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Influence of the metabolic control on latency values of visual evoked potentials (VEP) in patients with diabetes mellitus type 1

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ABSTRACT

The aim of our study was to investigate the relationship between the metabolic control parameters of diabetes mellitus (glycemia and HbA_{1c}) and visual evoked potentials (VEP) latency values. The study included 61 patients with diabetes mellitus type 1 that were hospitalized at the Clinic for Endocrinology, Diabetes and Metabolic Diseases due to poor metabolic control. All patients were divided into 3 groups. Group 1 consisted of patients on conventional insulin therapy (CT); Group 2 included patients on CT at the moment of hospitalization, with a change towards intensified insulin therapy (IIT); and Group 3 consisted of patients on IIT. Patients with diabetic retinopathy (DR) were excluded from the study. Metabolic control (glycemia and HbA_{1c}) and VEP parameters were compared at the beginning of the study and six months later. After six months of strict glycoregulation, significant improvement in VEP parameters was followed by significant improvement of evaluated parameters of metabolic control. We found statistically significant reduction in frequency of pathological VEP findings, prolonged P100 latency and low amplitude potentials in Group 2, while in Groups 1 and 3 we found that these parameters did not significantly change but the frequencies were lower. The results of our study confirmed that with good glycoregulation there is expectable improvement in VEP findings, even after short period of time. If changes in the retina could be detected before DR is noticed using this noninvasive diagnostic procedure and include patients in a strict glycoregulation, we could be in the position to prevent to the certain degree serious complications that may cause blindness.

Key words

Diabetes mellitus • Visual evoked potentials • Metabolic control • Diabetic retinopathy • Insulin therapy

Introduction

Diabetes mellitus (DM) is one of the most frequent and widely spread chronic diseases of the modern man. There is an increase of Type 1 DM (DM1) incidence over the time particularly in younger population (Patterson et al., 2009; Ostrauskas et al., 2011). As it is known, DM1 is associated with numerous microvascular complications: retinopathy, neuropathy and nephropathy, as well as macrovascular complications: cardiovascular, cerebrovascular and peripheral vascular (DCCT Research Group, 1993; DCCT Research Group, 1995; Hammes et al., 2011). Previously it was stressed out that DM1 is one of the important factors of avoidable blindness, and that glycemic regulation as well as maculopathy

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at baseline could be taken as risk factors for blindness (Grauslund, 2011).

It is estimated that 95% of DM1 patients will develop diabetic retinopathy (DR) over lifetime (Kramer et al., 2011). In the Unites States, DR is one among four most prevalent etiologies of vision loss in persons aged 40 years and older (Rosenberg and Sperazza, 2008). The severity of DR as DM1 complication refers to the fact that it is associated with the increased all-case and cardiovascular mortality risk (Kramer et al., 2011). Therefore, timely diagnosis and prompt treatment are of great benefit for the prevention of complications progression.

Up-to-now investigations regarding effects of DM1 metabolic control on the occurrence and development of DR have shown that in half of the patients, DR is initially decreased if good metabolic control is achieved. Further, it has been shown that there is a significant influence of DM1 metabolic control on visual evoked potentials (VEP) latency that is more expressed in newly disclosed DM1 patients (Liu et al., 1993; Parisi et al., 1997; Fierro et al., 1999). By VEP testing, information on the macular (central) area, optic nerve and higher central lesions can be obtained. In DM1 and DM type 2 (DM2) population above 14 years of age, after the new diagnosis criteria and strict metabolic control have been introduced, there is decrease in the prevalence of DR in DM2, but not in DM1 (Romero-Aroca et al., 2009). We hypothesized that VEP as noninvasive procedure, can be used to analyze the response of the optical nerve and optical brain center on light stimuli, and could be the one of potential tools for the early discovery of DR and prognosis during metabolic control and treatment. Visual evoked potentials changes could be detected in asymptomatic patients and thus be the predictors of future symptoms (Parisi et al., 1997).

Therefore, the objective of our study was to investigate the relationship between the metabolic control parameters of diabetes mellitus (glycemia and HbA_{1c}) and latency values of visual evoked potentials.

