Brainstem auditory and visual evoked potentials in Type 1 (insulin-dependent) diabetic patients

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Summary. Brainstem auditory evoked potentials and pattern shift visual evoked potentials were measured in 34 Type 1 (insulin-dependent) diabetic patients with long-standing disease and in 43 control subjects. Thirty-two percent of diabetic patients had abnormal brainstem auditory evoked potentials and 15% had abnormal visual evoked potentials. These abnormalities were not related to duration of diabetes, diabetic control or individual diabetic complications (retinopathy, nephropa-

thy, peripheral or autonomic neuropathy). The aetiology of the abnormalities must remain a subject for speculation. The findings of this study are consistent with a central diabetic neuropathy involving the brainstem in long-standing diabetic patients.

Key words: Brainstem, auditory evoked potential, visual evoked potential, neuropathy.

Glucose is an essential nutrient for the brain; it is not surprising, therefore, that perturbations in glucoregulation can cause cerebral functional or even structural impairment. However, in 1950 DeJong [1] described “diabetic encephalopathy” in a case with severe clinical and histological central nervous system abnormalities, and subsequently others have shown diffuse histopathological changes in the brains of subjects with long-standing diabetes which differ from the changes induced by hypoglycaemia [2]. These degenerative changes were ascribed to angiopathy or a primary diabetic abnormality.

In the past, measurements of electrocortical activity using electroencephalographic recordings have been employed to study patients with diabetes. Pathological abnormalities have been most strongly related to severe hypoglycaemia [3], although they have also been seen in diabetic ketoacidosis [4]. However, the electroencephalogram does not provide information about deeper brain structures such as the brainstem, where important nuclei, including those controlling the autonomic nervous system, are situated. Measurements of electrically evoked potentials provide an opportunity to evaluate the functional integrity of the neural pathways of the central nervous system. The clinical utility of evoked potentials derives from the close relation between the waveforms and anatomic structures, including various nuclei and tracts. Both brainstem auditory evoked potentials (BAEP) and pattern shift visual evoked poten-

tials (PSVEP) have been used extensively in the diagnostic evaluation of various disorders affecting the central nervous system. In this report we describe the results of BAEP and PSVEP evaluation of diabetic patients with long-standing disease.

Subjects and methods

Thirty-four subjects (13 males and 21 females) with Type 1 (insulin-dependent) diabetes mellitus were selected for this study from among patients attending the diabetic clinic at Southern Illinois University School of Medicine, Springfield, Ill, USA (Table 1). Written informed consent was obtained from each participant and the investigation protocol was reviewed and approved by the Committee for Research Involving Human Subjects. The age range of the patients was between 14 and 63 years (mean $\pm$ SD: 34 ± 13) and their duration of diabetes was between 9 and 42 years (mean $\pm$ SD: 20 ± 9). All the patients studied were managed with a combination of regular and isophane insulin twice daily (mean dose, units/24 h: 45 ± 16). Independent evaluation of each patient to ascertain the presence of diabetic complications was carried out using ophthalmoscopy, clinical neurological examination, evaluation of vibration sense using a Bio-thesiometer (Biomedical Instrument Co., Newbury, OH, USA) and autonomic nervous system testing. The latter included pulse and blood pressure responses to postural changes and the heart rate responses to deep breathing, to the Valsalva maneuver and to standing [5]. Nephropathy was diagnosed in patients with persistent proteinuria, regardless of the level of the serum creatinine. Retinopathy affected 23 subjects, peripheral neuropathy 15, autonomic neuropathy 13 and nephropathy 11. All the patients were euthyroid and had a serum creatinine less than $180 \mu\text{mol/l}$. Twenty-six patients had a visual acuity of 20/20, six patients had an acuity of 20/40 and the remaining two patients had an

acuity of less than 20/200 in at least one eye. None of the patients had any hearing impairment; the average click hearing threshold was between 25–30 dB Pe SPL (peak equivalent sound pressure level; normal hearing threshold is about 30 dB Pe SPL). None of the patients was receiving beta adrenergic blockers or drugs known to interfere with functioning of the nervous system.

