EVALUATION OF BRAINSTEM AUDITORY EVOKED POTENTIAL IN DIABETICS

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ABSTRACT

BACKGROUND: Brainstem auditory evoked potentials (BAEP) have been used for electrophysiological assessment of central neuropathy in diabetes. However, the role of this test in documenting the abnormality, the site of abnormality and relation of these abnormalities with metabolic control of diabetes are not clear as yet. The present study was done to explore the presence of abnormalities, if any, in the test parameters and relation of these with diabetic status.

METHODS: It was a cross sectional study with controls. Thirty patients of diabetes mellitus (group 1) and thirty healthy controls (group 2) were included in the study. All the patients were subjected to detail clinical history, clinical and neurological examination. Detail laboratory investigation including haemogram, fasting and postprandial plasma sugar (2 hours), HbA1c, urine R/E, 24 hour urine for proteins, ECG, RFT, LFT and lipid profile were done. BAEP was done in all the subjects

RESULTS: Mean peak latency of waves I, III, V and interpeak latency of I-III, III-V, I-V were prolonged in group 1, but were not statistically significant. Abnormal BAEP response was found in 8 patients (27%) in group 1. There was no significant relation between abnormal BAEP response with age, sex, type of diabetes, duration of diabetes since detection, fasting plasma sugar level, postprandial plasma sugar level, glycosylated haemoglobin, presence of retinopathy, nephropathy and peripheral neuropathy.

CONCLUSIONS: BAEP is a useful method for obtaining an early diagnosis of central and cranial nerve abnormalities in diabetic patients.

KEY WORDS: Brainstem auditory evoked potentials, BAEP, Central Neuropathy, Diabetic Neuropathy

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INTRODUCTION

Brainstem auditory evoked potentials have been proved as valuable tools for hearing assessment, diagnosis of neurological disorders and intraoperative monitoring of patients. Peripheral neuropathy is a known complication of diabetes mellitus. Studies on prevalence of diabetic neuropathy are difficult to evaluate because of lack of consistency in the definition of neuropathy and method used for its detection. However, depending on the diagnostic criteria employed, prevalence of diabetic neuropathy is reported to be 10-66%.[1,2]

A small percentage of patients develop neuropathy regardless of the duration of their diabetes and its adequate control, while others manifest with severe neuropathy at the presentation. The cause of marked variations in the course and extent of neuropathy in presence of a presumebly common metabolic abnormality is unknown; however, genetic susceptibility has been suspected. While peripheral and autonomic nervous dysfunction in diabetics is an established fact, information on central nervous dysfunction is as yet limited. Some authors have reported detection of evoked potential abnormalities in patients of diabetes with cognitive dysfunction.[3,4] Evoked potential abnormalities have been observed even before clinical evidence of cognitive dysfunction. Recent reports of value of certain therapeutic interventions in normalization of the cognitive dysfunction and evoked potentials,[5] have made the assessment of role of these tests in day to day practice even more pertinent. There are interindividual variability in peak latencies and interpeak latencies so a control data is required to derive normal values. The control data must be acquired under the same conditions which are used for the test population. Amplitude of various waves are also highly variable. Brainstem auditory evoked potentials (BAEP) has been used for electrophysiological assessment of central neuropathy in diabetes.[6-9] However, the role of these tests in documenting the abnormality, the site of abnormality i.e. whether central or peripheral and relation of these abnormalities with metabolic control of diabetes and presence or absence of peripheral neuropathy are not clear as yet. The present study was done to explore the presence of abnormalities, if any, in these tests parameters and relation of these with diabetic status. Early detection of subclinical central nervous system function abnormalities and interventions at the early stage, are futuristic concepts in management of diabetes mellitus.

METHODS

The study was conducted in the department of medicine of B. P. Koirala Institute of Health Sciences, Dharan between April 2005 and March 2006. It was a cross sectional study with controls. Thirty patients of diabetes mellitus between 25 to 65 years of age irrespective of their metabolic control or use of oral hypoglycemic agents or insulin were included in the study. Diabetes Mellitus was diagnosed according to WHO criteria: Symptoms of diabetes plus random blood glucose concentration ≥200 mg/dL or fasting plasma glucose ≥126 mg/dL or two-hour plasma glucose ≥200/dL. Random was defined as without regard to time since meal. Fasting was defined as no caloric intake for at least 8 hours. Thirty age and sex matched controls were also evaluated in the study. The following groups of patients were excluded from the study; haemodynamically unstable patients, patients on drugs known to confound results of BAEP like carbamazepine, methyldopa, reserpine and nitrofurantoin, patients with stroke and cranial nerve palsies, profound hearing loss, otitis media with or without effusion, encephalopathy, raised serum creatinine >2 mg/dl.

