrical response of the innermost retinal layers to visual stimuli represented by gratings or checkerboard alternative in contrast. This evidences come from the works of Maffei and Fiorentini who, after section of the optic nerve in cats, observed a decrease in amplitude and eventually the disappearance, of the electroretinographic signal evoked by pattern stimuli, while the electroretinographic signal evoked by flash stimuli was preserved in monkeys (Maffei and Fiorentini, 1981; Maffei and Fiorentini, 1982). The electrophysiological changes were related to ganglion cell degeneration (Hollander et al., 1984; Maffei et al., 1985; Trimarchi et al., 1990), and therefore the PERG was related to the bioelectric activity of the innermost retinal layers.

Extensive literature has been produced on PERG in diabetic patients with or without retinopathy. In diabetic patients without retinopathy data are controversial: some authors observed PERG in the normal range (Wanger and Persson, 1985; Coupland, 1987; Hardy et al., 1995), while others recorded pathological values also in patients with only 3.5 years of duration of disease (Trick et al., 1988; Falsini et al., 1989; Pragar et al., 1989; Caputo et al., 1990; Trick, 1991). A mild to moderate retinopathy is characterized by pathological results of PERG parameters (Arden et al., 1986; Coupland, 1987; Boschi et al., 1989; Jenkins and Cartwright, 1990).

In our experience all IDDM patients without retinopathy show impaired PERG, that, although not significantly, have a worsening trend with the duration of disease; a further impairment occurs in the presence of retinopathy. However, patients with a duration of disease longer than 11 years show an impairment of OPs; therefore, in these patients a contribution of preganglionic elements in the impairment of PERG cannot be excluded.

4.3. VEPs in basal conditions

VEPs represent a mass response of cortical and possibly subcortical visual areas and are employed in the assessment of the functional integrity of the visual pathways (Ceslea et al., 1982).

In all IDDM patients (DR –) we found a basal VEP P100 latency higher and N75-P100 amplitudes lower than in control eyes, independently from the duration of disease. The delay in VEP latency and the reduction in amplitude observed may be attributed to a reduced velocity of nervous conduction in the optic nerve. This hypothesis can be supported by our results that show an impaired PERG that is not related to the presence of retinopathy, but suggest that the innermost retinal layers are early and selectively affected by diabetes. In fact, in a previous study we observed a delayed VEP P100 latency in newly diagnosed IDDM patients (Parisi et al., 1995b).

RECOVERY TIME AFTER PHOTOSTRESS

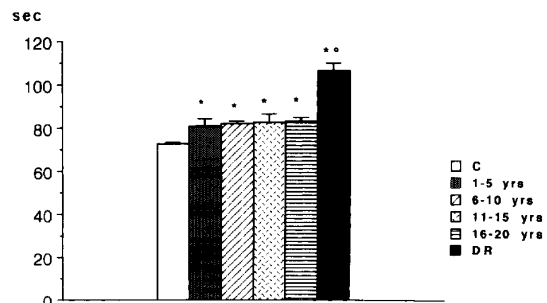


Fig. 8. Histograms of mean values of recovery time after photostress. Error bars represent one standard error of the mean. ANOVA: * $P < 0.01$ vs. C; **DR vs. 1–5, 6–10, 11–15, 16–20 years.

In addition, correlations between VEP abnormalities, peripheral neuropathy and reduced central conduction velocity (Pozzessere et al., 1989) have been observed; furthermore, histological studies (Reske-Nielsen et al., 1965) suggest the presence of optic neuropathy secondary to axonal degeneration due to dysfunction of the ganglion cell body (Martinelli et al., 1987). However, the influence of retinopathy cannot be excluded; in fact, IDDM DR+ patients showed a higher P100 latency and N75-P100 amplitude lower than controls and IDDM DR- patients.

4.4. VEPs after photostress

A major contribution to the VEP is given by the macular activity. An objective method to evaluate the macular function is to record VEP after photostress (Lovasik, 1992; Franchi et al., 1987).

