DOI: 10.7860/JCDR/2016/19336.8791

Original Article

Physiology Section

To Study Brain Stem Auditory Evoked Potential in Patients with Type 2 Diabetes Mellitus- A Cross-Sectional Comparative Study

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ABSTRACT

Introduction: Neuropathy is one of the commonest complications of Diabetes Mellitus (DM). Apart from having peripheral and autonomic neuropathy patients with type 2 DM may also suffer from sensory neural hearing loss, which is more severe at higher frequencies. However, few studies have done detailed evaluation of sensory pathway in these patients. In this study brain stem auditory evoked potential is used to detect the acoustic and central neuropathy in a group of patients with type 2 DM with controlled and uncontrolled blood sugar.

Aim: To study brain stem auditory evoked potential in patients of type 2 DM with controlled and uncontrolled blood sugar and to correlate the various parameters e.g., age (years), weight (kilograms), height (meters), BMI (kg/m^2), HbA1c (%) in patients with type 2 DM with controlled and uncontrolled blood sugar.

Materials and Methods: Cross-sectional comparative study conducted from January 2014 to January 2015. Total 60 patients with type 2 DM of either sex, between age groups of 35-50 years were enrolled from the Diabetic Clinic of Medicine department, of a tertiary care hospital. Based on the value of HbA1c, patients were divided in two groups with controlled and uncontrolled blood sugar and with each group comprising of 30 patients. BERA (Brainstem Evoked Response Audiometry) was done in both the groups on RMS ALERON 201/401. Recordings were taken at 70dB, 80dB and 90dB at 2KHz frequency. Absolute latency of wave I, III, V and interpeak latencies I–III, III-V and I-V were recorded.

Results: Mean±SD of the absolute latency of BERA waves I, III, V and interpeak latencies I–III, III-V and I-V at 2 KHz and at varying intensity of 70dB, 80dB and 90dB in uncontrolled group of DM were delayed and were significant as compared to controlled group of DM.

Conclusion: If BERA is done in diabetic patients, central neuropathy can be detected earlier in uncontrolled groups of diabetic patients.

Keywords: Brainstem evoked response of audiometry, Interpeak latency, Absolute latency, Central neuropathy

INTRODUCTION

Long standing diabetes can cause many micro and macro vascular complications causing significant morbidity and mortality. Pathologically it constitutes the triad of neuropathy, retinopathy, and nephropathy. A diffuse peripheral polyneuropathy involving autonomic and peripheral nerves is a well-known complication of Diabetes Mellitus (DM) [1]. Diabetic neuropathy occurs in 50% of individuals with long-standing type 1 and type 2 DM. Risk of developing diabetic neuropathy increases with duration of diabetes [2]. It is a progressive process that has a long asymptomatic stage. Diabetics suffer from hearing loss also which tends to be sensory neural, slowly progressive and bilateral with a more severe loss at higher frequencies [1]. Many studies on diabetic neuropathy in the past were concerned mainly with peripheral and autonomic nerves; however, with availability of more evolved evoked potential techniques, evaluation of sensory pathways in central nervous system becomes easier and more productive. Studies of Reske Neilson et al., and Makishima et al., have shown involvement of brain parenchyma in patients of long standing DM [3,4], thereby, suggesting the presence of central neuropathy. Other studies that have reported similar findings of central neuropathy in diabetic patients are Coshum Durmus et al., Toth et al., and Virtaniemi J et al., [5-7]. However, Verma et al., reported normal auditory brain stem evoked responses in patients of diabetes [8].

Brainstem Evoked Response Audiometry (BERA) is a non-invasive electrophysiological tool to detect retro cochlear lesion. Thus, it is of immense help in guiding us for detection of early impairment of the auditory nerve and of brain stem function [1]. The study of auditory brain stem evoked responses provides an opportunity to evaluate the functional integrity of auditory pathway from inner ear to upper brain stem. BERA is a non-invasive electrophysiological tool to detect retro cochlear lesion. Thus, it is of immense help in guiding us for detection of early impairment of the auditory nerve and of brain stem function [1]. The study of auditory brain stem evoked responses provides an opportunity to evaluate the functional integrity of auditory pathway from inner ear to upper brain stem. The present study aims to study auditory brain stem evoked response changes in patients of DM at 2KHz frequency. Further, an attempt was made to relate abnormal brainstem evoked responses with the blood glucose level and central neuropathy.

