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Impaired saccadic eye movement in diabetic patients: the relationship with visual pathways function

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Abstract. The aim of this study was to evaluate whether a correlation existed between saccadic eye movements and visual pathways function in diabetic patients. Saccadic or fast Eye Movement System (EMS) and Visual Evoked Potentials (VEPs) were assessed in 20 insulin-dependent diabetic mellitus (IDDM) patients without long-term complications and in stable metabolic control and in 21 age-matched control subjects. In IDDM patients we observed significantly ($p<0.01$) longer EMS latency, while EMS velocity and accuracy were similar to those of controls; VEPs showed a significant delay in N75, P100, N145 latencies and significant reduction of N75-P100 and P100-N145 amplitudes. In IDDM patients no relationships between EMS and VEP parameters were found. In conclusion, EMS latency delay suggests an impairment of the saccadic eye movement system, while impaired VEPs may be ascribed to a dysfunction of the visual pathways. The lack of correlation between VEPs impairment and EMS latency delay suggests that in our IDDM patients the delay of saccadic latency cannot be exclusively related to a visual pathways dysfuction and could be ascribed to a diffuse neuronal involvement.

Key words: diabetes, saccadic movements, visual evoked potentials, visual pathways

Introduction

The saccadic or fast Eye Movement System (EMS) is the ocular motor system which allows the eyes to move rapidly in order to fixate an intended target on the fovea [1]. The triggering peripheral stimulus of saccadic eye movement is the central and peripheral retinal input travelling through the visual pathways [2]. Reports exist about prolonged reaction time of the saccadic movements in diabetic patients [3], however it is not clear if this is caused by impairment of the afferent or the efferent system. The functional integrity of the whole afferent visual system can be assessed by recordings of Visual Evoked Potentials (VEPs) that represent a mass response of cortical, and possibly subcortical, visual areas to visual stimuli [4]. Several reports have shown VEP impairment in diabetic patients [5–10], indicating a dysfunction in the visual pathways.

In this study we examined both the saccadic eye movements and the visual evoked potentials in insulin-dependent diabetic mellitus (IDDM) patients and normal controls with the aim to evaluate whether a correlation existed between the saccadic eye movement and the visual pathways function.

Subjects and methods

Forty-one subjects were enrolled in the study. Each subject showed normal visual field (Goldmann perimetry), normal intraocular pressure (< 21 mmHg) and best corrected visual acuity of 10/10, and was free of any labyrinthine and/or neurological signs or symptoms. The subjects were distributed into two groups; Group C: 21 control subjects (mean age 31.7 $\pm$4.1 years); Group IDDM: 20 insulin-dependent diabetic (Type I) patients without neuropathy or retinopathy (mean age 25.7 $\pm$ 8.7 years). Diabetic peripheral neuropathy was excluded according to the San Antonio Consensus Conference guidelines [11]. Retinopathy was assessed by fluorescein angiography and, only patients without signs of retinopathy (level one, according to the Klein levels [21]) were included in the study. The IDDM patients had not exhibited ketoacidosis or diabetic coma during the two months preceeding the study, and only patients with stable metabolic control (HbA1c less than 8%) were included in the study. After informed consent, the following tests were performed in all subjects.

Saccadic or fast Eve Movement System (EMS)

The electronystagmographic examination of the eye movements on the horizontal axis was performed by projecting a bright spot onto a horizontal bar 100 centimeters long placed 100 centimeters in front of the subject examined. During the examination, the subject was seated in a semi-darkened room on a comfortable chair with his head fixed by an occipital support. Silver-silverchloride electrodes were fixed with collodium at the outer canthus of each eye, and the reference electrode was located on the forehead. The interelectrode resistance was maintained lower than 8 KOhms. The analog signal was amplified (gain 20.000), digitized and stored in a PC (Compaq 286n) for later analysis. The equipment employed was a three-channel computerized electronystagmography package (SITER, Racia, Bordeaux, France) and an automatic light bar visual stimulator (SOMAU, Racia, Bordeaux, France). The calibration of eye movements was performed at the beginning of each session. The eye movements recorded during calibration were then presented on the computer display to allow the operator to verify the correct calibration. Saccadic movements were induced by a series of lights, generated by LEDs,