Material and methods

Study group

The study included 61 eligible patients with DM1, with mean age of 30.4 ± 8.3 years (age range from 13-41 years), that were hospitalized due to the poor control of the DM1 at the Clinic for Endocrinology, Diabetes and Metabolic Diseases of the Clinical Center of Serbia in Belgrade. Only patients that fulfilled strict criteria of good glycoregulation over one year period were included in the study. Mean duration of DM for included participants was 5.96 ± 2.88 years. Body mass index was 21.17 ± 2.20 kg/m^2. In total, there were 44 male patients and 17 female patients.

While hospitalized study participants were educated in self-control of glycemia status. During the period of six months, patients were encouraged to achieve good glycoregulation. The presence of DR was excluded by ophthalmologic examination in all patients at the inclusion time. Prior inclusion in the study patients were informed about the study protocol and informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki.

All patients were divided into 3 groups according to the applied insulin therapy: Group 1 (19 patients on conventional insulin therapy (CT)); Group 2 (21 patients on conventional insulin therapy at the time of hospitalization that was later corrected by intensified insulin therapy (IIT)) and Group 3 (21 patients on IIT (4 doses per day)). Regarding the time of observation 3 groups of patients were compared at 2 time periods: group at the beginning of the study and group at the end of the study.

Ophthalmologic and neurological examinations were done in all patients. Ophthalmologic examination and in some cases with fluorescein angiography was used to exclude the presence of either retinopathy, increased blood pressure or any other ocular disease. Patients with diagnosed retinopathy, cataract, refractory anomalies, migraine, thyroid dysfunction and other conditions that might alter VEP findings were excluded from the study.

Study parameters

Further parameters of metabolic control were analyzed: glycemia levels (mmol/l), HbA_{1c} (%), as well as albumin values (mmol/l) and neurophysiologic parameters of VEP evaluation (N75 (ms), P100 (ms), N145 (ms) and amplitude (μV) for OS, OD and OU as well as difference in latency). Metabolic control parameters were drawn from the blood in the morning before meal. The VEP testing was done utilizing a structured light-emitting pattern-reversal with contrast of 100% and light adapted to medium luminance of 100 cd/m^2 measured at the angle of 15 minutes by

monocular and binocular stimulation in a dark room. For stimulation we used checkerboard patterns of single check size of about 1 degree of an arc. The entire visual angle was 18 degrees and the distance from the monitor 120 cm (Ristanovic and Hajdukovic, 1981). Silver-silver electrodes were placed on the scalp with the reference electrode at Fz, ground at Cz and active electrode at Oz according to PI of the International 10/20 System (Odom et al., 2004). The electrode impendence was set to be below 5 kΩ. Filter was positioned in the range of 1-250Hz. Analysis time was 500 ms, with the stimulus repeated period of 2/sec, and the number of repeated stimuli 256 in two series. The registered findings of VEP parameters were characterized as pathological or abnormal if there were prolonged P100 latency potentials, lowered amplitude potentials and increased interocular latency. The attributive characteristics that were evaluated included: pathological VEP findings, lower amplitude and prolonged P100 latencies.

Statistical analysis

All the data were presented as mean values with standard deviation (SD) for descriptive results for continuous variables, while categorical data were presented as percentages. The Wilcoxon signed rank test of matched pairs was carried out for each group separately at two points in time. For the analysis of attributive characteristics, we used the nonparametric Kruskal-Wallis and McNemars tests. Statistical significance was set on $p < 0.05$, non statistical significance was presented as 'n.s.' ($p > 0.05$).

Results

At the beginning of the study no statistically significant difference was found for the metabolic control parameters in any of the evaluated groups ($p > 0.05$) (Tables I-III). At that point all studied patients were poorly regulated in regard to the parameters of metabolic control, particularly HbA_{1c} (Tables I-III).

We found statistically significant difference in the favor of good metabolic regulation in patients on control check-up, while there was not significant difference in albumin values (Table I). There were highly significant differences regarding improvement in the values of glycemia and HbA_{1c} ($p < 0.01$), as the most important parameters indicating good metabolic regulation (Table I).

Statistically significant improvement (shortening) of tested VEP P100 latency potentials on both eyes by monocular stimulation was noticed (for OS and OD, $p < 0.01$) as well as differences in P100 OU latencies to be on the border of statistical significance ($p \approx 0.05$) (Table I). There was significant improvement for N145 OD latencies ($p < 0.05$) and for amplitude OS ($p < 0.05$) (Table I). Comparing attributive characteristics regarding VEP formation (pathological findings, lower amplitude and prolonged P100 latencies), we found non significant change of categorized characteristics. Good glycoregulation recorded in Group 1 at the end of the study also led to the registration of improved VEP parameters, primarily of P100 latency for OD, OS and OU.