MATERIALS AND METHODS

The study protocol was approved from the Institutional Ethics Committee. It was a cross-sectional comparative study, conducted from January 2014 to January 2015. Total 60 type 2 DM patients of either sex between the age of 35-50 years and duration of diabetes between 1-10 years were enrolled from the Diabetic Clinic of Medicine department, of a tertiary care hospital. We hypothesized that BERA waves latencies and inter-peak latencies would be increased in uncontrolled diabetic patients. Sample size determined by AI - Therapy Statistics BETA large effect size (0.8). Alpha value was taken as 0.05 and power of study at 80% for testing one tailed hypothesis. So total number of patients required: 52 (26 in each group). This study emphasizes on the changes

between controlled and uncontrolled blood sugar levels of diabetic patients as complications are more in diabetic patients so age and sex matched non diabetic subjects were not included in this study. Randomization was done and based on HbA1c [9] were divided into two groups.

a) Group 1 - n=30 controlled Type 2 DM patients having HbA1c below 7%.

b) Group 2- n=30 uncontrolled Type 2 DM patients having HbA1c equal and above 7%.

Patients were excluded from the study if they were having history of ear disease, occupational history of exposure to prolonged loud noise, intake of ototoxic drugs, strokes, head injury or family history of deafness. The patients with history of drug intake known to cause central neuropathy e.g., methyldopa, reserpine, phenytoin, anti-psychotic, anti-depressants were also excluded from the study. Diabetic patients with clinically apparent neuropathy involving the eighth cranial nerve manifesting as decrease or absent hearing loss were excluded from this study. Peripheral hearing loss was excluded by Rennies and Webers hearing tests. Peripheral neuropathy was excluded by doing pressure test with blunt object i.e., back of pen and proprioceptive tests i.e., sense of position for proximal and distal joints by rotating in various directions and keeps them in particular position and asked the subjects to keep the other limb in same position for large fiber nerves. Pain by pricking skin with a pin and pinching muscle tendon, touch by tactile localization and tactile discrimination tests. Temperature tests using cold and warm test tubes for small fiber nerves.

Body height (Ht) in centimeters was measured by having the subjects stand with their heels, buttocks and head against a wall. A flat object was placed on top of the subject's head and their height was marked on a tape measure affixed to the wall. Body weight was measured in kilograms (kg) with a standard portable weighing machine. BMI was calculated as body weight in kilogram divided by the square of body height in meters (kg/m^2) [10]. Diabetic patients attending the Diabetic clinic for routine check-up were on fasting. Fasting samples were collected in the clinic and fasting blood sugar was done. But, as the study emphasizes on the changes between controlled and uncontrolled blood sugar levels of diabetic patients as complications are more in uncontrolled diabetic patients which is better shown by HbA1c. HbA1c was done by A1C Care machine by Card method before conducting brain stem evoked response audiometry.

BERA audiometry was done in a sound treated room under standard conditions on RMS ALERON 201/401 model. The patient was instructed to be comfortable by all means. The test was carried out in relaxed sitting position. First the skin of forehead and of both mastoid process were made oil free. Patient was asked to remove any jewellery, hairpins, hearing aids or other metal objects that might interfere with the procedure. The recording electrodes were properly cleaned and standard adhesive paste (conducting medium) was applied in the recess of the electrodes and which were then adhered to cleaned surfaces of mastoid processes of both the ears. The reference electrode was kept on forehead. The head phone was applied in position. The low filter was set at 100Hz and high filter at 3000Hz. A brief click monoaural stimulus of short duration and low impedance was given. Recordings were taken at 70dB, 80dB and 90dB for 2KHz frequency. Atleast 2 recordings were taken to confirm the reproducibility of wave from and the absolute latencies of wave I, III, V and interpeak latencies I-III, III-V and I-V were recorded.

INTERPRETATION OF TEST RESULTS

The changes in brainstem auditory evoked potentials were recorded with diseases at different levels of the auditory pathway. Brainstem Auditory Evoked Potential (BAEP) is usually helpful in localizing the lesions in the brainstem as per waves. Absolute latency of wave I, wave III and wave V and inter-peak latencies of I-III, I-V and III –V waves were recorded.

STATISTICAL ANALYSIS

Statistical analysis was done on GRAPHPAD QUICKCALCS: t-test calculator.

The mean, standard deviation of all the baseline characteristics and the parameters i.e., latency of wave I, wave III, wave V and inter-peak latency of wave I-III, III-V and I-V were calculated. Baseline characteristics of the controlled and uncontrolled groups of diabetic patients were compared by using unpaired t-test.