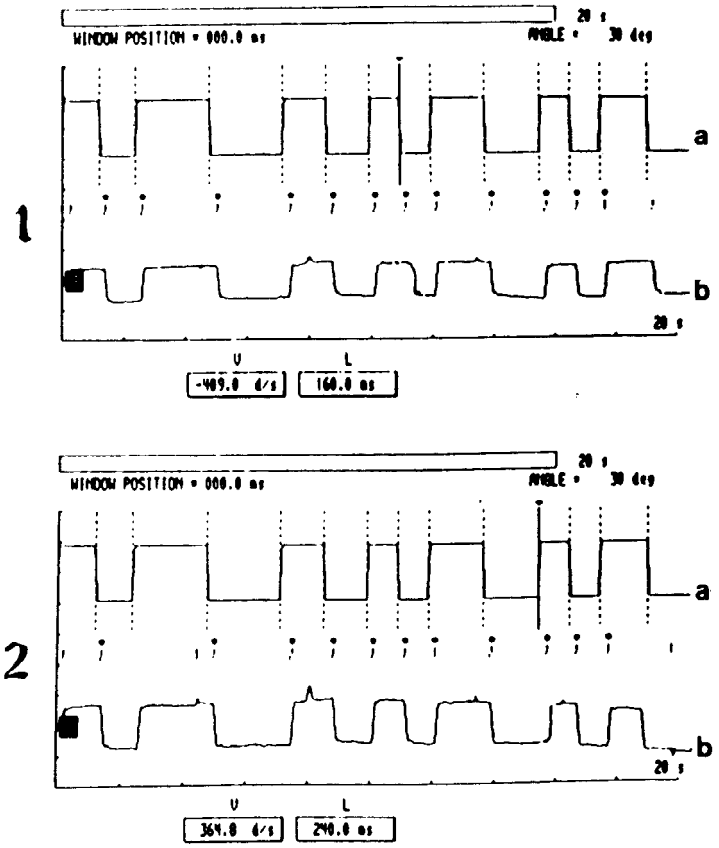

Figure 1. Examples of EMS recordings from a control subject (1) and from an IDDM patient (2). a: target position; b: subject tested layout; V: eye maximum velocity (deg/s); L: latency (ms).

separated by known angles and moved through a series of stepwise jumps. The patients followed the light which was switched on at a position of 15 degrees at each side of the primary position. This generated 30 degrees saccades with inter-saccade interval between I and 5 seconds, the analysis time was 40 s. We assessed at least three records in order to check the repeatability of the waveforms obtained. Examples of ENG layout of EMS are shown in Figure 1. The following parameters were analyzed:

– Latency (delay in milliseconds) between the start of the target movement and the start of saccades;

– Peak velocity (degrees/second): maximum eye velocity during the saccade;

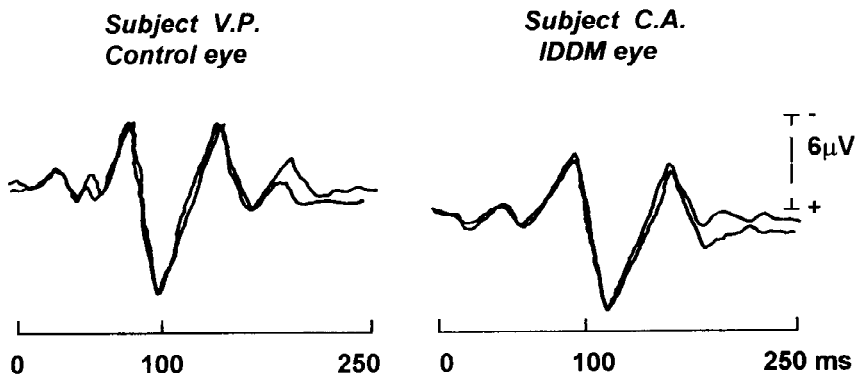

Figure 2. VEP recordings of a control subject (V.P.) and of a IDDM patient (C.A.). In the IDDM patient the recordings show delayed latencies and reduced amplitudes when compared to the control ones.