In Group 2 we registered a significant statistical difference regarding improvement of glycoregulation parameters (Table II). A statistically significant difference was recorded on control check-up regarding glycemia and HbA_{1c} values ($p < 0.01$).

When VEP parameters from Group 2 where compared at the beginning and at the end of the study, improved VEP findings were noticed. These findings were followed by registered improvement of glycoregulation parameters (Table II). There was a statistically significant difference regarding improvement of P100 latency potentials (shorter) (for OD, OS and OU, $p < 0.01$), followed by improvement in N145 latency (for OD $p < 0.01$; and OS and OU, $p < 0.05$) and P100 amplitude potentials (for OD and OS $p < 0.05$), as well as the difference of interocular latency ($p < 0.05$).

We found highly statistically significant reduction in frequency of pathological VEP findings and highly statistically significant improvement (shortening) for registered P100 latency potentials in Group 2 ($p < 0.01$) (Table II). Concerning P100 amplitude potential there was statistically significant reduction in frequency of low amplitude ($p < 0.05$) (Table II). In Group 2 improved glycoregulation was followed by induced improvement of VEP parameters.

In Group 3 we registered a highly statistically significant improvement regarding the values of glycoregulation parameters both for glycemia and HbA_{1c} ($p < 0.01$) (Table III).

By testing the observed VEP parameters, we registered a highly statistically significant improvement (shortening) of P100 potentials for mononuclear

Table I. - Mean values of metabolic control and VEP parameters at the beginning and end of the study in Group 1.

Group 1			
Evaluated parameters	At the beginning of the study	At the end of the study	P value
Metabolic parameters			
Glycemia (mmol/l)	10.17 ± 5.99	7.12 ± 1.94	*< 0.01*
HbA_{1c} (%)	10.46 ± 3.02	7.50 ± 0.90	*< 0.01*
Albumin (mmol/l)	41.89 ± 3.17	41.94 ± 3.06	n.s.
Insulin dosage (U/kgTT)	0.43 ± 0.19	0.45 ± 0.18	n.s.
VEP parameters			
N75 OD (ms)	76.43 ± 3.32	76.37 ± 2.97	n.s.
P100 OD (ms)	109.04 ± 16.09	107.52 ± 14.49	*< 0.01*
N145 OD (ms)	145.42 ± 16.91	144.00 ± 15.07	*< 0.05*
Amplitude OD (μV)	11.00 ± 5.08	10.73 ± 3.81	n.s.
N75 OS (ms)	76.84 ± 4.54	76.53 ± 3.76	n.s.
P100 OS (ms)	110.17 ± 16.71	108.53 ± 14.74	*< 0.01*
N145 OS (ms)	145.63 ± 18.17	142.47 ± 14.64	n.s.
Amplitude OS (μV)	8.68 ± 4.90	10.73 ± 3.84	*< 0.05*
Difference in latency	2.18 ± 2.22	2.26 ± 2.07	n.s.
N75 OU (ms)	75.55 ± 4.42	76.00 ± 3.04	n.s.
P100 OU (ms)	108.24 ± 14.76	108.78 ± 13.30	*≈ 0.05*
N145 OU (ms)	146.05 ± 17.60	144.63 ± 13.38	n.s.
Amplitude OU (μV)	9.68 ± 4.08	10.82 ± 3.88	*≈ 0.05*
Attributive characteristics			
Pathological VEP	9/19 (47.3%)	6/19 (31.5%)	n.s.
Low amplitude	5/19 (26.3%)	4/19 (21.1)	n.s.
Prolonged latency	7/19 (36.8)	6/19 (31.5)	n.s.

stimulation on both eyes (for OD and OS, $p < 0.01$), as well as borderline significant improvement for P100 latency potentials during binocular stimulation ($p \approx 0.05$). We also registered a highly statistically significant improvement (shortening) of interocular latency difference ($p < 0.01$) (Table III).

By categorizing the attributive characteristics in Group 3, we found that they did not significantly change but the frequencies were lower (Table III). In group 3 we registered improvement of glycoregulation that was also followed by the improvement of the observed VEP parameters (Table III).

