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Original Research Article

Comparative study of brainstem evoked response audiometry in diabetic patients and non-diabetic subjects to assess the involvement of central auditory pathway

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ABSTRACT

Background: Diabetes mellitus (DM) which is prevalent in world is associated with sensorineural hearing loss. Brainstem evoked response audiometry (BERA) is a simple, non-invasive procedure to detect early impairment of acoustic nerve and auditory pathway. The present study is under taken to evaluate the impact of DM on BERA parameters. Aim of the study was to compare the BERA of diabetic patients to those of age and gender matched controls to assess the involvement of central auditory pathway.
Methods: A cross sectional study was conducted on 35 diabetic patients, aged 35 to 55 years, who were on treatment for at least 2 years, and 35 age and sex matched control participants, were subjected for BERA at 70,80 and 90 dB. The waveforms, absolute latency of wave I, wave III, wave V and interwave/ inter peak latency of I-III, III-V and I-V were analyzed with respect to both groups.
Results: The absolute latency of wave III and wave V, interpeak/ interwave latency of I-III, interpeak/ interwave latency of I-V, III-V and absolute latency of wave V were highly significant at corresponding tested stimuli in the diabetic group compared to the control group.
Conclusions: Early involvement of central auditory pathway in diabetic patients, can be detected with fair accuracy with auditory evoked potential studies; if done on a regular basis warrants meticulous glycemic control and prevents further damage.

Keywords: BERA, DM, Absolute latency, Interwave/ inter peak latency

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, protein and fat metabolism resulting from either defect in insulin action or insulin secretion or both1. It can have long-term effects on the various organs of the body like the eye, kidneys, heart, peripheral vessels and nerves. The metabolic derangement is frequently associated with permanent and irreversible/ functional and structural changes in the cells of the body, vascular system being particularly susceptible, peripheral neuropathy is a frequent complication of the diabetes. Autonomic nervous system involvement and isolated nerve palsies are well known to occur in diabetics. Eber's papyrus was the first one to mention about diabetes as early as 1500 Banting et al discovery of Insulin was a significant milestone in the history of diabetes. Since then, many dedicated researches have helped us understand this disease better.

Neurophysiological studies in diabetic patients involving the CNS were done using evoked potential and measuring its latencies. Prolonged latencies of these evoked potentials measured using visual evoked potential, somatosensory evoked potential and brain stem auditory evoked potential have been reported often. In this study, BERA/Auditory brainstem response (ABR) of diabetic patients to those of age and gender matched controls were assessed for the involvement of central auditory pathway.

Objective

Objectives of the study were to assess the auditory function and incidence of central auditory pathway involvement in patients with diabetes compared to age and sex matched non diabetic subjects, using ABR/BERA, to compare the absolute latency of wave I, wave III and wave V between the study and control groups, to compare the interpeak latency I to III, III to V and I to V between the groups and to interpret the ABR values based on the duration of diabetes

METHODS

Study design

The study design was of cross-sectional comparative study.

Place of study

The study carried out at government Kilpauk medical college hospital.

Study period

The study conducted from November 2019 to October 2020.

Ethical committee approval:

The ethical committee approval was obtained.

Sample size

The 35 subjects in each group were selected for the study,

Calculated using sample size formula, n=(Za + Zb) 2S 2 / (X1-X2) 2.

Patient with clinical diagnosis of DM fulfilling following criteria were enrolled in the study.

Inclusion criteria

For cases

Patients diagnosed and treated for diabetes at the department of diabetes, government Kilpauk medical college hospital, according to WHO diagnostic criteria and with age between>35 years and <55 years were included in the study.

For controls

Age and sex matched with diabetic subjects from the general OPD and general population, after confirming that fasting and post prandial blood glucose within normal limits according to WHO diagnostic criteria were included.

Exclusion criteria

For both groups

Patients with external or middle ear disease, head injury and ear trauma, history of previous ear surgery, ototoxic drugs intake like aminoglycosides, family history of deafness, chronic exposure in noisy environment, medications that might affect the normal functioning the central nervous system (anti-depressants, anti-psychotics, methyldopa etc.,) and patient with any systemic illness that might affect the central nervous system (uremia, stroke, hepatic encephalopathy, multiple sclerosis, anemia, meningitis). Any history of radiotherapy or chemotherapy were excluded from the study.

For cases

Along with above mentioned exclusions and any patients with acute complications of diabetes like ketoacidosis, hypoglycaemia was excluded.

For controls

Along with above mentioned exclusions and past history of diabetes were excluded.

It is a comparative cross-sectional study. Total of 35 patients with DM belonging to either sex, with age ranging between 35 to 55 years and duration of diabetes ranging more than 1 year were enrolled. Control group with age and sex matched with study group were enrolled. Blood sugar profile and diabetologist opinion obtained. Detailed history taken and clinical examination done to rule out other causes of auditory dysfunction. Patient explained about the study and consent taken. Pure tone audiometry done before hand. BERA was done in all patients, latencies of waves I, III, and V and inter- peak latencies I-III, I-V and III-V were analysed. Mann-Whitney U test and Kruskal Wallis test was applied for statistical analysis. $P<0.001$ is highly significant, $p\geq0.05$ not significant.

