Original Article

Type-2 diabetes mellitus and auditory brainstem response

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ABSTRACT

Objective: Diabetes mellitus (DM) causes pathophysiological changes at multiple organ system. With evoked potential techniques, the brain stem auditory response represents a simple procedure to detect both acoustic nerve and central nervous system pathway damage. The objective was to find the evidence of central neuropathy in diabetes patients by analyzing brainstem audiometry electric response obtained by auditory evoked potentials, quantify the characteristic of auditory brain response in long standing diabetes and to study the utility of auditory evoked potential in detecting the type, site, and nature of lesions. **Design:** A total of 25 Type-2 DM [13 (52%) males and 12 (48%) females] with duration of diabetes over 5 years and aged over 30 years. The brainstem evoked response audiometry (BERA) was performed by universal smart box manual version 2.0 at 70, 80, and 90 dB. The wave latency pattern and interpeak latencies were estimated. This was compared with 25 healthy controls (17 [68%] males and 8 [32%] females). **Result:** In Type-2 DM, BERA study revealed that wave-III representing superior olivary complex at 80 dB had wave latency of (3.99 ± 0.24) ms $P < 0.001$, at 90 dB (3.92 ± 0.28) ms $P < 0.001$ compared with control. The latency of wave III was delayed by 0.39, 0.42, and 0.42 ms at 70, 80, and 90 dB, respectively. The absolute latency of wave V representing inferior colliculus at 70 dB (6.05 ± 0.27) ms $P < 0.001$, at 80 dB (5.98 ± 0.27) $P < 0.001$, and at 90 dB (6.02 ± 0.30) ms $P < 0.002$ compared with control. The latency of wave-V was delayed by 0.48, 0.47, and 0.50 ms at 70, 80, and 90 dB, respectively. Interlatencies I-III at 70 dB (2.33 ± 0.22) ms $P < 0.001$, at 80 dB (2.39 ± 0.26) ms $P < 0.001$, while at 90 dB (2.47 ± 0.25) ms $P < 0.001$ when compared with control. Interlatencies I-V at 70 dB (4.45 ± 0.29) ms $P < 0.001$ at 80 dB (4.39 ± 0.34) ms $P < 0.001$, and at 90 dB (4.57 ± 0.31) ms $P < 0.001$ compared with control. Out of 25 Type-2 DM, 13 (52%) had diabetic neuropathy, of which 12 (92%) showed abnormal BERA. In nonneuropathic [12 (48%)] only 6 (50%) showed abnormal BERA. **Conclusion:** Delay in absolute latencies and interpeak latencies by BERA demonstrates defect at level of brainstem and midbrain in long standing Type-2 diabetes subjects, which is more pronounced in those with neuropathy.

Key words: Auditory brainstem response, brainstem evoked response audiometry, type-2 diabetes mellitus

Introduction

Type-2 diabetes mellitus (T2DM) comprise of group of common metabolic disorders that share the phenotype of hyperglycemia. Since it often has a long asymptomatic period of hyperglycemia, many individuals with Type-2 diabetes have complications at the time of diagnosis, neuropathy being most frequent. Most of the clinical and diagnostic studies have focused on peripheral and autonomic nerves. With the refinement of brainstem evoked response audiometry (BERA), patients have abnormal auditory nerve and brainstem response to an acoustic stimuli and are more prone to develop sensorineural hearing loss. Six possible mechanisms for diabetes labrynthopathy namely microangiopathy at the cochlea, neuropathic brainstem involvement, metabolic effect hyperglycemia or hypertriglyceridemia, hyperviscosity resulting vascular problems, or a combination of above. The metabolic disturbances may be accompanied by temporary alteration in the intraneural vessel in the form of increased permeability.

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A relationship between diabetes and sensorineural hearing loss was reported first by Jordao.[1]

BERA is an important noninvasive device that encompasses diagnosis of lesions ranging from 8th nerve to the auditory cortex. It is based upon the study of electrical potentials generated by the auditory pathway in response to electrical stimuli. It is recorded by placing active electrodes positioned at vertex and reference electrode at mastoid or ear lobe. A stimulus is generated by using 100 μs rectangular pulse or click-troughs. There are seven wave forms traditionally designated with roman numerals from I to VII wave, each designated a specific site Figure 1.
Wave I: Acoustic nerve
Wave II: Cochlear nucleus
Wave III: Superior olivary complex
Wave IV: Nucleus of the lateral leminiscus
Wave V: Inferior colliculus
Wave VI: Is from medial geniculate body
Wave VII: Originate between medial geniculate body to auditory complex.

The amplitude of peaks are variable within subjects, while the latencies of peaks are stable. Of these, the first five waves are constant and are seen in nearly all normal individuals. There latencies are quite specific and their reproducibility is very good.

The differences in latency between these peaks are a measure of the conduction time between the brainstem generators.

