A 5-year follow-up visual evoked potentials and nerve conduction study in young adults with type 1 diabetes mellitus

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Abstract

Central nervous system impairment is common in diabetic patients, even in the early stages of the disease, and could be associated with peripheral neuropathy. The aims of this study were to prospectively investigate central nerve conduction in young adults with type 1 diabetes using pattern-reversal visual evoked potentials (PRVEP) and to determine how those results were related to clinical risk factors and the parameters of the peripheral nerve conduction study (NCS). A total of 36 type 1 diabetic patients (15 males) 5-24 years of age (mean 14.5 ± 4.7) underwent PRVEP and NCS annually for five years. For comparison, 39 healthy age and sex matched individuals (mean 14.8 ± 5.0) were evaluated as the control group. The P100 latencies of the PRVEP were prolonged at the study entry in the patients compared with the controls ($p < 0.001$). Significant correlations were not found between any of the parameters of PRVEP and the glycosylated hemoglobin levels; however, the changes in the parameters of the peripheral NCS were well correlated with metabolic control. The latencies and amplitudes of the P100 were not related to the majority of the parameters of the NCS. A prolonged PRVEP latency may be a sign of optic pathway dysfunction, which begins before apparent diabetic retinopathy. Poor glycemic control proved to be an important risk factor over the 5 years in terms of its relation to the development of peripheral neural pathway abnormalities. However, once central conduction was delayed, its changes were poorly related to diabetic control and the attributes of the peripheral nerve conduction study over the 5-year follow-up.

INTRODUCTION

The early detection of neurological alterations is an important task in the follow-up of diabetic patients, particularly for young persons with type 1 diabetes mellitus.[1] Nerve conduction studies (NCS) have been used for this purpose. Impairments of the central nervous system (CNS) and the peripheral nervous system are frequent complications of diabetes. Moreover, CNS impairment is common in diabetic patients, even in the early stages of the disease, and could be associated with peripheral neuropathy.[2,3] Nevertheless, little attention has been directed toward the chronic effects of diabetes on the CNS. While the peripheral and autonomic nervous systems' involvements determine a large spectrum of clinical manifestations, CNS involvement is usually clinically silent and can only be uncovered by neurophysiological investigations or psychometric tests. It is important to emphasize that despite many experimental and clinical studies, this association is still uncertain, and a screening tool is needed to confirm this association.[4]

Neurophysiological tests have proven to be objective and sensitive tools for the detection of even subclinical CNS impairments. 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.[4]

There are uncertainties regarding whether central conduction abnormalities are related to peripheral nerve conduction abnormalities in diabetic patients. Earlier studies revealed data about the central manifestations of diabetes, but these studies did not permit a comprehensive comparative analysis of peripheral and central nervous dysfunctions. Several studies have reported that central afferent dysfunction is associated with the most common forms of diabetic neuropathy.[5] However, contradictory results exist.[6] In addition to these uncertainties,

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most studies have focused on type 1 patients with longstanding diabetes or adults with type 2 diabetes mellitus. Moreover, the previous studies had cross sectional designs.[2,5,6]

The aims of this study were to prospectively evaluate central nerve conduction in young adults with type 1 diabetes using pattern-reversal VEP (PRVEP) and to investigate the relations between PRVEP changes and peripheral NCS parameters. Another aim was to establish the influences of several clinical risk factors on the function of the visual pathway.

METHODS

A total of 36 patients (15 males and 21 females) ranging in age from 5 to 24 years of age (mean 14.5 ± 4.7) with type 1 diabetes underwent neurological and electrophysiological examinations at study entry and annually for five years. No patient had a history of neurological or metabolic disease other than diabetes, and none were taking any medicine known to influence peripheral or optic nerve function. The diagnoses of type 1 diabetes were made by endocrinologists based on both clinical features and laboratory data. All of the patients were ketosis-prone, required insulin injections to sustain their lives; lacked endogenous insulin secretion as indicated by urinary C-peptide levels lower than 3.3 nmol/d and/or were positive for anti-islet autoantibodies.

The glycosylated hemoglobin (HbA1c) levels were checked every three months and averaged every year before the NCS. These levels were measured with a Hemoglobin A1c Autoanalyzer (VARIANT™ II Turbo HbA1c analyzer, Bio-Rad, CA, USA) in the clinical laboratory. Additionally, neuropathy symptom and sign scorings and neurological disability scorings were performed every year to detect clinical neuropathies.[7] The study protocol accorded with the Declaration of Helsinki and was approved by the Ethical Committee of Chungbuk National University Hospital. Written informed consent was obtained from the parents.