Forty-three healthy individuals with normal vision and hearing, of the same age range as the diabetic patients, were used as controls. The mean age of the control group (mean $\pm$ SD: 29 ± 10 years) did not differ significantly from that of the 34 diabetic patients (34 ± 13 years, $p > 0.06$).

Brainstem auditory evoked potential and pattern shift visual evoked potential studies were all carried out in the morning between 08.00 and 10.00 h. Patients received their usual insulin dose and had breakfast before the study. A blood glucose measurement was obtained after breakfast and immediately prior to the study. In addition, since each patient regularly attended our clinic, serial glycosylated haemoglobin measurements were available for the 12 month period preceding this study. The mean $\pm$ SD glycosylated haemoglobin level

was $11.3 \pm 2.91\%$ (Table 1). The measurement of glycosylated haemoglobin was carried out according to the modified method of Trivelli et al. [6]. The normal range by this method is 5.4–8.5%.

Evoked potential studies

Brainstem auditory evoked potentials (BAEP) were recorded with stimuli 60 decibels above the subject's measured hearing threshold. Rarefaction clicks at 11.1 and 33.1/s were used with two determinations made with stimuli to each ear. Wave I through wave V individual latencies, interpeak latencies between waves I–III, I–V and III–V, and the wave V amplitude were measured. Wave I latency values are considered an index of peripheral transmission, while wave I–V interpeak latency represents an index of central transmission time. Wave I is generated primarily by the portion of nerve VIII that is contiguous with the spiral ganglion in the mastoid bone, while waves II and III have a lower pontine origin in the brainstem. Waves IV and V possibly also have a mid-pontine origin in humans [7].

Pattern shift visual evoked potentials (PSVEP) were evaluated in all patients. Visual acuity was measured in all the subjects prior to testing. Checkerboard stimuli with 8×8 and 32×32 mm check sizes were used for the pattern shift visual evoked potential studies. Two studies were performed with each eye. The amplitude and latency of the positive wave – P1 (P100) was calculated. P1 (P100) is the clinically useful part of the visual evoked potential generated by the visual cortex, appearing about 100 ms after the pattern shift stimulus.

Statistical analysis: Pearson's correlation coefficient, analysis of variance (ANOVA) including point biserial correlation and Student's *t*-test were used to analyze the data. Statistical significance was determined at the 0.05 level

Results

Brainstem auditory evoked potentials (BAEP) (Table 2). In our laboratory, the brainstem auditory evoked potential latencies and interpeak latencies in nondiabetic male and female control subjects were in close agreement with other published norms. However, diabetic

Table 1. Clinical data of Type 1 (insulin-dependent) diabetic patients

Number of patients	34 (13m, 21f)
Age (yrs)	34 ± 13
Duration of diabetes (yrs)	20 ± 9
Blood glucose (mmol/l)	14 ± 5^a
HbA _{1c} (%)	11 ± 3^b
Insulin dosage (U/24 h)	45 ± 16
Heart rate variation on deep breathing (beats/min)	14 ± 8^c
Numbers of patients	
with retinopathy	23 ^d
with peripheral neuropathy	15
with autonomic neuropathy	13
with nephropathy	11

^{a, b} Results are expressed as mean $\pm$ SD, and, at the time of the experiment, based upon the means of several measurements performed during the 12 months preceding the experiment for each patient.

^c The heart rate variation was 5.8 ± 3.0 for patients with autonomic neuropathy and 19.5 ± 4.5 for patients without autonomic neuropathy ($p < 0.001$).

^d Fourteen patients had background and 9 patients had proliferative retinopathy.