Interpeak latencies I-III, III-V, and I-V are indicative of central conduction from brainstem to midbrain level, in auditory pathway.

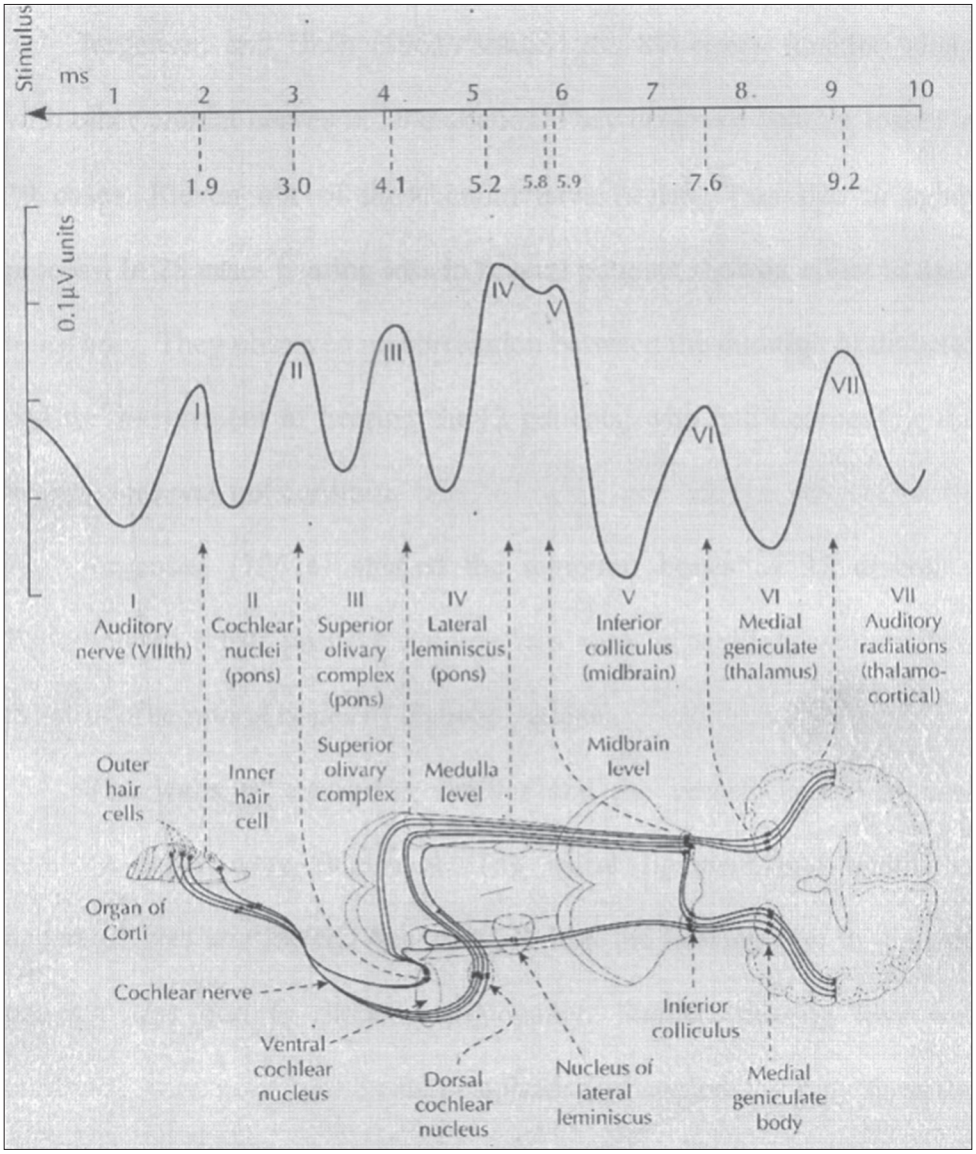

Figure 1: A normal bera waveform

Materials and Methods

The present study was conducted in the Department of Otolaryngology and Endocrine Division, JN Medical College. The study group comprises of 25 Type-2 diabetes subjects, 13 (52%) males and 12 (48%) females. The mean age of the study group was 46.8 years. A total of 25 healthy volunteers with a mean age of 45.7 years were taken as control.

Inclusion criteria

Age group: 30 years and above
Duration of disease: 5 years and above.

