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Original Article

Visual-evoked potentials in children and adolescents with newly diagnosed diabetes

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Abstract

Aim: Central nervous system impairment is common in patients with diabetes, even in the early stages of the disease. The aim of the study was to evaluate central nerve conduction changes in children and adolescents with newly diagnosed diabetes mellitus using pattern-reversal visual-evoked potentials.

Material and Methods: Pattern-reversal visual-evoked potentials were assessed in 48 patients with type 1 (age 11.9±2.9 years) and 18 patients with type 2 (age 14.8±1.3 years) diabetes less than a month after diagnosis and in 33 control subjects (age 12.9±3.9 years).

Results: P100 latencies were significantly delayed in patients with type 1 and 2 diabetes compared with control subjects ($p<0.001$). There was no correlation between P100 latencies and age at diagnosis. No correlations were found between P100 latencies and HbA1c values in patients with type 1 diabetes. However, P100 latencies were significantly associated with levels of HbA1c in patients with type 2 diabetes ($p<0.01$). There was a marked inter-individual variability in amplitudes of N75 to P100 in both patients with diabetes and controls. The amplitudes of N75 to P100 were not associated with levels of HbA1c in patients with diabetes. Negative correlations between amplitudes of N75 to P100 and age at diagnosis were noted in patients with type 1 diabetes ($p<0.05$).

Conclusions: The impaired visual-evoked potential latencies in children and adolescents with newly diagnosed diabetes mellitus suggest an early involvement of the optic pathway. Visual-evoked potential could be helpful for the early detection of central nerve conduction changes at this subclinical stage of the disease.

Keywords: Type 1 diabetes mellitus, type 2 diabetes mellitus, visual-evoked potential

Introduction

Given the long-term clinical course of diabetes mellitus, early detection of damage to the central nervous system (CNS) is an important task in the follow-up of children and adolescents (1). Moreover, CNS impairment in the preclinical stage is common in patients with diabetes. Neurophysiologic tests have proven to be an objective and sensitive tool for the detection of even subclinical CNS impairment. Visual-evoked potential (VEP) recordings represent a mass response of cortical and probably subcortical visual areas, and are used to assess the functional integrity of the visual pathway (2). The literature dealing with VEP findings in newly diagnosed young patients with diabetes is very limited (3-5).

The aim of this study was to evaluate central nerve conduction changes in children and adolescents with newly diagnosed diabetes mellitus using pattern-reversal VEP (PRVEP) and to investigate the influence of several clinical risk factors on the parameters of VEP.

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Materials and Methods

We studied 66 patients (30 males, 36 females; mean age 12.7 ± 2.9 years, range 5-18 years) less than a month after diagnosis of diabetes. The patients consisted of 48 with type 1 diabetes mellitus and 18 with type 2 diabetes mellitus. Ophthalmologic and neurologic examinations were peformed in all patients. Patients with retinopathy, refractory anomalies, migraine, thyroid dysfunction, and other conditions that might alter VEP findings were excluded from the study. At the time of study, no patient had clinical or laboratory signs of diabetic ketoacidosis and/or hypoglycemia. Patients were excluded if they had a history of neurologic or metabolic disease besides diabetes or had taken any medicine known to influence optic nerve function.

The level of glycosylated hemoglobin ($HbA1_C$) was measured using a Hemoglobin $A1_C$ Autoanalyzer (VARIANT™ II Turbo $HbA1_C$ analyzer, Bio-Rad, CA, USA) in the clinical laboratory.

The PRVEPs were recorded from an active electrode placed over the occipital region (O1, O2, Oz), with a reference electrode at Cz. The stimulus for this study was a monocular checkerboard with equal black and white checks, 76' of arc in size at a viewing distance of 90 cm. The temporal frequency was 2 Hz. The analysis time was 250 msec. Two measurements were performed for both eyes, averaging over 100 stimuli and excluding artifacts. The transient response was characterized by several waves with three peaks that appeared after 75, 100, and 145 msec in healthy controls. These peaks had negative (N75), positive (P100), and negative (N145) polarity, respectively. Visual function was evaluated via the latency of the first major positive component of the evoked response (P100) and the peak-to-peak amplitude of N75 to P100.

Thirty-three healthy children and young adults (18 males, 15 females) were recruited as control subjects with a mean age of 12.9 ±3.9 years (range, 5-20 years). The study protocol was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Chungbuk National University Hospital (01.12.2017/201611001). Written informed consent was obtained from the parents.

Statistical analysis

Averages of demographic variables and PRVEP parameters were compared between all patients with diabetes and healthy controls using Student's t-tests, and among patients with type 1 diabetes, patients with type 2 diabetes, and the control group using the ANOVA test. Post-hoc tests were performed using the Tukey method. We statistically tested the difference in latency and amplitude of PRVEP among the three groups with a general linear model after controlling the confounding factors such as HbA1c levels, age at diagnosis, and sex. Statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at p-value <0.05.