The p-value of less than 0.05 ($p<0.05$) was considered to be statistically significant. The p-value of less than 0.001 ($p<0.001$) was considered to be statistically highly significant.

RESULTS

In the present study BAEPs were studied and compared between controlled and uncontrolled groups of diabetic patients. The observations and results were as follows. [Table/Fig-1] represents the demographic data.

1. The mean values of wave III, wave V and inter-peak latency I-III, III-V, I-V of group 1 at 2KHz and 70dB were 3.48±0.17(ms), 5.48± 0.28(ms), 1.81±0.35(ms), 1.92±0.23(ms), 3.77±0.40(ms) and group 2 were 3.62±0.21(ms), 5.73±0.37(ms), 2.05±0.26(ms), 2.10 ±0.21(ms), 4.03±0.38(ms) respectively. The difference between groups in controlled and uncontrolled groups of diabetic patients was statistically significant (p-value<0.05) [Table/Fig-2].

Parameters	Group 1(n=30,Controlled Diabetic Patients) Mean± SD	Group 2(n=30,Uncontrolled Diabetic Patients) Mean± SD
Age(years)	38.90±3.80	39.50±2.66
Weight(Kg)	60.87±5.18	62.43±5.26
Height(meters)	1.58±0.04	1.58±0.04
BMI(kg/m^2)	24.24±1.91	24.75±2.02
HbA1c(%)	6.75±0.11	10.06±1.15
Duration of Diabetes (Years)	4.53±1.20	7.67±1.97

[Table/Fig-1]: Demographic data.

BERA Waves Latency (ms)	Group –1 (Controlled Diabetic Patients) Mean ± SD (msec)	Group – 2 (Uncontrolled Diabetic Patients) Mean ± SD (msec)	p-value
I	1.58 ± 0.20	1.62 ± 0.21	0.50(NS)
III	3.48 ± 0.17	3.62 ± 0.21	0.0046(S)*
V	5.48 ± 0.28	5.73 ± 0.37	0.0052(S)*
Interpeak Latency I - III	1.81 ± 0.35	2.05 ± 0.26	0.0046(S)*
III – V	1.92 ± 0.23	2.10 ± 0.21	0.0038(S)*
I - V	3.77 ± 0.40	4.03 ± 0.38	0.014(S)*

[Table/Fig-2]: Absolute latency and Inter-peak latency in controlled group of diabetic patients and uncontrolled group of diabetic patients at 2 KHz and 70dB.
BERA waves and IPL: Inter-peak latency

2. The mean values of wave III and inter-peak latency of I-III, I-V of group1 at 2KHz and 80dB were 3.50±0.17(ms),1.84 ± 0.29(ms), 3.78±0.37(ms) and group 2 were 3.65±0.24(ms), 2.01±0.31(ms), 4.00±0.35(ms) respectively. The difference between groups in controlled and uncontrolled groups of diabetic patients was statistically significant (p-value < 0.05).
3. The mean values of wave V and inter-peak III-V of group 1 at 2KHz and 80 dB were 5.42±0.25(ms), 1.97±0.12(ms) and group 2 were 5.75±0.30(ms), 2.17±0.21(ms) respectively.

BERA Waves	Group – 1 (Controlled Diabetic Patients) Mean ± SD (msec)	Group – 2 (Uncontrolled Diabetic Patients) Mean ± SD (msec)	p-value
I	1.73±0.23	1.75±0.21	0.76 (NS)
III	3.50±0.17	3.65±0.24	0.0079(S)*
V	5.42±0.25	5.75±0.30	0.0001(HS)**
Interpeak Latency I-III	1.84±0.29	2.01±0.31	0.04(S)*
III – V	1.97±0.12	2.17±0.21	0.0001(HS)**
I- V	3.78±0.37	4.00±0.35	0.02 (S)*

[Table/Fig-3]: Absolute latency &Inter peak latency in controlled group of diabetic patients and uncontrolled group of diabetic patients at 2 KHz and 80dB.
BERA waves and IPL: Interpeak latency

BERA Waves	Group – 1 (Controlled Diabetic Patients) Mean ± SD (msec)	Group – 2 (Uncontrolled Diabetic Patients) Mean ± SD (msec)	p-value
I	1.66 ± 0.20	1.74 ± 0.20	0.11 (NS)
III	3.50 ± 0.19	3.66 ± 0.22	0.0038 (S)
V	5.49 ± 0.26	5.77 ± 0.30	0.0003 (HS)
Interpeak Latency I - III	1.80 ± 0.28	2.00 ± 0.29	0.01(S)
III – V	1.97 ± 0.05	2.19 ± 0.20	0.0001(HS)
I - V	3.89 ± 0.37	4.09 ± 0.32	0.028(S)

[Table/Fig-4]: Absolute latency &Inter peak latency in controlled group of diabetic patients and uncontrolled group of diabetic patients at 2KHz and 90dB.
SD: Standard Deviation,NS: Not significant, HS: Highly Significant.
**P< 0.001: Statistically highly significant.
*P< 0.05: Statistically significant.