As previously observed macular function assessed by VEP after photostress is impaired in IDDM patients, with and without clinical retinopathy (Parisi et al., 1994). This impairment appears early during the history of the disease: these alterations are not present in newly diagnosed diabetic patients (Parisi et al., 1995b; Uccioli et al., 1995), but are completely developed in diabetic patients with a mean duration of disease as short as 3.3 years. The fact that VEPs after photostress parameters are not further modified in IDDM patients with longer duration of disease indicates a relative stability of the macular function during the disease. The marked deterioration of VEP after photostress associated with the presence of non-proliferative retinopathy indicates a further impairment of the macular function.

VEPs after photostress show an increase in latency and a decrease in amplitude. Van Lith et al. (1978) have shown that miosis induces a P100 prolongation due to a reduction of retinal illumination. Similarly, miosis induced by dazzling could explain the increased P100 latency observed after photostress; since similar values of pupil size are observed after photostress, this factor cannot explain the differences between controls and diabetic patients with longer duration of disease or patients with background diabetic retinopathy.

The VEP recovery to its basal state after photostress depends on the resynthesis of photopigments, a process for which an adequate blood flow seems to be essential (Bianchini et al., 1987) and on the trophism of macula-papillo-macular bundle system (Bucci et al., 1991; Parisi and Bucci, 1992). An involvement of the photoreceptor layer in diabetic patients has been indicated by several studies (Gjotterberg, 1974; Simonsen, 1975; Bresnik and Palta, 1987a,b; Shirao et al., 1991) performed using the flash-ERG. However, since the flash-ERG reflects the activity of the outer layers of the whole retina (Armington, 1974), and the contribution of the macular region is negligible, this test does not give information on the functional status of the macular photoreceptors.

Using the focal ERG, a method for studying the function

of the different layers in the central retina, the photoreceptors appear unaffected; on the contrary, an involvement of the inner retinal layers that showed a selective neurosensory deficit early in the course of diabetes has been observed (Ghirlanda et al., 1991).

Therefore, the impaired macular function, observed in our patients, is likely to be due to a reduced function of the inner retinal layers of the central retina.

The impairment of the macular function in IDDM patients without retinopathy could be related to metabolic control (Strowig and Raskin, 1992). However, the specific role of the metabolic control has not been ruled out from our data because our patients, although in stable metabolic control, were in unsatisfactory glycemic control. We must also underline that newly diagnosed IDDM patients with similar metabolic control do not show any macular impairment (Parisi et al., 1995a; Uccioli et al., 1995), suggesting that this phenomenon, even if appears early, requires some time to fully develop.

4.5. Conclusions

In conclusion, retinal, macular and visual pathways functions are differently impaired in IDDM (DR-) patients with different disease duration.

The nervous conduction of visual pathways is firstly involved, being impaired in newly diagnosed IDDM patients. The function of the innermost retinal layers and of the macula appears to be impaired later, in patients with at least 1 year of duration of disease. Finally, the middle and the outer retinal layers are involved in patients with at least 10 years of disease.

References

- Algan, M., Ziegler, O., Gehin, P., Got, I., Raspiller, A., Weber, M., Genton, P., Saudax, E. and Drouin, P. Visual evoked potentials in diabetic patients. *Diabetes Care*, 1989, 12: 227–229.
- Algvare, P. Studies on the oscillatory potentials of the clinical electroretinogram. *Acta Ophthalmol. (Suppl.)*, 1968, 96: 11.
- Arden, G.B., Hamilton, A.M.P., Wilson-Holt, J., Ryan, S., Yudkin, J.S. and Kurtz, A. Pattern electroretinograms become abnormal preproliferative stage: possible use as a screening test. *Br. J. Ophthalmol.*, 1986, 70: 330–335.
- Armington, J.C. *The Electroretinogram*. Academic Press, New York, 1974.
- Bianchini, E., Franchi, A., Manni, R., Villani, L.G., Cordella, M. and Botta, G.C. Carotid occlusive disease: an electrophysiological macular investigation. *J. Cardiovasc. Surg.*, 1987, 28: 524–527.
- Boschi, M.C., Frosini, R., Menicucci, R. and Sodi, A. The influence of early diabetes on pattern electroretinogram. *Doc. Ophthalmol.*, 1989, 71: 369–374.
- Bresnik, G.H. and Palta, M. Temporal aspects of the electroretinogram in diabetic retinopathy. *Arch. Ophthalmol.*, 1987a, 105: 660–664.
- Bresnik, G.H. and Palta, M. Predicting progression to severe proliferative diabetic retinopathy. *Arch. Ophthalmol.*, 1987b, 105: 810–814.
- Bucci, M.G., Parisi, V., Giannini, R. and Rossini, P.M. Recordings of visual evoked potentials after photostress in artificially increased intraocular pressure. *Clin. Vision Sci.*, 1991, 6: 431–436.
- Caputo, S., Di Leo, M.A.S., Falsini, B., Ghirlanda, G., Porciatti, V., Mine-