Detailed clinical history and physical examination including meticulous neurological examination, ophthalmic fundus examination and otological assessment was carried out in all the subjects according to Pro-forma. All the patients were subjected to laboratory examination including haemogram, fasting and postprandial plasma sugar (2 hours), glycosylated haemoglobin, urine routine and microscopy, 24 hour urine for proteins, electrocardiogram, renal function tests, liver function tests and lipid profile. All the patients and controls were submitted to electrophysiological evaluation including BAEP and blink reflex. Nihon Kohden NeuroPack-2 machine was used for the electrophysiological assessment. The study was carried out in a quiet sound proof room, keeping subject in a comfortable supine position.

Brainstem auditory evoked potential was elicited by brief acoustic rarefaction click produced by delivering monophasic square pulses of 100 microseconds duration to headphones at a rate of 13 Hz. Sensory threshold for hearing was determined in all subjects for each ear and BAEP was recorded at 60 dBSL level. The contralateral ear was masked with continuous white noise at intensity of 40 dB. The evoked potentials within 10 msec of stimulation was recorded by using 2 channels with electrodes placed at the vertex (Cz electrode according to the international 10-20 system of electrode placement) and both the earlobes (the earlobes ipsilateral and contra lateral to the stimulated ear are labeled Ai and Ac, respectively). The electrical activity was filtered with a pass band of 100 Hz 3 KHz. The responses to 2000 auditory stimuli were averaged with sweep of 10 milliseconds. Two recordings were taken for each ear. Absolute peak latencies (APL) of waves I, III, V and interpeak latencies (IPL) of waves I-III, III-V and I-V were

recorded in milliseconds. We calculated average of two response. These absolute peak latencies and interpeak latencies obtained from diabetics were compared with those of control group. The collected data was entered into Microsoft Excel Spreadsheet. The data was analyzed using SPSS ver 11.5 Mean and standard deviation of absolute peak latencies (of waves I, III, V), interpeak latencies (I-III, III-V and I-V) of both Group 1 and Group 2 were calculated. Independent samples test was used to compare the means. Pearson correlation was use to see relation between continuous variable.

RESULTS

All together 30 diabetic (Group 1) and 30 matched healthy controls were recruited in this study.

Mean age of patients in Group 1 was 45.97 years (SD = ±12.28 years; Range = 25-64 years). Mean age of Group 2 consisting of healthy controls was 40.60 years (SD = ±9.55 years; Range = 2764 years). The two groups were similar with respect to age with no significant difference (p-value 0.064). The two groups had similar proportion of males and females. There were 17 (57%) females and 13 (43%) males in Group 1 while Group 2 consisted of 16 (53%) females and 14 males. Most of subjects (15) were from Sunsari and surrounding districts. There were four patients (13%) of type 1 diabetes and 26 patients (87%) of type 2 diabetes. There were 5 smoker and 8 social alcohol drinker. The mean duration of diabetes since detection was 48.6 months (range 0.5 to 168 months). Pulse rate, blood pressure, weight, height, BMI, MMSE were comparable in two groups. None of our subjects had postural drop of blood pressure. Clinical evaluation revealed evidence of peripheral neuropathy in 13 (43%) patients. Microalbuminuria was seen in twelve patients (40%) and overt proteinuria was seen in eighteen patients (60%). Retinopathy was found in 6 diabetic patients (20%). Four (13%) were having background retinopathy and 2 (7%) were having proliferative retinopathy. Fasting plasma glucose was ranging from 69 to 335mg/dL. Mean was 163±73.3 mg/dL. In our study we found 14 (47%) patients were euglycemic and 16 (53%) were hyperglycemic. Eleven patients were having postprandial plasma sugar <200 mg/dL (37%) and nineteen patients were having postprandial plasma sugar ≥200 mg/dL (63%). Group 1 patients had glycosylated haemoglobin in the range of 7 to 17.72. Mean was 9.41± 2.19. Mean (±SD) for latency of waves I, III, V and interpeak latency of I-III, III-V, I-V was calculated in milliseconds for both group 1 (diabetic) and group 2 (control). We have calculated mean and SD of latencies and IPLs for right and left ear separately. We also calculated absolute latencies and IPLs by taking average of latencies and IPLs of right and left ear. Mean to mean comparison was done between the two groups.

