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The Evaluation of Pattern-Reversal Visual Evoked Potentials in Children with Type 1 Diabetes Mellitus

Gürkan Gürbüz[1,*], Selvinaz Edizer[1], Aycan Ünalp[1], Özlem Nalbantoğlu[1], Selma Tunç[1], Özlem Bağ[1], Ünsal Yılmaz[1], Rana Malatyali[1] and Behzat Özkan[1]

[1]Dr. Behçet UZ Children's Hospital, Izmir, Turkey

[*]*Corresponding author*: Dr. Behçet UZ Children's Hospital, Pediatric Neurology, Izmir, Turkey. Email: drgurkangurbuz@hotmail.com

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Abstract

Background: Asymtomatic santral nervous system disorder is frequently found in patients with diabetes. Neurophysiological tests were found to be objective and sensitive tool for detecting subclinical optic nerve and CNS disorders.
Objectives: Our aim is to evaluate of the central nerve conduction changes using visual evoked potentials (VEP) and to demonstrate the effects of various risk factors on VEP parameters in children with type 1 diabetes mellitus (T1DM).
Methods: Sixty children aged between 6 and 18 years and followed-up with a diagnosis of T1DM were enrolled in the study. Thirty healthy, age-matched children were enrolled as the control group. All patients and controls underwent the pattern reversal visual evoked potentials (PRVEP) test. Patients' HbA1c values, age, sex and duration of disease were evaluated from their hospital files.
Results: Both right and left VEP latencies were significantly longer in the diabetic group than in the control group ($P = 0.001$ and $P = 0.001$, respectively). The mean duration of T1DM in the patient group was 5.5 years (min: 1 - max: 15). There was a positive correlation between longer VEP latency values and duration of DM, with coefficients of 0.49 for the right eye and 0.513 for the left eye ($P < 0.001$ and $P < 0.001$, respectively).
Conclusions: We found that optic nerve conduction diminished significantly in children with T1DM. Visual evoked potential datas showed a significant prolongation of the latency of P-100. We recommend that all diabetic children be scanned with neurophysiological tests such as PRVEP for optic neuropathy.

Keywords: Children, Visual Evoked Potential, Type 1 Diabetes Mellitus, Optic Neuropathy

1. Background

Diabetes mellitus (DM) is a chronic metabolic disorder with high levels of morbidity and mortality. Type 1 diabetes mellitus (T1DM) begins in childhood and precipitates microvascular complications such as neuropathy, nephropathy, retinopathy and macrovascular complications such as atherosclerosis due to prolonged duration of the disease (1, 2).

The incidence of T1DM continues to increase, and it has serious short-term and long term implications. Peripheral neuropathy is a frequent complication of diabetes mellitus. The incidence of cranial neuropathies has not been studied in detail and it is underestimated. The actual pathophysiology of central nervous system (CNS) dysfunction is not clear but may be similar to the pathogenesis of diabetic peripheral neuropathy, including multifactorial; vascular and metabolic factors. Optic nerve involvement is seen only in 0.6% incidence of diabetes, referred to as optic atrophy (3). Since diabetes mellitus is a longterm disease, early detection of CNS injuries are important for children and adolescents (4, 5).

Neurophysiological tests were found to be an objective and sensitive tool for detecting subclinical CNS disorders. Visual evoked potential is a neurophysiological method of evaluating the optic nerve and visual cortex. It measures visual potentials and bioelectric potentials of the occipital cortex and provides reliable information about the functioning of these areas. Visual evoked potential recordings show cortical and perhaps subcortical mass responses and can be used to assess functional integrity in the visual pathways (6).

2. Objectives

Our aim was to evaluate of the optic nerve conduction changes using visual evoked potentials (VEP) and to demonstrate the effects of various risk factors on VEP parameters in children with T1DM.