- Ila, A. and Greco, A.V. Evidence for early impairment of macular function with pattern ERG in type I diabetic patients. *Diabetes Care*, 1990, 13: 412–418.
- Celesia, G.G., Poleyn, R.E., Holden, J.E., Nickles, R.J. and Gatley, J.S. Visual evoked potentials and PET mapping: can the neuronal potentials generators be visualized? *Electroenceph. clin. Neurophysiol.*, 1982, 54: 243–256.
- Celesia, G.G., Bodis-Wollner, I., Chatrian G.E., Harding, G.F.A., Sokol, S. and Spekrijse, H. Recommended standards for electroretinograms and visual evoked potentials. Report of an IFCN Committee. *Electroenceph. clin. Neurophysiol.*, 1993, 87: 421–436.
- Cirillo, D., Gonfiantini, E., Bongiovanni, L., Robert, J.J. and Pinelli, L. Visual evoked potentials in diabetic children and adolescents. *Diabetes Care*, 1984, 7: 273–275.
- Collier, A. and Mitchell, J.D. Visual evoked potentials and contrast sensitivity function in diabetic retinopathy. *Br. Med. J.*, 1985, 291: 248.
- Comi, G., Martinelli, V., Galardi, G., Medagliani, S., Poggi, A., Beccaria, L., Meschi, F. and Flores D'Arcais, A. Visual evoked potentials in diabetic teenagers: influence of metabolic control and relationship with peripheral neuropathy. *Methods Pediatr. Systems Ophthalmol.*, 1986, 9: 85–87.
- Comi, G., Martinelli, V., Galardi, G., Medagliani, S., Beccaria, L., Meschi, F., Rosti, L., Bressani, N. and Chiumello, G. Evaluation of central nervous conduction by visual evoked potentials in insulin-dependent diabetic children. Metabolic and clinical correlation. *Acta Diabetol. Lat.*, 1987, 24: 157–162.
- Coupland, S.G. A comparison of oscillatory potentials and pattern electroretinograms measures in diabetic retinopathy. *Doc. Ophthalmol.*, 1987, 66: 207–218.
- Falsini, B., Porciatti, V., Scalia, G., Caputo, S., Minnella, A., Di Leo, M.A.S. and Ghirlanda, G. Steady-state electroretinogram in insulin-dependent diabetics with no or minimal retinopathy. *Doc. Ophthalmol.*, 1989, 73: 193–200.
- Fiorentini, A., Maffei, L., Pirchio, M., Spinelli, D. and Porciatti, V. The ERG in response to alternating gratings in patients with diseases of the peripheral visual pathway. *Invest. Ophthalmol. Vis. Sci.*, 1981, 21: 490–493.
- Franchi, A., Magni, R., Lodigiani, R. and Cordella, M. VEP pattern after photostress: an index of macular function. *Graefes Arch. Clin. Exp. Ophthalmol.*, 1987, 225: 291–294.
- Ghirlanda, G., Di Leo, M.A.S., Caputo, S., Falsini, B., Porciatti, V., Marietti, G. and Greco, A.V. Detection of inner retina dysfunction by steady-state focal electroretinogram pattern and flicker in early IDDM. *Diabetes*, 1991, 9: 1122–1127.
- Gjotterberg, M. The electroretinogram in diabetic retinopathy. A clinical study and critical survey. *Acta Ophthalmol.*, 1974, 52: 521–533.
- Hardy, K.J., Fisher, C., Heath, P., Foster, D.H. and Scarpello, J.H.B. Comparison of colour discrimination and electroretinography in evaluation of visual pathways dysfunction in aretinopathic IDDM patients. *Br. J. Ophthalmol.*, 1995, 79: 35–37.
- Hollander, H., Bisti, S., Maffei, L. and Hebel, R. Electroretinographic responses and retrograde changes of retinal morphology after intracranial optic nerve section. *Exp. Brain Res.*, 1984, 55: 483–494.
- Heynen, H., Wachtmeister, L. and Van Norren, D. Origin of the oscillatory potentials in the primate retina. *Vision Res.*, 1985, 25: 1365–1373.
- Jenkins, T.C.A. and Cartwright, J.P. The electroretinogram in minimal diabetic retinopathy. *Br. J. Ophthalmol.*, 1990, 74: 681–684.
- Klein, B.E.K., Davis, M.D. and Segal, P. Diabetic retinopathy: assessment of severity and progression. *Ophthalmology*, 1984, 91: 10–17.
- Lanting, P., Strjers, R.L.M., Bos, J.E., Faes, T.J.C. and Heimans, J.J. The cause of increased pupillary light reflex latencies in diabetic patients: the relationship between pupillary light reflex and visual evoked potential latencies. *Electroenceph. clin. Neurophysiol.*, 1991, 78: 111–115.
- Lovaski, J.V. An electrophysiological investigation of the macular photostress test. *Invest. Ophthalmol. Vis. Sci.*, 1992, 33: 436–442.