Discussion

At the beginning of the study, based on the analyzed glycoregulation parameters, glycemia and HbA_{1c}, according to the American Diabetes Association Clinical Practice Recommendations 2001 (2001), the observed patients were classified into a group with poorly regulated metabolism. On the examination day mean glycemia value was 9.45 ± 4.95 mmol/l. The value of HbA_{1c}, as a parameter of long-term metabolic control, was 10.65 ± 2.01%. Such values present indicators of poor glycoregulation in studied population prior inclusion in the study. After the period of six months we have shown that there was significant improvement of glycoregulation ($p < 0.01$), decrease of mean values of glycemia and HbA_{1c}, in all 3 groups of evaluated patients, classifying these participants into a well regulated group. By the introduction of insulin therapy (IIT), the DCCT Research Group has indicated the possibility of delaying the occurrence of retinopathy, as well as a slowing-down the progression of microvascular complications. By utilizing IIT and the reduction of HbA_{1c} by 1.4%, Hanssen et al. registered a decreased risk of the development of retinopathy and nephropathy (Hanssen, 1997).

Table II. - Mean values of metabolic control and VEP parameters at the beginning and end of the study in Group 2.

Group 2			
Evaluated parameters	At the beginning of the study	At the end of the study	P value
Metabolic parameters			
Glycemia (mmol/l)	8.49 ± 3.84	6.74 ± 1.47	< 0.01
HbA_{1c} (%)	10.14 ± 2.32	7.22 ± 0.63	< 0.01
Albumin (mmol/l)	41.24 ± 5.79	41.23 ± 5.16	n.s.
Insulin dosage (U/kgTT)	0.46 ± 0.26	0.53 ± 0.25	< 0.01
VEP parameters			
N75 OD (ms)	73.25 ± 6.14	72.86 ± 4.79	n.s.
P100 OD (ms)	105.48 ± 8.41	101.03 ± 5.73	*< 0.01*
N145 OD (ms)	149.95 ± 15.60	143.76 ± 10.88	*< 0.01*
Amplitude OD (μV)	10.76 ± 3.57	12.24 ± 3.59	*< 0.05*
N75 OS (ms)	75.19 ± 4.81	74.33 ± 4.75	n.s.
P100 OS (ms)	105.82 ± 9.56	101.53 ± 6.69	*< 0.01*
N145 OS (ms)	148.86 ± 16.04	141.81 ± 10.42	*< 0.05*
Amplitude OS (μV)	10.71 ± 4.15	12.00 ± 3.48	*< 0.05*
Difference in latency	3.23 ± 2.98	2.30 ± 2.10	*< 0.05*
N75 OU (ms)	74.79 ± 4.19	74.76 ± 4.49	n.s.
P100 OU (ms)	105.95 ± 9.46	103.33 ± 8.37	*< 0.01*
N145 OU (ms)	150.95 ± 17.29	144.57 ± 14.42	*< 0.05*
Amplitude OU (μV)	11.76 ± 4.74	11.95 ± 3.84	n.s.
Attributive characteristics			
Pathological VEP	11/21 (52.4%)	3/21 (14.2%)	*< 0.01*
Low amplitude	7/21 (33.3%)	4/21 (19.0%)	*< 0.05*
Prolonged latency	9/21 (42.8%)	3/21 (14.2%)	*< 0.01*

Previous findings shown that prolonged latencies, particularly P100, could occur and be registered very early in patients with DM1 (Sima et al., 1992; Karlica et al., 2010). Later published studies indicated differences between P100 latency potentials of healthy population and patients with DM1 (Ziegler et al., 1994; Parisi et al., 1997). It is possible as well to register prolonged VEP P100 latencies in patients with insulin-independent and insulin-dependent diabetes mellitus (Szabela et al., 2005a,b). This noninvasive diagnostic procedure (Aguggia et al., 1993) can register prolonged VEP latencies even without any clinical changes in the visual system and in newly disclosed patients with DM1 (Bergamaschi et al., 1991; Akinici et al., 1994; Uccioli et al., 1995; Parisi et al., 1998).

Our results showed that the mean values of P100 latency potentials were considerably prolonged in relation to healthy population (Odom et al., 2004), although being within the physiological range. No statistically significant difference was detected at the beginning of the study regarding the registered VEP parameters among the studied groups ($p > 0.05$), presenting the similar pathological changes before inclusion into the therapy for the entire evaluated group of patients.