The nerve conduction studies were performed with a standard technique using surface electrodes.[8] The following 18 variables were recorded: motor conduction velocity; amplitude of the compound muscle action potential (CMAP); terminal latencies of the median, ulnar, posterior tibial, and peroneal nerves; sensory conduction velocity; and the amplitudes of the sensory nerve action potentials in the median, ulnar, and sural nerves. The sensory conduction velocities were

calculated by dividing the distance between the stimulation and recording electrodes by the peak latency.

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 that subtended 76° of visual space at a viewing distance of 90 cm. The temporal frequency was 2 Hz. The analysis time was 250 msec. Two measurements were performed for each eye and averaged over 100 stimuli following the exclusion of artifacts. The transient response was characterized by several waves with three peaks that appeared after 75, 100 and 145 msec in the healthy controls. These peaks had negative (N75), positive (P100), and negative (N145) polarities, respectively. The 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 between the N75 and P100 components.

Recordings were performed at the study entry (n=36) and subsequently after one (n=35), two (n=35), three (n=35), four (n=35), and five (n=36) years. PRVEP was performed when the blood glucose levels were stable to exclude the possibility that the PRVEP abnormalities were due to hypoglycemia or ketosis. Thirty-nine healthy children and youths (25 males, 14 females) were recruited as the control group, which had a mean age of 14.8 years ± 5.0 (range= 5-25 years).

Statistical analysis

We performed a cross-sectional analysis of the data from the diabetic patients and health controls at the study entry. The averages of the demographical variables and PRVEP and NCS parameters were statistically compared between the patients and controls using Student's t-tests. Using the patient data acquired at the study entry, we tested for statistically significant effects of the NCV parameters, HbA1c level, age of diagnosis, and duration of illness on the latencies and amplitudes of the PRVEP. Pearson's correlation analyses were used for the univariate analyses, and a user-specified significance threshold of 0.05 was selected to account the number of correlation analyses performed between the PRVEP and NCS parameters.

The P100 latencies and N75-P100 amplitudes of PRVEP changed with the lapse of time. We assessed the effects of sex, age of onset, duration of diabetes, and level of HbA1c on the P100 latencies

and N75-P100 amplitudes of PRVEP. Because the PRVEP and NCS parameters and HbA1c levels of the diabetic patients were repeatedly measured at unequally spaced time intervals during the follow-up period, we adopted hierarchical general linear models (HGLMs) to test the statistical relationships between the latencies and amplitudes of the PRVEPs with the NCS parameters, HbA1c levels, age of diagnosis, and duration of illness. The SAS procedure PROC MIXED was used, and p-values less than 0.05 were considered significant in the HGLM analyses.

RESULTS

The clinical and demographic characteristics of the young adults with type 1 diabetes upon entry into the PRVEP study and during the 5-year follow-up are presented in Table 1. We did not observe any age differences between the patient and control groups. No patients exhibited symptoms ascribed to optic neuropathy or retinopathy at entry into the initial PRVEP study or during the five-year period of study. There were not gender differences in the P100 latencies or N75-P100 amplitudes of the PRVEP. No patients exhibited symptoms of peripheral neuropathy at the time of diagnosis or during the five-year period of study. However, three patients exhibited areflexia during the period.

The mean P100 latency of the PRVEP was significantly prolonged in diabetic patients at study entry compared with mean value of the control group. A small reduction of mean N75-P100 amplitudes were found in diabetic patients compared to age-matched normal control values. However, no statistically significant differences

were observed.

Examining latencies and amplitudes of PRVEP in diabetic patients during five years, we did not observe statistically significant correlations of the P100 latencies of the PRVEP with the clinical factors including the HbA1c serum levels and the age of onset (Table 2). On the contrary, the P100 latency was inversely related to the duration of diabetes. The N75-P100 amplitude values were inversely related to the age of onset and the illness duration (Table 3). There were no differences in the P100 latencies or N75-P100 amplitudes between the right and left eyes over the 5 years.