- Maffei, L. and Fiorentini, A. Electroretinographic responses to alternating gratings before and after section of the optic nerve. *Science*, 1981, 211: 953–955.
- Maffei, L. and Fiorentini, A. Electroretinographic responses to alternating gratings in the cats. *Exp. Brain Res.*, 1982, 48: 327–334.
- Maffei, L., Fiorentini, A., Bisti, S. and Hollander, H. Pattern ERG in the monkey after section of the optic nerve. *Exp. Brain Res.*, 1985, 59: 423–425.
- Marmor, M.F., Holder, G.E., Porciatti, V., Trick, G.L. and Zrenner, E. Guidelines for basic pattern electroretinography. Recommendation by the International Society for Clinical Electrophysiology of Vision. *Doc. Ophthalmol.*, 1996, 91: 291–298.
- Martinelli, V., Merenda, M., Natali-Sora, M.G., Meschi, F., Beccaria, L. and Comi, G.C. Correlation between pattern electroretinography and visual evoked potentials in diabetes. *Electroenceph. clin. Neurophysiol.*, 1987, 66: S64.
- Martinelli, V., Filippi, M., Meschi, F., Pozza, G., Canal, N. and Comi, G.C. Electrophysiological study of optic pathways in insulin dependent diabetes mellitus. *Clin. Vision Sci.*, 1991, 6: 437–444.
- Ogden, T.E. The oscillatory wave of the primate electroretinogram. *Vision Res.*, 1973, 13: 1059–1074.
- Parisi, V. and Bucci, M.G. Visual evoked potentials after photostress in patients with primary open-angle glaucoma and ocular hypertension. *Invest. Ophthalmol. Vis. Sci.*, 1992, 33: 436–442.
- Parisi, V., Uccioli, L., Monticone, G., Parisi, L., Menzinger, G. and Bucci, M.G. Visual evoked potentials after photostress in insulin-dependent diabetic patients with or without retinopathy. *Graefes Arch. Clin. Exp. Ophthalmol.*, 1994, 232: 193–198.
- Parisi, V., Del Giudice, R., Falleni, C., Bramati, M., Guinetti, C., Pernini, C. and Macchi, A. L'esplorazione elettrofisica delle vie ottiche: metodiche e valori normativi. *Riv. Med. Mil.*, 1995a, 3: 298–305.
- Parisi, V., Uccioli, L., Monticone, G., Parisi, L., Pernini, C., Neuschuler, R., Menzinger, G. and Bucci, M.G. Visual evoked potentials after photostress in newly diagnosed insulin-dependent diabetic patients. *Graefes Arch. Clin. Exp. Ophthalmol.*, 1995b, 233: 601–604.
- Porciatti, V. and Von Berger, G.P. Pattern electroretinogram and visual evoked potentials in optic nerve disease: early diagnosis and prognosis. *Doc. Ophthalmol. Proc. Ser.*, 1983, 40: 117–126.
- Pozzessere, G., Rizzo, P.A., Valle, E., Mollica, M.A., Sanarelli, L., Morano, S., Pietravalle, P., Di Mario, U. and Morocutti, C. A longitudinal study of multimodal evoked potentials in diabetes mellitus. *Diabetes Res.*, 1989, 10: 17–20.
- Pragar, T.C., Garcia, C.A., Mincher C.A., Mishra, J. and Chu, H.H. The pattern electroretinogram in diabetes. *Am. J. Ophthalmol.*, 1989, 109: 279–284.
- Puvanenderan, K., Davethasan G. and Wong, P.K. Visual evoked responses in diabetes. *J. Neurol. Neurosurg. Psychiatry*, 1983, 46: 543–547.
- Reske-Nielsen, E., Lundbeak, K. and Rafeelsen, O.J. Pathological changes in the central and peripheral nervous system of young long-term diabetics (diabetic encephalopathy). *Diabetologia*, 1965, 1: 233–241.
- Ristanovic, D. and Haidukovic, R. Effects of spatially structured stimulus field on pattern reversal visual evoked potentials. *Electroenceph. clin. Neurophysiol.*, 1981, 51: 599–610.
- Sartucci, F., Tognoni, G., Guerrini, V., Calisti, L., Federico, G., Saggese, G. and Murri, L. Combined use of pattern electroretinogram and visual evoked potentials in evaluation of early visual system involvement in type I diabetic children and adolescents. *Ital. J. Clin. Neurophysiol.*, 1993, 2: 10–24.
- Shirao, Y., Okumura, T., Ohta, T. and Kawasaki, K. Clinical importance of electroretinographic oscillatory potentials in early detection and objective evaluation for diabetic retinopathy. *Clin. Vision Sci.*, 1991, 6: 445–450.
- Simonsen, S.E. Prognostic value of ERG (oscillatory potentials) in juvenile diabetics. *Acta Ophthalmol.*, 1975, 123 (suppl.): 223–224.
- Strowig, S. and Raskin, P. Glycemic control and diabetic complications. *Diabetes Care*, 1992, 15: 1126–1140.
- Tomoda, H., Celesia, G.G. and Toleikis, S.C. Effect of spatial frequency