As shown in the table 1, latency of waves I, III, V and IPL of waves I-III, III-V, I-V in group 1 were greater than it is in control group. The difference could not reach to a statistically significant level. P-value was >0.05.

Table 1 Mean and SD of latencies and IPLs for right ear (ms)

Latency and interpeak latency (ms) of right ear	Group 1 (n: 30)	Group 2 (n: 30)	P-value
Wave I	1.6233±0.1454	1.5937±0.1441	0.431
Wave III	3.8247±0.2415	3.7237±0.1923	0.078
Wave V	5.7283±0.2917	5.6043±0.2202	0.068
IPL I-III	2.2013±0.1961	2.1300±0.2288	0.200
IPL III-V	1.9037±0.1607	1.8807±0.2149	0.641
IPL I-V	4.1050±0.2735	4.0107±0.2382	0.160

Similarly we calculated mean and SD of latencies and IPLs of left ear in group 1 and group 2 and compared each other. The mean and SD of latencies and IPLs of left ear in group 1 and group 2 are given in table 2 In left ear also mean latencies and IPLs of group 1 were prolonged than group 2 but the difference could not reach to a statistically significant level. (p >0.05)

Table 2 Mean and SD of latencies and IPLs for left ear (ms)

Latency and interpeak latency (ms) of left ear	Group 1 (n: 30)	Group 2 (n: 30)	P-value
Wave I	1.6210±0.1427	1.5983±0.1565	0.560
Wave III	3.8470±0.2650	3.7407±0.2054	0.088
Wave V	5.7717±0.3056	5.6637±0.2108	0.117
IPL I-III	2.2260±.2340	2.1423±0.2396	0.176
IPL III-V	1.9247±0.1931	1.9230±0.1905	0.973
IPL I-V	4.1507±0.3043	4.0653±0.2277	0.224

We also calculated absolute latencies and IPLs by taking average of latencies and IPLs of right and left ear. Mean±SD of absolute latencies and IPLs was calculated. Mean of Absolute latencies and IPLs were prolonged in group 1, but was not statistically significant.(Table 3)

Table 3 Mean and SD of absolute latencies and IPLs (ms)

Absolute latency and interpeak latency (ms)	Group 1 (n: 60)	Group 2 (n: 60)	P-value
Wave I	1.62217±0.13737	1.5900±0.14502	0.476
Wave III	3.8358±0.2454	3.7322±0.1889	0.072
Wave V	5.7500±0.29266	5.6400±0.20389	0.080
IPL I-III	2.21367±0.20657	2.1617±0.22394	0.169
IPL III-V	1.91417±0.16677	1.90183±0.18787	0.789
IPL I-V	4.1278±0.2797	4.0380±0.2215	0.173

Based on absolute latency and interpeak latency we established criteria for abnormal BAEP response. We used sum of mean plus two standard deviation (SD) of latency and interpeak latency as upper limit of normal: Latency of wave I >1.88604 ms; Latency of wave III >4.11 ms; Latency of wave V >6.04178 ms; Interpeak latency I-III >2.58405; Interpeak latency III-V >2.27757; Interpeak latency I-V >4.4810. Based on above criteria we found abnormal BAEPs in 8 patients (27%) in group 1. Five patients had abnormal prolongation of latency of wave III and wave V, t was commonest abnormality found in our patients. Prolonged IPL of I-III component was found in one patients and prolonged interpeak latency of I-V component was found in three patients. None of our patient had prolongation of IPL of III-V component. We also analyzed latency and interpeak latency of BAEP and blink reflex with continuous variables like age, fasting plasma sugar, postprandial plasma sugar, HbA1c, duration of diabetes since detection, microalbuminuia and GFR by using Pearson correlation. No significant relation between it was found (p-value >0.05).

DISCUSSION

The basis for the various CNS complications of diabetes is poorly understood. Some of the postulated mechanisms are10 : decreased cerebral blood flow due to impaired autoregulation, altered neurotransmitter metabolism, altered brain-energy metabolism, structural defects of brain i.e., decreased brain volume and weight, and loss of cortical neurons, non-enzymatic glycosylation of brain tissue, increased CNS sorbitol levels. Some workers have reported improvement with Ginkgo biloba extract in evoked potentials (visual evoked potential) in diabetic rats.5 This might have implications in the management of diabetics.