Table 2. Brainstem auditory evoked potentials (latencies) in 34 Type 1 diabetic patients and in 43 nondiabetic control subjects

Males			Females		
Wave	Nondiabetic (<i>n</i> = 17)	Diabetic (<i>n</i> = 13)	Wave	Nondiabetic (<i>n</i> = 26)	Diabetic (<i>n</i> = 21)
<i>Left ear</i>			<i>Left ear</i>		
I	1.69 ± 0.173	1.75 ± 0.219	I	1.65 ± 0.127	1.61 ± 0.166
III	3.85 ± 0.168	4.05 ± 0.274^b	III	3.82 ± 0.163	3.84 ± 0.207
V	5.85 ± 0.222	6.14 ± 0.410^b	V	5.66 ± 0.148	5.79 ± 0.267^b
I–III	2.18 ± 0.173	2.30 ± 0.169	I–III	2.15 ± 0.168	2.22 ± 0.179
I–V	4.18 ± 0.189	4.39 ± 0.334^a	I–V	4.01 ± 0.235	4.18 ± 0.271^b
III–V	2.00 ± 0.135	2.09 ± 0.291	III–V	1.84 ± 0.178	1.96 ± 0.175^a
<i>Right Ear</i>			<i>Right Ear</i>		
I	1.76 ± 0.222	1.73 ± 0.183	I	1.73 ± 0.143	1.71 ± 0.188
III	3.89 ± 0.148	4.00 ± 0.112^a	III	3.83 ± 0.178	3.87 ± 0.230
V	5.88 ± 0.181	6.11 ± 0.288^b	V	5.71 ± 0.209	5.87 ± 0.281^a
I–III	2.13 ± 0.173	2.26 ± 0.191	I–III	2.09 ± 0.173	2.16 ± 0.184
I–V	4.10 ± 0.181	4.40 ± 0.371^a	I–V	3.98 ± 0.245	4.15 ± 0.276^a
III–V	1.97 ± 0.107	2.11 ± 0.284	III–V	1.89 ± 0.178	1.99 ± 0.188^a

The stimulation frequency used was 11.1 clicks/s, and results are expressed in milliseconds (mean $\pm$ SD).

^a $p < 0.05$; ^b $p < 0.03$

Table 3. Pattern shift visual evoked potentials (latencies) in 34 Type 1 diabetic patients and in 43 nondiabetic control subjects

Males			Females		
	Nondiabetic (<i>n</i> = 17)	Diabetic (<i>n</i> = 13)		Nondiabetic (<i>n</i> = 26)	Diabetic (<i>n</i> = 21)
<i>Left eye</i>			<i>Left eye</i>		
P1 _a	94.65 ± 5.31	96.25 ± 4.75	P1 _a	93.47 ± 4.31	91.79 ± 7.41
P1 _b	95.21 ± 2.66	100.15 ± 5.00 ^a	P1 _b	93.35 ± 4.81	95.12 ± 5.66
<i>Right eye</i>			<i>Right eye</i>		
P1 _a	94.17 ± 4.11	95.73 ± 5.25	P1 _a	94.91 ± 5.38	92.18 ± 5.31
P1 _b	95.75 ± 3.51	96.45 ± 4.03	P1 _b	93.98 ± 4.24	95.55 ± 5.88

Results are expressed in milliseconds (mean ± SD); P1_a refers to checkerboard stimulus size 8 × 8 mm; P1_b refers to checkerboard stimulus size 32 × 32 mm; ^a *p* < 0.05

patients clearly differed from controls using 11.1/s rarefaction clicks. The wave III latency in males and wave V latency in both males and females were significantly increased (*p* < 0.05). The I–V interpeak latency in both males and females, and III–V interpeak latency in females, were also significantly increased in the diabetic patients (*p* < 0.05). Using 33.1/s rarefaction clicks, significantly increased latency to wave V (*p* < 0.05) was detected in the male diabetic patients. The wave V amplitude recorded with the right ear was significantly decreased in males only (*p* < 0.05) at 11.1/s rarefaction clicks.

On an individual basis, 11 of 34 (32%) diabetic patients had abnormalities beyond two standard deviations in wave V latency and I–V interpeak latencies. Six of these patients (17% of the total patients) had abnormalities beyond 3 standard deviations.