– Accuracy (%): defined as the ratio of the saccade amplitude derived from the target displacement amplitude. We considered a saccade amplitude $\pm 15\%$ of the target amplitude inaccurate [2, 3].

Visual Evoked Potentials (VEPs)

Details about the method of VEP recordings applied here have previously been published [13]. Under examination the subjects were seated in an acoustically isolated room in front of the display that was surrounded by a uniform field luminance of 5 cd/m^2. Prior to the experiment, each subject was adapted to the room light for 10 minutes and the pupil diameter was about 5 millimeters. Mydriatic or miotic drugs were never used. The stimulation was monocular, after occlusion of the other eye. The visual stimuli were checkerboard patterns (contrast 70%, mean luminance 110 cd/m^2) generated on a TV monitor and reversed in contrast at the rate of two reversals. At the viewing distance of 114 centimeters the single check size subtended 15 min of visual arc. The screen of the monitor subtended 18 degrees and in order to maintain stable fixation a small target (0.4°) was placed in the center of the stimulation field. Cup shaped electrodes of silver-silver-chloride were fixed with collodium in the following positions: active electrode at Oz, reference electrode at Fpz, ground on left arm. The interelectrode resistance was kept below 3 KOhm. The signal was amplified (gain 20000), filtered (band-pass 19100 Hz) and averaged with automatic rejection of artifacts (100 events free from artifacts were averaged for every trial) using a DM6000 apparatus (Biomedica Mangoni, Pisa, Italy). The analysis time was 500 milliseconds. The resulting waveforms were superimposed to check for the repeatability of the results. The transient response was characterized by several waves with

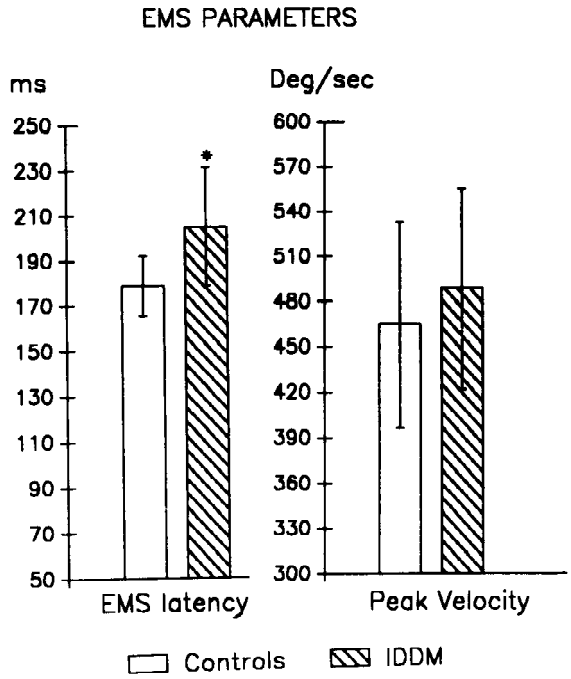

Figure 3. Graphic representation of mean values of EMS parameters. Error bars represent one standard deviation of the mean. *: $p<0.01$ vs controls.

three peaks, that in normal subjects appeared after 75, 100 and 145 ins. These peaks had negative (N75), positive (P100) and negative (N145) polarity, respectively. For all VEPs recorded, the peak latency and the peak amplitude of each of the waves were measured directly on the displayed records by means of a pair of cursors. Examples of VEP recordings are shown in Figure 2.