Results

The clinical and demographic characteristics, and mean latencies and amplitudes of the patients and control subjects are shown in Table 1.

For control subjects and patients with diabetes, we found no significant differences in P100 latencies and amplitudes of N75 to P100 between the sexes or between the right and left eyes. The mean value of P100 latencies in both eyes were significantly longer in patients with type 1 and 2 diabetes than in control subjects (Figure 1, $p<0.001$). In patients with diabetes, we found no significant correlation between P100 latencies and age at diagnosis. No correlations were found between P100 latencies and HbA1c values in patients with type 1 diabetes (Figure 2). P100 latencies were associated with HbA1c levels in patients with type 2 diabetes (Figure 3, $p<0.01$).

There was a marked inter-individual variability in amplitudes of N75 to P100 in both patients with diabetes and control subjects. Both right and left amplitudes of N75 to P100 were decreased in patients with type 2 diabetes compared with control group in univariate analysis ($p<0.05$). Age was negatively correlated with N75 to P100 amplitudes among all patients with diabetes in multivariate analysis ($p<0.05$). We found significant negative correlations between N75 to P100 amplitudes and age at diagnosis onset in patients with type 1 diabetes ($p=0.0179$). The amplitudes were not associated with HbA1c levels in patients with either type 1 and 2 diabetes.

Table 1. Clinical and electrophysiologic data in the patients and control subjects

	Control (n=33)	Type 1 DM (n=48)	Type 2 DM (n=18)
Sex	18M, 5F	17M, 31F	13M, 5F
Age (years)	12.9±3.9	11.9±2.9	14.8±1.3
HbA1c (%)		13.1±3.0	10.4±2.4
Lat (Rt, ms)	99.7±3.7	113.4±12.4a	111.6±9.3a
Lat (Lt, ms)	101±3.7	113.6±12.1a	114±8.6a
Amp (Rt, μV)	9.2±4.8	7.9±3.8	6.2±2.2b
Amp (Lt, μV)	9.5±5.1	8.0±3.1	6.8±2.4b

[a] p<0.01 by ANOVA test, Amp-amplitude, [b] p<0.05 by ANOVA test, DM- diabetes mellitus, Lat-latency, Lt-left, Rt-right

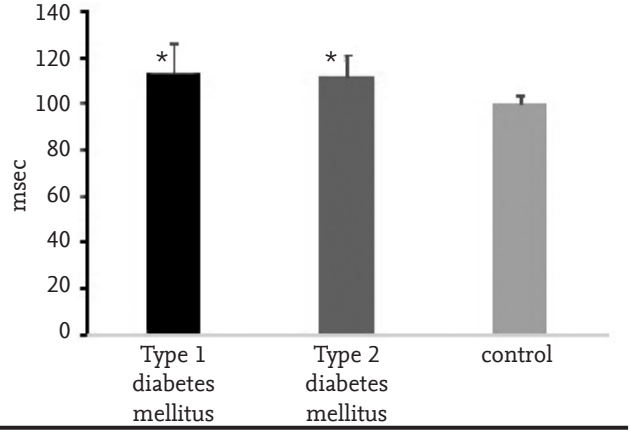

Figure 1. Histogram of mean values of VEP's P100 latency
***p<0.0001**

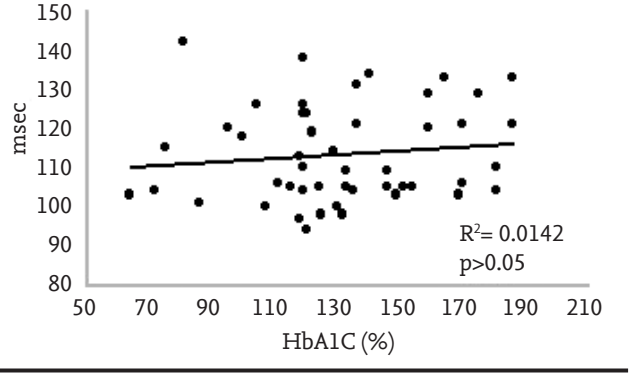

Figure 2. Relation between HbA1c and VEP latency in type 1 diabetic patients

Examples of PRVEP recordings in the normal controls, patients with type 1 diabetes mellitus, and patients with type 2 diabetes mellitus are shown in Figure 4.