The results of central conduction using the PRVEP in the young adults with type 1 diabetes for five years were compared with the results of peripheral nerve conduction. The latencies and amplitudes of the PRVEP were poorly correlated with the parameters of the peripheral nerve conduction study (Table 4). In contrast, most of the electrophysiological parameters of the peripheral NCS were correlated with the degree of hyperglycemia and metabolic control (Table 5).

DISCUSSION

Evoked potentials have been widely used in the assessment of central conduction along the visual, auditory, and somatosensory pathways in patients with diabetes because evoked potentials represent an inexpensive, non-invasive, and relatively reproducible tool for detecting abnormalities in the sensory pathways.[5,6,9] The function of the entire visual pathway can be objectively assessed by recording cortical potentials evoked by patterned stimuli. However, no agreements

Table 1: Clinical characteristics and changes of P100 values in patients during five year follow-up and controls

| | N (Male) | Clinical characteristics | | | | Latency (ms) | | Amplitude (µV) | |
		DM onset (yr)	Exam age (yr)	Duration (yr)	HbA1c (%)	Right	Left	Right	Left
Control	39 (25)		14.8± 5.0			99.9±4.9	101.2±4.0	9.3±5.3	9.0±5.0
Initial study	36 (15)	9.2±3.7	14.5±4.7	5.3±4.6	10.6±3.0	115.4±13.5*	114.9±13.1*	8.1±4.0	7.8±3.4
1ˢᵗ yr FU	35 (14)	9.4±3.8	15.7±4.5	6.3±4.5	9.6±2.4	109.4±10.9	110.3±11.4	7.2±3.7	7.7±3.4
2ⁿᵈ yr FU	35 (15)	9.4±3.9	16.8±4.6	7.4±4.6	9.7±2.3	109.0±11.5	109.6±8.8	7.0±2.9	7.6±2.8
3ʳᵈ yr FU	35 (15)	9.4±3.9	17.6±5.1	8.2±5.0	10.1±2.5	109.1±10.6	110.0±11.9	6.3±2.4	6.6±2.6
4ᵗʰ yr FU	35 (15)	9.3±3.8	19.0±4.9	9.6±4.7	9.9±2.4	115.2±13.4	114.5±13.4	6.9±2.6	7.1±3.1
5ᵗʰ yr FU	36 (15)	9.2±3.7	19.8±5.0	10.7±4.6	9.5±2.4	114.2±10.8	112.3±10.3	6.5±2.9	6.4±2.7

* $p<0.001$ between control and initial study

Data are presented as mean±SD. DM, diabetes mellitus; Exam, examination; FU, follow-up

Table 2: Hierarchical general linear model for the latency of visual evoked potential

Variables	β	SE(β)	DF	t value	*p*
Sex (male=1, female=2)	0.947	0.715	171	1.32	0.1872
Age of onset (yr)	-0.155	0.094	171	-1.65	0.1015
Duration of diabetes (yr)	-0.237	0.050	171	-4.74	<.0001
HbA1c	-0.015	0.074	171	-0.2	0.8408

SE: standard error, DF: degree of freedom, NS: not significant

Table 3: Hierarchical general linear model for the amplitude of visual evoked potential

Variables	β	SE(β)	DF	t value	p
Sex (male=1, female=2)	-0.365	2.255	171	-0.16	NS
Age of onset (yr)	-0.785	0.307	171	-2.56	0.0114
Duration of diabetes (yr)	-0.413	0.197	171	-2.09	0.0377
HbA1c	0.503	0.331	171	1.52	NS

SE: standard error, DF: degree of freedom, NS: not significant

Table 4: Pearson correlation coefficients between variables of peripheral nerve conduction study and average amplitude and latency of visual evoked potential

NCS variables	Visual evoked potential	
	Amplitude	**Latency**
Median motor		
TL	-0.087	-0.080
CV	-0.126	-0.178*
CMAP	0.027	0.131
Ulnar motor		
TL	0.008	0.013
CV	-0.147*	-0.117
CMAP	-0.088	-0.080
Tibial nerve		
TL	-0.008	0.042
CV	-0.091	-0.141*
CMAP	0.081	-0.018
Peroneal nerve		
TL	0.024	-0.137*
CV	-0.060	-0.035
CMAP	0.040	-0.088
Median sensory		
CV	-0.038	-0.079
SNAP	0.223	-0.041
Ulnar sensory		
CV	-0.179**	-0.213**
SNAP	0.069	0.102
Sural nerve		
CV	-0.053	-0.062
SANP	0.057	-0.117