Statistics

All results are expressed as mean ± standard deviation (SD). Analysis of variance (ANOVA) was performed in order to evaluate the differences between IDDM and Control groups. The correlations between EMS and VEP parameters were evaluated by Pearson's test. $P<0.01$ was considered significant.

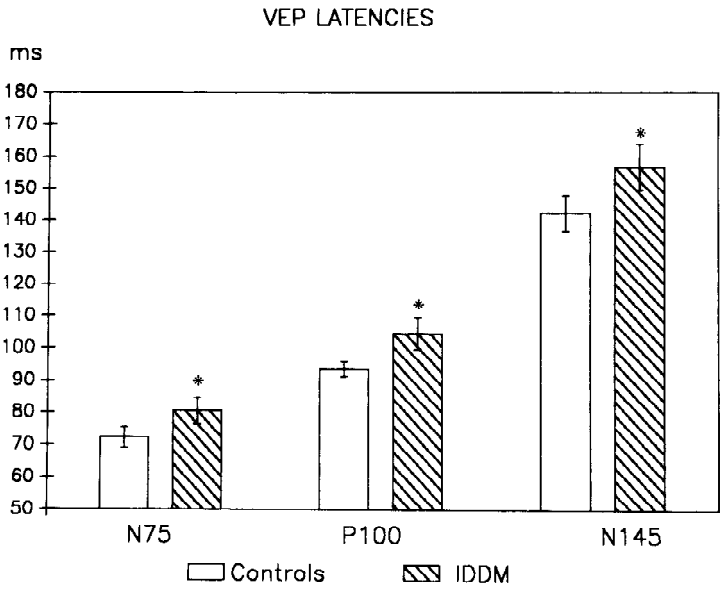

Figure 4. Graphic representation of mean values VEP latencies. Error bars represent one standard deviation of the mean. *: $p<0.01$ vs controls.

Results

Saccadic or Eye fast Movement System (EMS)

The mean data are presented in Figure 3. In IDDM patients we found EMS latency significantly delayed with respect to controls [$F(1, 39)= 16.49$, $p<0.01$], while peak velocity was similar to controls [$F(1, 39)= 2.42$, $p<0.128$]. No inaccurate or morphologically abnormal saccades were detectable in Controls and IDDM subjects.

Visual Evoked Potentials (VEPs)

The mean data are reported in Figure 4. In control subjects the VEP parameters (N75, P100 and 145 latencies and N75-P100 and P100-N145 amplitudes) were within our 95% confidence intervals [13]. In IDDM patients VEP latencies and amplitudes were both impaired when compared with those of controls. N75, P100 and N145 latencies were significantly delayed [respectively: $F(1, 39)= 52.30$, $p<0.01$; $F(1, 39)= 85.59$, $p<0.01$; $F(1, 39)= 52,51$, $p<0.01$] with respect to those of controls. N75-P100 and P100-N145 amplitudes were significantly reduced [respectively: $F(1, 39)= 60.43$, $p<0.01$; $F(1, 39)= 16.78$, $p<0.01$] with respect to control ones.