Exclusion criteria

Patients who gave history of ear disease due to exposure to prolonged loud noise, intake of ototoxic drugs (ampicillin, chloroquine, metronidazole, and other drugs), stroke, head injury, or family history of deafness were not included. Patients taking medications (methyldopa, reserpine, phenytoin, antipsychotic antidepressant, etc.), which interfere with the functioning, were excluded from this study. The brain evoked response audiometry was obtained by employing a conventional far-field scalp averaging technique. The equipment used was intelligent Hearing system (smart EP) Hewlett HIS. BERA model no TH72312 HT (universal smart box manual version 2.0) and year of manufacturing was 2006. The study and control group were listed 2-3 times. Intensity of 70, 80, and 90 dB was used to determine threshold response. The impedance between skin and electrodes were kept less than 5 kΩ. The stimulus rate of check was set 19.3/s with sweeps of 1024 and frequency of 100 Hz to 3 kHz. In our study we used rarefaction phase of recording because it produces better resolution of the BERA waves. The hearing threshold was defined as the minimum intensity needed to elicit the wave V, paired Student *t*-test was used for statistical analysis.

Observations and Result

BERA was performed in 25 Type-2 diabetes subjects. The absolute latencies III, V waves were performed at 70, 80, and 90 dB. The interpeak latencies between I-III, III-V, and I-V were also performed [Table 1].

Significant differences was found in latencies of wave III and interpeak III-IV, while highly significant difference was found in latencies of wave V and interpeak I-III, I-V between control and study group at 70 dB. Highly significant difference was found in latencies of wave III, V, and interpeak I-III, I-V while significant difference was found in interwave III-V between control and study group at 80 dB. Significant difference was found in latencies of wave V and interpeak III-V, while highly significant difference was found in wave III and interpeak I-III, I-V between control and study group at 90 dB. The duration of DM was 5-10 years in 13 (52%) patients and among these patients, BERA was delayed in 7 (53.84%) subjects. Twelve (48%) patients had history of diabetes for >10 years and among these patients, BERA was delayed in 11 (91.66) subjects.

Table 1: Comparison of absolute latencies and interpeak latencies in control and in patients with diabetes mellitus at 70, 80, and 90 dB

Wave latencies	Intensity (in dB)	Control group Mean±S.D. (ms)	Diabetic group Mean±S.D. (ms)	*P* value
I	70	1.58±0.15	1.59±0.14	0.795
III	70	3.54±0.38	3.93±0.28	0.01
V	70	5.57±0.33	6.05±0.27	<0.001
I-III	70	1.96±0.27	2.33±0.22	<0.001
III-V	70	2.02±0.14	2.12±0.18	0.045
I-V	70	3.99±0.26	4.45±0.29	<0.001
I	80	1.62±0.22	1.59±0.21	0.672
III	80	3.57±0.35	3.99±0.24	<0.001
V	80	5.51±0.34	5.98±0.27	<0.001
I-III	80	1.95±0.25	2.39±0.26	<0.001
III-V	80	1.93±0.07	1.99±0.07	0.028
I-V	80	3.89±0.30	4.39±0.34	<0.001
I	90	1.44±0.07	1.44±0.06	0.939
III	90	3.50±0.41	3.92±0.28	<0.001
V	90	5.52±0.39	6.02±0.30	0.002
I-III	90	2.05±0.36	2.47±0.25	<0.001
III-V	90	2.02±0.06	2.09±0.14	0.036
I-V	90	4.08±0.34	4.57±0.31	<0.001

Among the 25 in the study group, 13 (52%) cases had neuropathy, 1 (4%) case had nephropathy, and 2 (8%) cases had retinopathy.

Among the 25 patients, 13 (52%) patients had peripheral neuropathy and the BERA was delayed in 12 (92.3%) patients. Whereas, the incidence of delayed BERA was only 50% in patients without peripheral neuropathy.

Discussion

T2DM subjects are more prone to develop sensorineural hearing loss. Histological findings in the inner ear of these patients show characteristic microangiopathy with Periodic Acid Schiff positive substance in the vessel wall of stria vascularis.[2] Makanshima and Tanaka[3] found atrophy of spiral ganglia in basal to middle turn of the cochlea with the demyelination of myelin sheaths of VIII nerve in Type-2 diabetes patients. BERA is an important noninvasive device for diagnosis of lesions ranging from 8th nerve to the auditory cortex. Rosen *et al.*[4] found that out of 265 diabetes patients, 152 had bilateral symmetrical hearing loss mainly the high frequencies, so called sensory neural