RESULTS

In our study, a statistically significant prolongation was observed in wave III latency at 70, 80 and 90 dBnHL in diabetic group compared to the control group. Similarly,

the latency of wave V was significantly delayed in 70, 80 and 90dBnHL in diabetic group as compared to the

controls with wave V being highly significant at 70 and 90 dB. There was no significant interaural latency difference. In diabetic patients, latencies of waves I, III, and V and inter- peak latencies IIII, I-V and III-V were significantly delayed. No relation was found with the duration of DM. In our study, we concluded that diabetes and BERA abnormalities are significantly associated which has also been substantiated by numerous preceding studies as in Donald et al in their study conducted ABR tests on 20 IDDM patients and found that the latency of wave III, wave V, interwave latency I-III and I-V were significantly delayed.[2] For wave III the delay was by 0.30 ms ($p<0.05$- significant) and the delay in latency of wave V was by 0.45 ms ($p<0.001$- highly significant) on 70, 80, and 90 dB respectively. Likewise, the interpeak/interwave latency of wave I-III and the interpeak latency wave I-V was delayed by 0.24 ms ($p<0.01$) and 0.35 ms ($p<0.05$) respectively.

Table 1: Distribution of DM among the study participants.

Variables	Frequency	Percentage (%)
DM (case)		
Type I	5	15
Type II	30	85
Non-diabetic (control)	35	100

Table 2: Distribution of age among the study participants.

Age (Years)	Diabetes		Control	
	Frequency	%	Frequency	%
<40	5	14	5	14
41-50	18	51	19	54
>50	12	34	11	31

The mean age of the study participants was 46.9±5.1 years.

Table 3: Distribution of sex among the study participants.

Sex	Diabetes		Control	
	Frequency	%	Frequency	%
Male	21	60	21	60
Female	14	40	14	40

Table 4: Gender distribution in the diabetes.

Diabetes mellitus	Frequency	Percentage (%)
Type I		
Male	3	60
Female	2	40
Type II		
Male	18	60
Female	12	40

Table 5: Comparison of absolute latency and interwave latency with 90db stimulus among diabetic and control groups.

Absolute and interwave latency	Diabetes		Control		P value
	Mean	SD	Mean	SD	
Wave 1					
Right	1.7	0.2	1.43	0.1	0.563
Left	1.7	0.2	1.43	0.09	0.691
Wave 3					
Right	3.78	0.16	3.54	0.2	0.051*
Left	3.76	0.16	3.55	0.20	0.020*
Wave 5					
Right	5.71	0.19	5.31	0.38	<0.001
Left	5.68	0.21	5.29	0.38	<0.001
Wave 1-3					
Right	2.04	0.13	2.02	0.12	0.029*
Left	2.03	0.13	2.01	0.12	0.030*
Wave 3-5					
Right	1.92	0.07	1.76	0.2	<0.001
Left	3.97	0.11	1.73	0.19	<0.001
Wave 1-5					
Right	3.97	0.11	3.87	0.3	0.015*
Left	3.95	0.10	3.85	0.29	0.014*

*Mann-Whitney U test was applied. $P<0.05$ was considered significant $p\leq0.001$ is the highly significant, $p\geq0.05$ not significant.

Table 6: Comparison of absolute latency and interwave latency with 80db stimulus among diabetic and control groups.

Absolute and interwave latency	Diabetes		Control		P value
	Mean	SD	Mean	SD	
Wave 1					
Right	1.72	0.07	1.64	0.15	0.071
Left	1.71	0.70	1.63	0.13	0.092
Wave 3					
Right	4.26	0.13	3.64	0.18	0.052*
Left	4.24	0.15	3.65	0.20	0.049*
Wave 5					
Right	6.26	0.21	5.76	0.20	0.041*
Left	6.14	0.08	5.76	0.19	0.008*
Wave 1-3					
Right	2.53	0.084	1.99	0.06	<0.001
Left	2.52	0.12	2.02	0.73	<0.001
Wave 3-5					
Right	2.0	0.8	2.12	0.06	<0.001
Left	1.88	0.8	2.11	0.64	<0.001
Wave 1-5					
Right	4.53	0.15	4.12	0.07	<0.001
Left	4.42	0.07	4.13	0.09	<0.001

*Mann-Whitney U test was applied. $P<0.05$ was considered significant $p\leq0.001$ is the highly significant, $p\geq0.05$ not significant.

Table 7: Comparison of absolute latency and interwave latency with 70db stimulus among diabetic and control groups.