*$p < 0.05$, **$p < 0.01$.
CMAP, compound muscle action potential; CV, conduction velocity; SNAP, sensory nerve action potential; TL, terminal latency

Table 5: Pearson correlation coefficients between variables of peripheral nerve conduction study and age, age of onset, duration of diabetes, and serum HbA1c level

NCS variables	Age (yr)	Age of onset (yr)	Duration of diabetes (yr)	serum HbA1c level
Median motor				
TL	0.336**	0.181**	0.217**	0.212**
CV	0.228**	0.167*	0.115	-0.467**
CMAP	0.032	0.051	-0.003	-0.270**
Ulnar motor				
TL	0.198**	-0.097	0.280**	0.250**
CV	0.120	0.170*	-0.001	-0.519**
CMAP	0.262**	0.007	0.271**	-0.267**
Tibial nerve				
TL	0.258**	0.186**	0.131	0.378**
CV	-0.065	0.062	-0.114	-0.439**
CMAP	0.090	-0.012	0.106	-0.228**
Peroneal nerve				
TL	0.239**	-0.013	0.260**	0.294**
CV	-0.140*	0.099	-0.220**	-0.575**
CMAP	0.120	0.138*	0.024	-0.291**
Median sensory				
CV	0.070	0.138*	-0.030	-0.274**
SNAP	-0.035	-0.007	-0.029	-0.111
Ulnar sensory				
CV	0.288**	0.249**	0.116	-0.375**
SNAP	-0.032	0.189**	-0.175*	-0.251**
Sural nerve				
CV	-0.064	0.041	-0.098	-0.285**
SANP	0.006	0.094	-0.063	-0.292**
VEP latency	-0.333**	-0.230**	-0.176*	0.113
VEP Amp	-0.310**	-0.051	-0.289**	0.094

*$p < 0.05$, **$p < 0.01$.

Amp, amplitude; CMAP, compound muscle action potential; CV, conduction velocity; SNAP, sensory nerve action potential; TL, terminal latency

have been reached regarding the influences of glycemic control and other related clinical factors on central conduction impairments in patients with type 1 diabetes. One reason for this lack of agreement is that there are no prospective data on the long-term influences of these factors on the responses to electrophysiological tests of the central conduction pathways. We believe that our study overcomes some of the limitations of previous reports.

Clinical optic neuropathy is uncommon in diabetes, but many studies have reported subclinical optic neuropathy as demonstrated by PRVEP.[2-5,10] Our study also revealed that the P100 latencies were longer in the young adults with type 1 diabetes than the controls at study entry. The high levels of HbA1c at study entry were decreased by strict blood glucose control for one year. In concert with the control of hyperglycemia, the P100 latency was also shorter than the initial latency after one year. This result indicates that delays in central nerve conduction are related to reversible metabolic changes. However, the mean P100 latency of the first year follow-up was still

significantly longer than values in the control group. Additionally, the changes in latency were not correlated with metabolic control at any later time. Similar to the results of our study, one study with a six-month follow-up revealed that early functional abnormalities of the optic nerve can be detected at the onset of diabetes and that glycemic control can reverse these abnormalities.[11] It is important to emphasize that when tight metabolic control is achieved, these abnormalities disappear, suggesting that VEP impairments are only functional and completely reversible within a few years after the onset of type 1 diabetes in children and adolescents.[11] However, considering the life-long course of diabetes, six months is still too short of a time to observe the effects of chronic hyperglycemia on the optic nerve or retina.

In patients with type 1 diabetes, VEP responses with longer latencies and decreased amplitudes have been observed.[12,13] Prolonged latencies with normal amplitudes have been observed in type 1 diabetic patients with disease durations shorter than six months.[14,15] However, many authors have not found significant correlations between VEP parameters and HbA1c or glycemia.[2,6,10,15,16] In addition, it is known that acute hyperglycemia does not influence the neurophysiological abnormalities that are detected in patients with diabetes. These abnormalities are probably due to structural changes in the central nervous pathways rather than functional damage to the optic pathways induced by acute short-term hyperglycemia.[17] Likewise short-term metabolic control as expressed by HbA1c or glycemia values does not seem to have any practical influence on the response to electrophysiological tests.[18] However, the relevant previous studies suffered from several limitations, including cross-sectional designs, relatively short-term follow-up periods, and being limited to adults with diabetes.