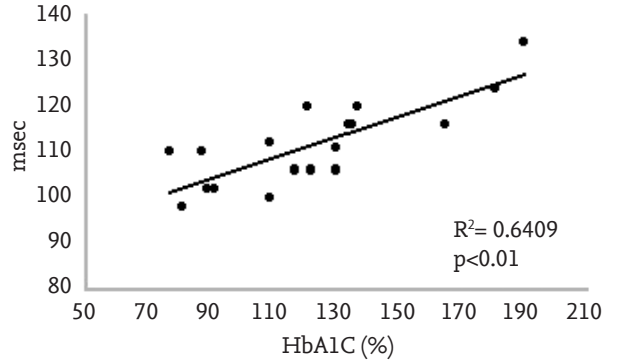

Figure 3. Relation between HbA1c and VEP latency in type 2 diabetic patients

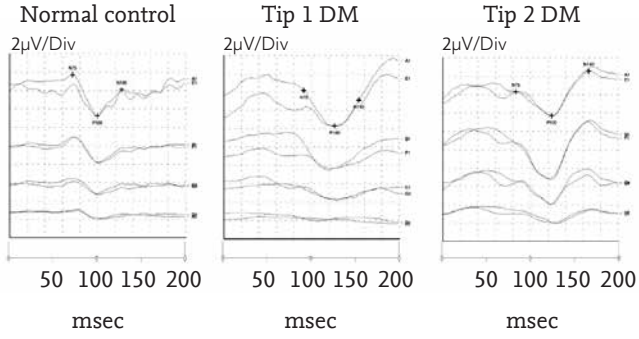

Figure 4. Examples of VEP recordings in normal control, patient with type 1 diabetes mellitus, and patient with type 2 diabetes mellitus. Note delayed P100 latencies and similar amplitudes with respect to those of control subject.

Discussion

There are strengths to our study. First, our patient group included those with type 1 and type 2 diabetes. Second, we used a strict inclusion criterion of less than one month for newly diagnosed diabetes mellitus.

We found significantly longer P100 latencies in patients with newly diagnosed diabetes in this study compared with control subjects. These data are in agreement with those reported in young persons with newly diagnosed insulin-dependent diabetes (3-5). Their studies included 30 (mean age: 17.6 years), 14 (mean age: 24.8 years), and 10 patients (mean age: 25.2 years) with insulin-dependent diabetes mellitus, respectively. The patients of previous studies were older than our patients. Additionally, although the

previous studies included patients with newly diagnosed diabetes, the duration of diabetes in their patients was far longer than in our patients. Nevertheless, some broad generalizations can be drawn from published research and our own data. Visual-evoked potential abnormalities are detectable in children and adolescents with newly diagnosed diabetes, thus they might not necessarily only be a complication of longstanding diabetes mellitus.

There is only one report in the literature examining the relationship between P100 latencies and clinical factors such as age, sex, and HbA1c levels in children and adolescents with newly diagnosed diabetes (3). It showed that no significant correlation was found between latency and age, duration of diabetes, and mean glycosylated hemoglobin. Likewise, we found no significant correlation between P100 latencies and age at diagnosis in patients with type 1 or type 2 diabetes. P100 latencies were associated with HbA1c levels in our patients with type 2 diabetes. However, no such correlation was found in patients with type 1 diabetes. Presumably, the difference might be partly caused by the duration of type 2 diabetes. Although we included patients less than a month after their diabetes was diagnosed, we could not assure the actual clinical onset of type 2 diabetes mellitus.

The high inter-individual variability observed in the N75 to P100 amplitude recordings in the control group led us to consider that this parameter was not reliable for interpretation. Although limited by the number of patients with type 2 diabetes mellitus, the N75 to P100 amplitudes in patients with type 2 diabetes were decreased compared with the control group. These findings justify the undertaking of a future study to determine the effect of type 2 diabetes on amplitudes of PRVEP in more children and adolescents. However, age was negatively correlated with amplitudes of PRVEP in patients with diabetes in a general linear model after controlling for confounding clinical factors. We found negative correlations between N75 to P100 amplitudes and age at diagnosis in patients with type 1 diabetes. Considering the age of our patients, we believe that there is dramatic attenuation in PRVEP amplitudes between childhood and adolescence secondary to developmental effects (6, 7).

The impaired VEP latencies in children and adolescents with newly diagnosed diabetes suggest an early involvement of the optic pathway. Visual-evoked potential could be helpful for early detection of central nerve conduction changes and can be a useful tool in the subclinical stage of disease. However, whether this abnormality is a transient functional phenomenon or a consequence of pathologic changes of optic nerve fibers is not conclusive (3-5, 8). Strict metabolic control might influence electrophysiologic parameters because P100 latencies were associated with HbA1c levels in our patients with type 2 diabetes. However, the long-term effects of hyperglycemia on the latency of P100 in children and adolescents with newly diagnosed diabetes remain to be answered with a prospective study.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Chungbuk National University Hospital Institutional Review Board.

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.L.; Design - S.L.; Supervision - S.L., H.H.; Resources - S.L.; Materials - H.H.; Data Collection and/or Processing - S.L., H.H.; Analysis and/or Interpretation - S.L., H.H., H.K.; Literature Search - S.L.; Writing Manuscript - S.L.; Critical Review - S.L., H.H., H.K.

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Conflict of Interest: No conflict of interest was declared by the authors.

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