The difference between groups in controlled and uncontrolled groups of diabetic patients was statistically highly significant (p-value <0.001) [Table/Fig-3].

4. The mean values of wave III and interpeak latency of I-III, I-V at 2KHz and 90 dB in group 1 were 3.50±0.19(ms),1.80± 0.28(ms), 3.89±0.37(ms) and group 2 were 3.66±0.22(ms), 2.00±0.29(ms), 4.09±0.32(ms) respectively. The difference between groups in controlled and uncontrolled groups of diabetic patients was statistically significant (p-value <0.05).
5. The mean values of wave V and interpeak III-V of group 1 at 2KHz and 90dB were 5.49±0.26(ms), 1.97±0.05(ms) and group 2 were 5.77±0.30(ms), 2.19±0.20(ms) respectively. The difference between groups in controlled and uncontrolled groups of diabetic patients was statistically highly significant (p-value < 0.001) [Table/Fig-4].

DISCUSSION

In the present study, BAEPs were studied and compared between the controlled and uncontrolled diabetic patients. The latency of wave I was found to be equal in both the groups of controlled and uncontrolled diabetic patients. This suggests that 8th nerve transmission till the level of cochlear nucleus was not altered. There was a significant delay in the latencies of wave II and III. The interpeak latency I – III, III – V and I – V was delayed in group 2 of uncontrolled diabetic patients group. This suggests delayed transmission of the auditory pathway at the level of brainstem and midbrain, which indicates pathology at these levels.

Similar studies of Reske Neilson et al., and Makishima et al., showed degenerative abnormalities of the brain tissue and atrophy of the spiral ganglion of the cochlea in patients of DM [3,4], thereby, suggesting the presence of central neuropathy. Based on histological findings, they concluded that microangiopathy of the stria vascularis was the main causative factor leading to central neuropathy in these patients [11]. Makishima and Tanaka had noticed that in patients with type-2 diabetics spiral ganglia in basal to middle turn of the cochlea tends to get atrophied along with the demyelination of the eighth cranial nerve [4]. Ren and Zhao reported hearing loss in middle aged diabetic patients [12]. Diabetic patients mean duration of diabetes in group 1 was 4.53±1.20 years and in group 2 was 7.67±1.97 years respectively. In our study there was a positive correlation in controlled and uncontrolled groups of diabetes patients, which was found statistically highly significant (p< 0.001). Our results are in agreement with Pozzessere et al., who reported that evoked potential abnormalities are correlated with glycemic control [13]. Similar findings related to duration of diabetes and hearing loss were also reported by Mitchell et al., [14]. The overall findings indicate a central disturbance of auditory pathway and the microvascular complications and the duration of diabetes was associated with prolonged auditory brainstem latencies [7].

Abnormal brain stem evoked responses and BERA abnormalities were more common in patients with duration of illness more than 7 years as compared to patients with duration of illness less than 4 years. Jorgenson et al., stated that microangiopathy is responsible for diabetic neuropathy which is a long term complication and this explains a higher incidence of abnormal brain stem evoked responses in patients with duration of illness more than 6-7 years [15]. The diffuse involvement of periventricular region, brainstem, and spinal cord are responsible for causing prolongation of central transmission time in diabetics [16].

LIMITATION

Smoking is a risk factor and it was not included in this study.

CONCLUSION

Diabetic patients can suffer not only from peripheral and autonomic neuropathy but also from central neuropathy. This study suggests that if brain stem evoked response audiometry is carried out at frequency 2KHz and at varying intensity in diabetic patients, involvement of central neuronal axis can be detected earlier in uncontrolled group of diabetic patients and will help to reduce morbidity and mortality in diabetic patients.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Feb 06, 2016**
Date of Peer Review: **Mar 28, 2016**
Date of Acceptance: **Sep 29, 2016**
Date of Publishing: **Nov 01, 2016**