We have demonstrated that for the patients with excluded changes in term of retinopathy, it was possible to register a considerable prolongation of P100 latency potentials in relation to healthy population. In 47.54% (29/61) of patients we registered VEP pathological findings at the beginning of the study, while in 39.35% (24/61) of patients prolonged latencies were registered. Such findings are also in accordance with previous studies (Sima et al., 1992; Akinici et al., 1994; Uccioli et al., 1995; Parisi et al., 1997; Parisi et al., 1998; Szabela et al., 2005b).

Recognizing that changes can be found by VEP registration which are in correlation with increased values of glycemia and HbA_{1c}, as well as changes

Table III. - Mean values of metabolic control and VEP parameters at the beginning and end of the study in Group 3.

Group 3			
Evaluated parameters	At the beginning of the study	At the end of the study	P value
Metabolic parameters			
Glycemia (mmol/l)	9.75 ± 4.97	6.87 ± 1.35	*< 0.01*
HbA_{1c} (%)	11.33 ± 2.44	7.51 ± 0.80	*< 0.01*
Albumin (mmol/l)	41.90 ± 3.22	41.95 ± 2.82	n.s.
Insulin dosage (U/kgTT)	0.64 ± 0.25	0.66 ± 0.23	*< 0.05*
VEP parameters			
N75 OD (ms)	75.62 ± 5.20	75.33 ± 3.62	n.s.
P100 OD (ms)	109.90 ± 15.52	106.95 ± 13.27	*< 0.01*
N145 OD (ms)	148.71 ± 19.28	145.24 ± 16.82	n.s.
Amplitude OD (μV)	10.14 ± 3.76	10.33 ± 3.24	n.s.
N75 OS (ms)	75.19 ± 5.27	75.05 ± 3.46	n.s.
P100 OS (ms)	112.35 ± 18.77	107.81 ± 13.95	*< 0.01*
N145 OS (ms)	149.76 ± 21.14	147.09 ± 18.59	*< 0.05*
Amplitude OS (μV)	10.19 ± 3.90	10.95 ± 3.28	n.s.
Difference in latency	4.13 ± 5.58	2.28 ± 2.90	*< 0.01*
N75 OU (ms)	74.98 ± 3.32	75.28 ± 3.59	n.s.
P100 OU (ms)	109.29 ± 19.46	107.57 ± 15.74	*≈ 0.05*
N145 OU (ms)	147.19 ± 21.66	146.71 ± 19.61	n.s.
Amplitude OU (μV)	10.09 ± 4.46	10.85 ± 3.23	n.s.
Attributive characteristics			
Pathological VEP	9/21 (42.8%)	7/21 (33.3%)	n.s.
Low amplitude	8/21 (38.0%)	5/21 (23.8%)	n.s.
Prolonged latency	8/21 (38.0%)	6/21 (28.6%)	n.s.

that can be confirmed by optic nerve biopsy, even without clinical signs of DR, scientists have also become interested in the influence of good glycoregulation. The study of Cabrera De Buc and Somfai (2010), indicated that even in patients without registered DR, neurodegenerative changes can be found. Controlled study of strict metabolic control performed by Zeigler et al. (1994), registered a considerable shortening of P100 latency potentials in 58% of patients, although P100 latency potential values were still more prolonged than in healthy population. It is considered that acute variations in glycemia in patients with DM1 could be in correlation with registered prolonged potentials (Schneck et al., 1998). Our findings showed that improved glycoregulation was also followed by the improvement of registered VEP parameters.

The up-to-dated overview of the literature pointed out that studies mainly compared the significance of good glycoregulation with the clinical finding of retinopathy or follow-up of good glycoregulation in correlation with VEP findings over a short period of time. Parisi et al. (1998), have indicated that the effect of good glycoregulation has been possible to be registered after three months by neurophysiological studies on neuropathy up to the time when the improvement of VEP is registered. The results of our study confirmed that with good glycoregulation there is expectable improvement in VEP findings, even after short period of time. Such statement is justified in the work of Fierro et al. (1999), who were the first to publish the paper on the significance of good glycoregulation on the registration of multimodal evoked potentials over one year period.

Given the facts above, on preliminary basis it looks as though diagnosis and prognosis of DR by the VEP testing may be possible, but further studies are necessary to evaluate the sensitivity and specificity of the VEP testing. If changes in the retina could be detected before DR is noticed using this noninvasive

diagnostic procedure and include patients in a strict glycoregulation, we could be in the position to prevent to the certain degree serious complications that may cause blindness.

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