3. Methods

3.1. Study Group

Patients with T1DM aged 6 to 18 years and under monitoring by the Department of Pediatric Endocrinology of Dr. Behçet UZ Children's Hospital, Turkey, a tertiary hospital for the pediatric age group, were enrolled in this study. Inclusion criteria for case group were (1) having been diagnosed with Type 1 Diabetes Mellitus for at least one year, (2) coming to their control regularly, (3) lack of hemoglobinopathy and (4) lack of ophthalmological problems. Healthy children similar in age to the patient group were included as the control group. Subjects with hemoglobinopathies, who used drugs that cause retinal degeneration, with myopia of more than 6 diopter or other ocular diseases, such as glaucoma, uveitis, optic neuritis and ocular operations were excluded. Ophthalmological evaluations of both patients and controls were performed with ophtalmoscope in ophthalmology outpatient clinic of our hospital and all retinal examinations were normal. Neurological examinations were performed in the pediatric neurology clinic, and patients with neurological deficit or progressive neurological disorder were excluded. VEP recording was performed in the neurophysiology unit. All patients and their parents were informed about the study and signed informed consent forms. VEP latency and amplitude were adopted as the primary evaluation scale. Age, sex, disease duration and HbA1c values (showing 3-month glycemic levels) were evaluated from hospital records. All financial expenses were funded by the Behçet UZ foundation. The study was conducted following approval from Dr. Behçet UZ Children's Hospital Ethical Committee on 14.01.2016 (2016/01 - 04, 2015/47) and in concordance with the principles of the 1975 Declaration of Helsinki, revised in 2008.

3.2. VEP Recording Protocol

Patients were seated opposite the screen in a semi-dark room. The pattern VEP test was performed according to the ISCVE 2016 revised protocol (7). Silver electrodes were attached at the Oz (active electrode), Cz (reference electrode) and Fpz (ground electrode) positions. Electrode impedance was approximately 5 kOhm. The luminence values for the black and white checks were 2 and 200 cd/m^2, respectively. The background was 100 cd/m^2. Stimulation was performed on both eyes, fixating on a small dot in the center of the stimulus array. Monoocular checker board with equal black and white checks, at a distance of 90 cm. The temporal frequency was 1.5 Hz (3 checks in one second). At least two measurements were performed by 100 stimuli in each individual. In each recording 200 sweeps were averaged. Visual function was evaluated via the latency of the first major positive component of the evoked response (P100). All VEP transcripts were evaluated by the same pediatric neurologist using P100 latencies and amplitudes.

3.3. Statistical Analyses

SPSS 22.0 (IBM Corparation, Armonk, New York, United States) software was used to analyze the variables. Normal distribution of the data was evaluated using the Levene test of variance homogeneity with the Shapiro-Wilk test. The Mann-Whitney U test was used with the Monte Carlo simulation technique. The independent-samples *t* test was used together with Bootstrap results when comparing two independent groups in terms of quantitative data. The parametric methods used to compare independent multiple groups in terms of quantitative data were the general linear model Two-way ANOVA (Univariate) test. The Pearson correlation test was used to examine correlations between variables after age and gender factors of variables had been checked. When categorical variables were compared, the Pearson chi-square test was used based on Exact results. Quantitative variables were expressed as mean $\pm$ SD (standard deviation) and median range (maximum - minimum), and categorical variables were expressed as number (%). Variables were examined at a 95% confidence level, and $P < 0.05$ was considered significant.

4. Results

Demographic and laboratory data, VEP latency and VEP amplitude values of the patients and control group are given in Table 1.

Sixty of the 90 cases in this study were diabetic patients (31 females, 29 males) and 30 were healthy controls (13 girls, 17 males). Mean ages were 13.5 years (min: 6 - max: 17) in the patient group and 13 years (min: 6 - max: 18) in the control group. No significant difference was determined between the patient and control groups in terms of mean age ($P = 0.434$) and gender ($P = 0.507$) (Table 1).

Mean VEP latency in the patient group was 118.08 ms ($\pm$ 14.89) for the right eye and 119.33 ms ($\pm$ 13.20) for the left eye. In the control group the values were 109.87 ms (

Table 1. Demographic Data of the Patient and Control Groups[a]

	Control (N = 30)	Patient (N = 60)	P Value
Gender, No. (%)			0.507
Female	13 (43.3)	31 (51.7)	
Male	17 (56.7)	29 (48.3)	
Age, median (max - min)	13.5 (17 - 6)	13 (18 - 6)	0.437

Abbreviations: max, maximum; min, minimum.
[a] Pearson chi-square test (exact), Mann Whitney U test (Monte Carlo).

± 8.49) for the right eye and 109.4 ms (± 8.81) for the left eye. Both right and left VEP latencies were statistically significantly longer in the diabetic group than in the control group (P = 0.001 and P = 0.001, respectively) (Table 2).