Evoked potentials represent the summated activity of large populations of neurons firing in synchrony; the electrical signal produced by a single cell is too small to be seen at the scalp. If the timing of neuronal activity is delayed uniformly across the cell population, a delayed evoked potential component will result. If the delay is nonuniform and the electrical signals are desynchronized, a process called temporal dispersion, the summation may not produce a recognizable evoked potential component. Because the same pathophysiology Evoked potential studies including BAEP have been used as one of the parameters for determining subclinical abnormalities in the brain stem in diabetics.11,12 Brainstem auditory evoked potential recording is a sensitive, noninvasive neurophysiological method for selectively recording the electrical events which occur along the auditory pathway in the brain stem. It provides an objective measure of neurological dysfunction in the auditory system and brainstem. A standard BAEP consists of seven waveforms labeled I-VII, recorded from the human scalp within 10 milliseconds of appropriate acoustic stimulus. First five of these wave forms are routinely used in clinical practice because of their consistency. Abnormalities in the responses provide evidence of abnormality of cochlear (Eight) nerve and / or brainstem. The generators of the first five recorded Potentials are believed to be from the region of the cochlear nerve (wave I), dorsal cochlear nucleus (wave II), superior olive (wave III-pons level), lateral leminscus (wave IV) and inferior colliculus (wave V-midbrain level). Measurement of peak-to-peak amplitudes and the latencies may provide useful information about these structures. Interpeak latencies (IPL) assess the function of the eight nerves and lower pons level (I-III IPL) and upper pons / midbrain level (III-V IPL) of the brainstem. I-V IPL equates to the central conduction time. In our study of BAEP latency of waves I, III, V and IPL of wave I-III, III-V, I-V in diabetic patients were greater than control group. The difference could not reach to a statistically significant level. P-value was >0.05. Previous study done by Verma A et al13 also had shown similar results. Brainstem auditory evoked responses were recorded in 22 diabetic patients with a variable duration of diabetes (mean 5.8 years) and in controls of comparable age. Variations in the form of individual wave latency, interpeak latencies and V wave amplitude were compared in the both groups. No difference was found in any of the parameters. Different researchers have found variable results in BAEP wave latencies in patients with diabetes. Al-Azzawi et al found highly significant difference in the increased latency of waves I, III and V, intepeak latency of waves I - III, I - V and III V of each type of diabetes as compared to control.11 Alexander et al evaluated BAEP in twenty patients with Tropical Pancreatic Diabetes (TPD). The latencies of BAEP Wave III ($p < 0.009$) and V ($p <$

0.47) as well as the Interpeak Latencies I-III ($p < 0.002$), and I-V ($p < 0.019$) were significantly prolonged in patients with TPD then age and sex matched healthy volunteers.12 In our study there was no significant difference in abnormal BAEP and duration of diabetes but interpeak latency of waves III-V was significantly prolonged in group of our of patients having diabetes for more than 5 years compared to patients having diabetes for less than 5 years (p-value 0.041). Zehra A et al found no significant correlation between the duration of diabetes and latencies of BAEP waves.14 Similarly Durmus C et al also found no relation between BAEP latency and the duration of diabetes.($p > 0.05$).15 Whereas Virtaniemi et al found that the duration of diabetes were associated with the prolongation of auditory brainstem latencies.16 We also used Pearson's correlation to correlate absolute latencies and IPLs with fasting plasma sugar levels, postprandial plasma sugar level and HbA1c. No significant correlation was seen. Durmus et al have found blood glucose level were not associated with prolonged BAEP latencies (p-value > 0.05).15 Zehra A et al also found no significant correlation between blood glucose levels and the latencies of BAEP waves.14 Dolu et al found no correlation between BAEP and the degree of hyperglycemia and metabolic control.17 There was no significant difference in BAEP or BR with patients in CKD stage1 or 2 or retinopathy.

CONCLUSIONS

It therefore appears that the BAEP is a useful method for obtaining an early diagnosis of central and cranial nerve abnormalities in diabetic patients. It is an easy non-invasive technique that provides data that can not be obtained through clinical examination. The differences in the incidence of electrophysiological abnormalities in previous studies and the present one may be related to patient selection and different recording technique.

CONFLICT OF INTEREST:

The Authors have no conflict of interest with the material presented in this paper

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