hearing loss. Friedman *et al.*[5] demonstrated symmetrical sensorineural deafness in 55% of Type-2 diabetes patients with neuropathy. Dejong[6] described central nervous system (CNS) manifestation in Type-2 diabetes patients. Donald *et al.*[7] conducted BERA on 20 insulin-dependent diabetes patients and concluded that the latency of wave III to be delayed by 0.30 ms ($P < 0.05$) on 70, 80, and 90 dB with delay of wave V by 0.45 ms ($P < 0.001$). The interpeak latency wave I-III was delayed by 0.24 ms ($P < 0.01$) and I-V delayed by 0.35 ms ($P < 0.05$). Fedele *et al.*[8] recorded BERA from scalp of 30 normoacoustic insulin-dependent diabetes subjects and found peripheral transmission time (wave I) and central transmission time (wave I-V) to be delayed. Goldsher *et al.*[9] reported abnormal brainstem response in Type-2 diabetes patients with neuropathy in 94% of cases. Panda and Prabhakar[10] compared 25 diabetic with peripheral neuropathy and 15 diabetic without peripheral neuropathy and found delay in absolute latencies of wave III and V with prolonged interpeak latencies of I-III and I-V in diabetic with peripheral neuropathy as compared with diabetic without neuropathy. Mehra *et al.*[11] recorded BERA in 20 Type-2 diabetes individuals and found that the 8th cranial nerve transmission till the level of cochlear nucleus to be normal. The delay in latencies of wave III, IV, V, and interpeak latencies I-III were delayed by 0.32 ms with delay in interpeak latency I-V by 0.35 ms ($P < 0.05$). Kurien *et al.*[12] evaluated hearing threshold on 30 diabetes patients and demonstrated poor hearing threshold in these patients but could not demonstrate relationship between duration of diabetes to level of hearing loss. Virtanierni *et al.*[13] found wave V latency to be delayed in diabetes patients. The overall finding seems to indicate a central disturbance of auditory pathway and the microvascular complications and the duration of diabetes were associated with prolonged auditory brainstem latencies. Tay *et al.*[14] performed a prospective hearing survey sample on 102 diabetes patients and found that these patients had worse hearing threshold levels specially at low and mid frequencies ($P < 0.001$) and also demonstrated correlation between duration of diabetes and level of hearing loss. Sharma *et al.*[15] studied 25 diabetes subjects and found on audiometry, a delayed wave latencies at 2, 4, and 6 kHz 64%, 72%, and 84%, respectively, suggesting that if BERA is conducted at higher frequencies like 6 kHz in diabetes patients, the involvement of central neural axis can be detected earlier. He also noticed peripheral neuropathy in 85.71% with abnormal brainstem response while 36.36% subjects without neuropathy had abnormal brainstem response. Durmus *et al.*[16] measured the delay in neural conductance along the auditory pathway in 43 diabetes patients. Their auditory brainstem response (ABR) recording revealed that absolute latencies of wave I, III, and V were prolonged significantly in the diabetes group when compared with the control group ($P < 0.05$). A 5 year prospective study was undertaken in VA national center for rehabilitation Auditory research, Portland, USA,[17] for ABR in 416 nondiabetes and 375 diabetes veterans. Patients with diabetes had significantly delayed latencies of wave III and V in the right ear and significantly prolonged interpeak I-III and I-V latencies in both ears. Ren *et al.*[18] assessed the auditory function of 50 diabetes subjects using Pure tone audiometry and showed elevated threshold at 4000 and 8000 Hz with increased wave V and interwave I-V latencies ($P < 0.01$) [Tables 2 and 3].

Conclusion

BERA is a simple noninvasive procedure to detect early impairment of acoustic nerves and CNS pathways. latency of wave I was found to be equal in the diabetes and controls suggesting that the 8th nerve transmission till the level of cochlear nucleus is not altered in diabetics. The delay in the latency III, V, and the interpeak latency I-III, III-V, I-V in diabetes group suggests brainstem and midbrain involvement. Diabetes with peripheral neuropathy have more incidence of delayed BERA tracing. The study suggests that

Table 2: BERA response showing delayed latency in mSec as observed in Type 2 diabetic subjects

Various studies	Latency of wave I	*P* value	Latency of wave III	*P* value	Latency of wave V	*P* value
Donald *et al*. 1981	1.80	<0.05	4.07±0.31	<0.05	6.13±0.35	<0.001
Mehra *et al*. 1987	1.75±0.12	<0.05	4.18±0.20	<0.05	6.23±0.35	<0.05
Sharma *et al*. 2000	1.29±0.13	<0.001	3.61±0.13	<0.001	5.66±0.22	0.001
Present study 2009	1.59±0.14	>0.05	3.99±0.24	<0.001	6.05±0.27	0.001

Table 3: Studies showing delay of Peak Inter latencies in BERA response

Various studies	Delay of peak inter latencies of I-III	*P* value	Delay of peak inter latencies of III-V	*P* value	Delay of peak inter latencies of I-V	*P* value
Donald *et al*. 1981	0.24 ms	<0.01	Not determined		0.35 ms	<0.05
Mehra *et al*. 1987	0.32 ms	<0.05	Not determined		0.35 ms	<0.05
Sharma *et al*. 2000	0.20 ms	<0.001	0.12 ms	<0.001	0.40 ms	<0.001
Present study 2009	0.44 ms	<0.001	0.10 ms	<0.05	0.50 ms	<0.001

if BERA is carried out on Type-2 diabetes patients, then involvement of central neuronal axis can be detected earlier.

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