Mean VEP amplitude values in the control group were 15.5 μV (min: 7 - max: 45) for the right eye and 18 μV (min: 7 - max: 37) for the left eye. In the patient group these values were 18.5 μV (min: 5 - max: 53) for the right eye and 20 μV (min: 5 - max: 57) for the left eye. No statistically significant difference was observed between right and left VEP amplitudes in the diabetic children and control groups (P = 0.623 and P = 0.198, respectively) (Table 2).

The mean duration of T1DM in the patient group was 5.5 years (min: 1 - max: 15). Correlation analysis (positive correlation of 0.490 for the right eye and 0.513 for the left eye) revealed a high positive correlation between VEP latency values and duration of T1DM (P < 0.001 and P < 0.001, respectively) (Table 3).

The mean HbA1c value of the patient group was 8.8 mg/dL (min: 6.4 - max: 14.9). The partial correlation test revealed a positive correlation between VEP latencies and HbA1c values. A moderate positive correlation was also observed with the correlation coefficient of 0.340 for the right eye and 0.419 for the left eye (P = 0.009; P = 0.001, in order). No significant positive correlation was determined between VEP amplitude values and DM duration or HbA1c values (P = 0.248 and 0.441, respectively) (Tables 2 and 3).

5. Discussion

In this study, we found that in type 1 diabetes mellitus there are longer VEP latency values than those of healthy control group. We have discussed that this finding can be an early marker of injury of optic pathway and central nervous system.

Type 1 diabetic patients suffer micro and macrovascular complications due to lengthy of hyperglycemia exposure, limited childhood diet compliance and poor metabolic control (1). Diabetic neuropathy is the most common condition in nervous system diseases.

Table 2. VEP Latency and VEP Amplitude Values of the Patient and Control Groups[a]

	Control (n = 30)	Patient (n = 60)	P Value
VEP amplitude R	15.5 (45 - 7)	18.5 (53 - 5)	0.623
VEP amplitude L	18 (37 - 7)	20 (57 - 5)	0.198
VEP latency R[b]	109.87 ± 8.49	118.08 ± 14.89	0.001
VEP latency L[b]	109.40 ± 8.81	119.33 ± 13.20	0.001

Abbreviations: SD, standard deviation; max, maximum; min, minimum; R, right; L; left.
[a] Pearson chi-square test (Exact); Mann Whitney U test (Monte Carlo); Independent *t* test (Bootstrap).
[b] Values are expressed as mean ± SD.

Peripheral and autonomic nervous system involvement are well known, but the frequency of central diabetic neuropathy is not. Central nervous system and optic pathway degeneration can be detected early by using VEP (3). Visual evoked potentials are an inexpensive neurophysiological technique that does not require sedation and that can be easily applied to children, adolescents and adults. It provides information about the functional status of the visual pathway that magnetic resonance imaging (MRI) and computerized tomography (CT) are unable to elicit. Visual evoked potentials were initially globally used to detect optic nerve demyelination in multiple sclerosis. It was then realized that it can also be used in hypertensive, uremic and hyperinsulinemic retinal effects (8-10).

The relationship between VEP changes and metabolic status in adult patients with type 1 and type 2 diabetes mellitus has been investigated since the 1980s. Comi et al. found that VEP is a simple and reliable method that can be used in the early detection of CNS functions in diabetic children (11). However, studies involving T1DM in childhood are more limited (12, 13).

In our study, mean VEP latencies in T1DM were statistically significantly longer than in the control group. This was in accordance with previous studies of adults and children. The prolongation of the P100 latencies are indicative of structural damage to myelinated optic nerve fibres (14, 15).

One previous study investigated 15 healthy subjects, 15 patients newly diagnosed and 15 previously diagnosed T1DM patients. The VEP latencies of the T1DM group were significantly higher than those of the controls, in the same line with our study. Significant difference was also observed among the VEP amplitude values. However, this finding was in contrast to ours. They suggest that latence values gradually increase while decreasing amplitudes over time in children with T1DM as the years pass (16).

When the members of the patient group were evaluated among themselves, VEP latencies and HbA1c and diabetes duration were compared to assess the association with metabolic control and VEP's. The correlations between VEP latency and mean T1DM duration and HbA1c values were both significant (P < 0.001 and P < 0.001, respectively). Elia et al. found no significant relationship between VEP latencies and mean HbA1c values in a study of 50 type 1 diabetic adults and 33 healthy control subjects (17). However, 50% of the patient group had low HbA1c levels (‹8 mg/dL), and this may explain the absence of a positive correlation in that study (17). The presence of higher HbA1c levels in T1DM than in type 2 DM in this study indicates the importance of VEP in the early stages. Similar to our study, Verrotti et al. evaluated a patient group with a mean HbA1c of 9.4 mg/dL and demonstrated that HbA1c values increased in tandem with the latency of VEP (12).