A few previous studies have found correlations between disease duration and VEP pathologies[2,13], but we were unable to identify such associations. Although trends toward worsening have been observed, no correlations with disease duration have been confirmed.[6,9,10,16,19] In contrast, we observed inverse correlations between the P100 parameters and illness duration. When analyzing the prospective neurophysiological measurement data, we should consider developmental and aging changes in human sensory systems. Given the young ages of our patients, it is crucial to consider developmental changes in this study. Cortical developmental changes do not appear to be complete until 17 years of age or later. PRVEP amplitudes exhibit significant decreases during childhood and adolescence.[20,21] These developmental changes in the P100 latencies and N75-P100 amplitudes in children and adolescents could partially explain the inverse relationships between the P100 parameters and illness duration in our study. In other words, the developmental changes were due to more than only the changes induced by chronic hyperglycemia as the years passed. Most previous cross-sectional studies have not considered the effects of age and developmental stage on the latencies and amplitudes. In addition, we should consider the interocular amplitude abnormalities when analyzing the N75-P100 amplitudes. The normal interocular variability of PRVEP amplitudes is too great to be of much use except occasionally when comparing two eyes in one patient. Because the PRVEP amplitude is directly related to visual acuity, it is affected by any process that produces changes in visual acuity. In most cases with conduction defects in the optic nerve, latency abnormalities accompany and very often precede amplitude abnormalities.[21] Previous studies have reported decreased amplitudes of PRVEP or a lack of a significant difference in patients with diabetes compared with controls.[11,12] However, there have been no long-term prospective studies that have assessed changes in amplitudes of PRVEP in patients with diabetes. The majority of studies have included patients with longstanding diabetes. We believe that changes in the amplitude of PRVEP in young adults with type 1 diabetes are of limited value due to variability in the amplitudes.

The exact pathophysiology of central nervous dysfunction is not clear, but it seems to be multifactorial and to involve vascular and metabolic factors similar to the pathogenesis of diabetic peripheral neuropathy. Several authors have reported that VEP abnormalities are more frequent in patients with clinical neuropathies than in those without neuropathies, but other studies have reported equivocal results.[5,6,13,22] Such contradictory results stem from different study designs, different methods of measuring peripheral nerve function, different or incomplete definitions of peripheral neuropathy, and differences in the demographics of the subjects. Our study prospectively compared components of the PRVEP with the various parameters of the NCS. The changes in the P100 latencies were not significantly associated with most of the attributes of the NCS. However, poor glycemic control

proved to be an important risk factors over the 5 years because it was related to the development of subclinical polyneuropathy as has been reported in a previous study.[1]

This study has several limitations. First, we initially designed this study for adolescents with newly diagnosed type 1 diabetes, but only 7 of 36 patients had been diagnosed fewer than six months prior to the beginning of the study. Second, in the majority of newly diagnosed patients with type 1 diabetes mellitus, the initiation of insulin treatment improves the residual β-cell function and heralds partial remission (i.e., the honeymoon period). However, the duration of this honeymoon period is variable and can last from several months to 1 to 2 years.[24] Related to this point, our newly diagnosed diabetic patients exhibited improved glycemic control in the initial year of their diseases. These findings likely affected the clinical courses of our patients. Third, in the majority of the patients, hyperglycemia was not well controlled. Most people's understanding of diabetes in this age group is limited because the incidence and prevalence of type 1 diabetes in children and adolescents are quite low in Korea.[23] This lack of understanding might be one reason for the poor control of hyperglycemia in this study.

In conclusion, the P100 latencies of the PRVEP in the young adults with type 1 diabetes were prolonged at study entry compared with those of the controls. These data may suggest that an impairment of the VEP should be regarded as an early involvement of the CNS in type 1 diabetes. Due to the long duration clinical course of type 1 diabetes in young adults, once central conduction is delayed, the patients' ages, disease durations, and metabolic control did not affect the latency of the P100 of the PRVEP at least within the early stages of the disease. In contrast, poor glycemic control proved to be an important risk factor over the 5-year follow up in terms of the development of peripheral neural pathway abnormalities.

DISCLOSURE

Conflicts of Interest: None

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