- on simultaneous recorded steady-state pattern electroretinograms and visual evoked potentials. *Electroenceph. clin. Neurophysiol.*, 1990, 80: 81–88.
- Trick, G.L. Pattern evoked retinal and cortical potentials in diabetic patients. *Clin. Vision Sci.*, 1991, 6: 209–217.
- Trick, G.L., Burde, R.M., Gordon, M.O., Kilo, C. and Santiago, J.V. Retinocortical conduction time in diabetics with abnormal pattern reversal electroretinogram and visual evoked potentials. *Doc. Ophthalmol.*, 1988, 70: 19–28.
- Trimarchi, C., Biral, G., Domenici, L., Porciatti, V. and Bisti, S. The flash and pattern electroretinogram generators in the cat: a pharmacological approach. *Clin. Vision Sci.*, 1990, 6: 19–24.
- Uccioli, L., Parisi, V., Monticone, G., Parisi, L., Durola, L., Pernini, C., Neuschuler, R., Bucci, M.G. and Menzinger, G. Electrophysiological assessment of visual pathways in newly diagnosed IDDM patients. *Diabetologia*, 1995, 38: 804–808.
- Van Lith, G.H.M., Van Marle, G.W. and Van Dokmak, G.T.M. Variation in latency times of visually evoked cortical potentials. *Br. J. Ophthalmol.*, 1978, 62: 220–222.
- Wachtmeister, L. and Dowling, J.E. The oscillatory potentials of the mudpuppy retina. *Invest. Ophthalmol. Vis. Sci.*, 1978, 17: 1176–1188.
- Wanger, P. and Persson, H.E. Early diagnosis of retinal changes in diabetes. A comparison between electroretinography and retinal biomicroscopy. *Acta Ophthalmol.*, 1985, 63: 716–720.
- Ziegler, O., Guerci, B., Algan, M., Lonchamp, P., Weber, M. and Drouin, P. Improved visual evoked potentials latencies in poorly controlled diabetic patients after short-term strict metabolic control. *Diabetes Care*, 1994, 10: 1141–1147.