Table 3. Correlation Analysis of Duration of T1DM and HbA1c with VEP Values[a]

(n = 60)	Duration of T1DM		Hba1c	
	R	P Value	r	P Value
VEP latency R	0.490	< 0.001	0.340	0.009
VEP latency L	0.513	< 0.001	0.419	0.001
VEP amlitude R	0.154	0.248	-0.103	0.441
VEP amlpitude L	0.171	0.200	-0.207	0.120

Abbreviations: r, Correlation coefficient; R, right; L, left.
[a] Partial Correlation test; Age and gender are under control.

A number of studies have also discussed metabolic control and VEP latancies; Ziegler et al. showed that even 3-day normoglycemia shortened the latency of VEP, although it was still longer than in the control group (18).

No significant relationship was observed between VEP amplitudes and duration of DM and HbA1c levels in this study. Heranvian et al. (19) reported significantly lower VEP amplitudes in a diabetic group, while VEP amplitudes were not included by Elia et al. (17) and Uberall et al.'s (15) studies of childhood T1DM. This may be due to the fact that VEP amplitudes exhibit considerable variation in terms of head-shape, distribution of cerebral sulcuses, attention deficit, obesity, and technical problems. VEP latency also exhibits less individual variability than amplitude (20). We observed no statistically significant relationship between VEP amplitude values and other parameters. This made us think that formation of the retinopathy would be later than optic neuropathy.

Parisi et al. (21) performed VEP, after baseline VEP followed by photostress in 10 newly diagnosed T1DM patients and 10 healthy children. Although the VEP latencies of the patient group were significantly higher than those of the controls, no significant difference was found in VEP values after photostress performed for better evaluation of macular functions. This shows that newly diagnosed T1DM cases do not have impaired macular functions. With these supportive findings, VEP can be assessed at baseline at the time of T1DM diagnosis and reapplied at specific intervals to assess the CNS impairment during the course of disease (22). As ours was a cross-sectional study, VEP was performed in cases of T1DM diagnosed at least one year previously, so no newly diagnosed T1DM cases were included. The prolongation of the latency of VEP may not depend solely on the fact that DM is a long-standing disease. Because in previous studies compared to control patients of new diagnosed T1DM patients latency of P100 potentials was found to be prolonged (5, 6, 12, 16, 21-25). Deterioration of VEP latency in newly diagnosed T1DM children indicates that the optic pathway is affected early. VEP may be useful for early detection of central nerve conduction changes and may be a good assessment tool in the subclinical phase of the disease. However, it is not clear that this abnormality is the result of a transient functional phenomenon or pathological changes in the optic nerve (12, 25).

The small group of patients and non-prospective method are the limitations of the current study.

5.1. Conclusions

In conclusion, duration of T1DM and levels of HbA1c were significantly associated with VEP latency alterations. VEP assessment in children with diabetes at time of diagnosis and routine intermittent follow-up may represent a useful guide in terms of monitoring CNS impairment. Prospective studies will be more useful to illuminate the pathogenesis in the future.

Footnotes

Authors' Contribution: Study concept and design: Gürkan Gürbüz, Aycan Ünalp, Behzat Özkan, analysis and interpretation of data: Gürkan Gürbüz, Ünsal Yılmaz, Selvinaz Edizer, drafting of the manuscript: Gürkan Gürbüz, Özlem Bağ, Rana Malatyali, Selma Tunç, critical revision of the manuscript for important intellectual content: Gürkan Gürbüz, Aycan Ünalp, Ünsal Yılmaz, Özlem Nalbantoğlu, statistical analysis: Gürkan Gürbüz, Ünsal Yılmaz, Aycan Ünalp, Selvinaz Edizer.

Conflict of Interests: No conflict of interests.

Ethical Considerations: The study was conducted following approval from the Dr. Behçet UZ Childrens' Hospital Ethical Committee on 14.01.2016 (2016/01-04, 2015/47) and in concordance with the principles of the 1975 Declaration of Helsinki, revised in 2008. All patients and their parents were informed about the study and signed informed consent forms.

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