Wave latency and interpeak latency were not significantly correlated (*p* > 0.05) with age, duration of diabetes, blood glucose at the time of testing, and prevailing HbA_{1c} using Pearson's correlation coefficient; nor were they significantly correlated with the presence of retinopathy, nephropathy, peripheral neuropathy or autonomic neuropathy using point biserial correlation.

Pattern shift visual evoked potentials (PSVEP) (Table 3). Using different check sizes, no differences were observed in females when the diabetic and nondiabetic (laboratory control) subjects were compared with regard to mean values for P1 (P100). In the males, however, the P1 latency from the left eye was increased in subjects with diabetes compared to the subjects without diabetes using a large check size (3.2 × 3.2 cm) (*p* < 0.05); the right eye did not show this pattern.

On an individual basis, 5 of 34 diabetic patients (15%) showed abnormal visual evoked potential studies. Four of these patients had proliferative retinopathy and one had background retinopathy. If two of these patients who had marked reduction in visual acuity in one eye are excluded, abnormal visual evoked potentials would have been recorded in only 3 of 32 diabetic patients (9%). There was no correlation between

PSVEP and age, duration of diabetes, blood glucose at the time of testing, and prevailing HbA_{1c} using Pearson's correlation coefficient; or with retinopathy, nephropathy, peripheral or autonomic neuropathy using point biserial correlation.

Discussion

Our results demonstrate definite abnormalities in the brainstem auditory evoked potentials of subjects with long-standing Type 1 diabetes. Since wave I latency was normal in our patients, it must be concluded that the observed abnormalities are central (brainstem). Although abnormal BAEP have been noted by other workers [8–10], our findings indicate that not only are these abnormalities relatively common in diabetic patients, but that in nearly a third of our subjects they fall outside two standard deviations from the mean for normal subjects. Whether these changes result from primary neural involvement or represent neural dysfunction secondary to vascular involvement remains speculative. Our study failed to show any correlation between BAEP and several clinical parameters including age, duration of diabetes, blood glucose at the time of testing and presence of diabetic complications. Although there was no correlation between BAEP and diabetic control as determined by glycosylated haemoglobin, it must be noted that the group of patients we studied had been in unsatisfactory to poor metabolic control. Among the issues which remain to be addressed are how early after the onset of diabetes these abnormalities develop, and whether certain measures, such as tight control of diabetes, can prevent or reverse these abnormalities. Only longitudinal studies can answer these questions.

Diabetic patients as a group did not appear to have significant visual evoked potential abnormalities, although we identified 5 individual patients who showed some alteration in these potentials. Moreover, when comparing diabetic patients with nondiabetic controls, only one of the latencies measured was significantly different, a finding which could be explained by chance

considering the low level of significance recorded. Our findings are therefore in contrast to previous reports in which between 30 and 63% of diabetic patients were found to have abnormalities [11, 12]. The wide discrepancy between the results of different studies remains unexplained. Whether PSVEP abnormalities are the result of peripheral optic nerve involvement or represent cortical involvement is also unclear. Among all the diabetic patients we studied, there were only three who had both brainstem and visual evoked potential abnormalities. These patients are noteworthy for the severity of their diabetes and its widespread complications.

This study clearly establishes the high frequency of brainstem auditory evoked potential abnormalities in diabetic patients with long-standing disease and further corroborates the view that a central diabetic neuropathy occurs in diabetes [1]. The lack of correlation between abnormal BAEP and diabetic complications does raise the possibility that the mechanism(s) explaining the abnormal BAEP may be different from the factors leading to the well recognized complications of retinopathy, nephropathy and neuropathy. Metabolic perturbations including episodes of hypo- or hyperglycaemia and chronic hyperglycaemia or instability of diabetic control are possible causative factors for the abnormal BAEP. Among the group of patients we studied, the possible effect of chronic hyperglycaemia is certainly an important consideration. However, insulin itself may be implicated because it is involved with electrolyte transport in the brain [13]. On the other hand, the histological changes found by Aronson [14] in the brainstem of male and female Type 1 diabetic patients suggest that angiopathy may also play an important role.

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