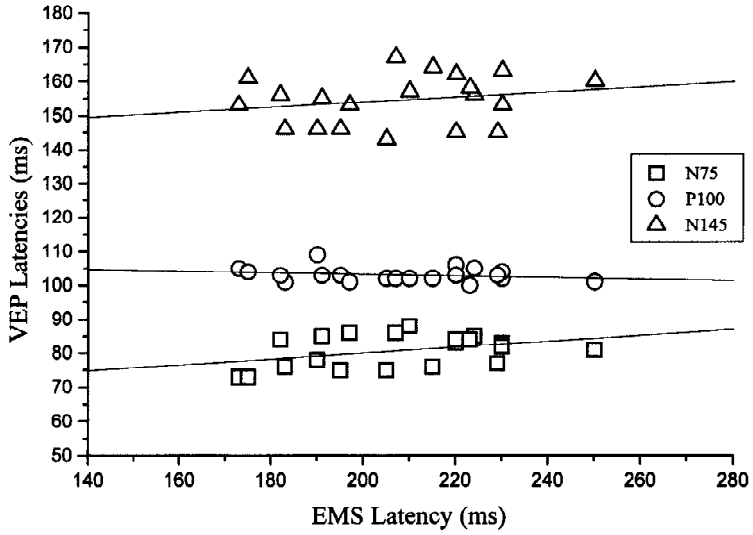

Figure 5. VEP N75, P100 and N145 latencies plotted against EMS latency. Linear regression analysis: N75 vs EMS (r=0.383, t=4.570, p=0.096); P100 vs EMS (r=0.246, t=2.055, p=0.295); N145 vs EMS (r=0.229, t=7.313, p=0.375).

EMS vs VEPs

In IDDM patients EMS parameters (EMS latency, EMS velocity) were matched to VEPs parameters (N75, P100 and N145 latencies; N75-P100 and P100-N145 amplitudes): the statistical analysis did not reveal any significant correlations. In Figure 5 are presented the relationship between the delay in EMS latency and the delay in VEPs latencies.

Discussion

Our study indicates that EMS latency is impaired in IDDM patients. This is in agreement with previous studies [3]. Since saccadic eye movement results from sensory input, central nervous system control and motor outputs [2], its impairment might be ascribed to a selective or widespread involvement of the visual pathways, or different central nervous system areas, or of the oculomotor neuromuscular structures. EMS parameters can be differently influenced by various brain areas: specifically EMS peak velocity seems to be related to brainstem reticular formation function, while EMS latency seems to depend mainly on higher function [2]. However, an increase of EMS latency may be found in the case of reduced transmission velocity of central neural pathways and also in the presence of impaired visual pathways [2, 14].

We focused our attention on the contribution of the visual pathways function to EMS impairment in IDDM patients. In our IDDM patients with impaired EMS latency, VEPs revealed impaired function of the visual pathways (increased N75, P100, N145 latencies and reduced N75-P100 and P100-N145 amplitudes) in the absence of retinopathy and in the presence of a normal visual acuity. It is known that VEPs represent a mass response of cortical and possibly subcortical visual areas to visual stimuli [4]; nevertheless, different structures of the visual system may contribute to the impaired VEP responses observed in IDDM patients. The different visual system structures can be evaluated by several electrophysiological methods such as Electroretinographic signals (ERGs) evoked by flash or patterned stimuli that reveal the bioelectric activity of different retinal layers [15, 16], VEPs after photostress that represent an objective way to evaluate the macular function [17], simultaneous recordings of VEP and Pattern-ERG that give an index of neural conduction in the postretinal visual pathways [18]. Impaired function of the outer, middle and innermost retinal layers [19–27], of the macula [13, 28, 29] and of neural conduction in the postretinal visual pathways [26] has been observed in diabetic patients. This leads us to believe that an involvement of the different structures may contribute to the VEP abnormalities observed. We recently observed that retinal, macular and visual pathways function are differently impaired in IDDM patients with different disease duration and without signs of retinopathy: the 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 [13].

Since we found both EMS and VEP impaired responses in IDDM patients, we performed the analysis between EMS and VEP parameters to evaluate the contribution of the visual pathways dysfunction to prolonged saccadic latencies. The lack of correlation between the VEPs impairment and the EMS latency delay suggests that the latter cannot be exclusively ascribed to the dysfunction observed in the visual pathways. This suggests that other neural structures may be involved in the delay of EMS latency in IDDM patients. Our results are in accordance with another analogous study in which the pupillary light reflex was matched with the visual pathways function in IDDM patients: no correlation between pupillary light reflex and VEP were found [8].

In conclusion, in our IDDM patients the delay of saccadic latency cannot be exclusively related to a visual pathways dysfunction and could be ascribed to a diffuse neuronal involvement [30].

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