Absolute and interwave latency	Diabetes		Control		P value
	Mean	SD	Mean	SD	
Wave 1					
Right	1.5	0.55	1.49	0.5	0.081
Left	1.5	0.06	1.49	0.4	0.075
Wave 3					
Right	3.8	0.13	3.5	0.06	0.002*
Left	3.8	0.13	3.5	0.67	0.017*
Wave 5					
Right	6.30	0.42	5.70	0.07	<0.001
Left	6.30	0.43	5.69	0.73	<0.001
Wave 1-3					
Right	2.29	0.16	2.08	0.8	<0.001
Left	2.31	0.17	2.08	0.9	<0.001
Wave 3-5					
Right	2.47	0.3	2.12	0.09	<0.001
Left	2.46	0.3	2.11	0.08	<0.001
Wave 1-5					
Right	4.77	0.45	4.21	4.19	<0.001
Left	4.78	0.46	0.88	0.98	<0.001

*Mann-Whitney U test was applied. P<0.05 was considered significant p≤0.001 is highly significant, p≥0.05 not significant.

Table 8: Duration of diabetes and latency.

Duration (Years)	Variables	Wave 1		Wave 3		Wave 5		Wave 1-3		Wave 3-5		Wave 1-5		P value
		Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	
<5	Mean±SD	1.5	1.5	3.8	3.8	5.8	5.8	2.3	2.3	2.03	2.04	4.36	4.3	<0.001
		0.14	0.14	0.2	0.2	0.3	0.3	0.1	0.1	0.24	0.22	0.3	0.3	
5-10	Mean±SD	1.6	1.6	3.9	3.9	5.9	5.9	2.2	2.2	2.08	2.04	4.3	4.3	<0.001
		0.1	0.1	0.2	0.2	0.3	0.3	0.2	0.2	0.2	0.2	0.3	0.3	
>10	Mean±SD	1.6	1.6	3.9	3.9	6.09	6.04	2.2	2.1	2.09	2.09	4.4	4.3	<0.001
		0.2	0.1	0.2	0.2	0.3	0.3	0.2	0.3	0.3	0.3	0.4	0.4	

The mean duration of diabetes among the study participants was 8.1±3.5 years. Kruskal Wallis test was applied. P<0.05 was considered significant p≤0.001 is highly significant.

The absolute latency of wave III and wave V was significant across all 70-, 80- and 90-dB stimuli with absolute latency of wave V being highly significant at 70 and 90 dB in the diabetic group compared to the control group. The interpeak/ interwave latency of I-III was significant at 70 and 90 dB. The interpeak/ interwave latency of I-V, III-V was highly significant across all the 70-, 80- and 90-dB stimuli compared to the control group.

DISCUSSION

The hearing difficulties associated with diabetic patients are of gradual onset and are bilateral, symmetric and progressive high frequency sensorineural hearing loss. Cochlear, Retro cochlear or combined cochlear and retro cochlear involvement of acoustic nerve are considered as the probable cause for this hearing difficulties encountered in patients with diabetes. Though the pathogenesis of hearing loss in these patients has not been fully clarified, it involves a multifactorial process.

Use of an objective, reliable and non-invasive method like ABR/ BERA can detect even the subclinical involvement of the auditory pathway, by recording the electrical potentials occurring along the auditory pathway. As a result, ABR/BERA can be used as a reliable, non-invasive tool for diagnosing lesions starting vestibulocochlear nerve to the auditory areas in brain. Delay in the latency of ABR waves were reported in various reports from the time when the ABR was started as a tool for diagnostic purpose. But the earliest to use BERA and to identify the delays in latency in the wave associated with auditory nerve in DM patients was done by Donald et al.[2]

Fedelle et al also reported the prolonged latency of all the components of ABR.[3] They studied 30 normo acoustic IDDM subjects between 15 and 41 years and compared with 20 age and sex matched controls. There was substantial impairment in the latencies of all ABR waves as compared with control groups. They noted major delay in the peripheral (wave 1) and central transmission (wave

1-5) in the diabetic group. They also observed that the shift in wave 1 to 5 will be considerably increased if the stimulus repetition rates were increased.

A term called "central diabetic neuropathy" was put forward, which implies that the latency delays where considerably more in the components of ABR that occur late. This signifies that brainstem level involvement has occurred in patients with diabetes. This finding correlates well with the findings of Donald et al, Khardori et al and Virtaniemi et al[2,4,5]

In our study, a statistically significant prolongation was observed in wave III latency at 70, 80 and 90 dBnHL in diabetic group compared to the control group. Similarly, the latency of wave V was significantly delayed in 70, 80 and 90dBnHL in diabetic group as compared to the controls with wave V being highly significant at 70 and 90 dB. There was no significant interaural latency difference.

Donald et al in their study conducted ABR tests on 20 IDDM patients and found that the latency of wave III, wave V, interwave latency I-III and I-V were significantly delayed.[2] For wave III the delay was by 0.30 ms ($p<0.05$- significant) and the delay in latency of wave V was by 0.45 ms ($p<0.001$- highly significant) on 70, 80, and 90 dB respectively. Likewise, the interpeak/interwave latency of wave I-III and the interpeak latency wave I-V was delayed by 0.24 ms ($p<0.01$) and 0.35 ms ($p<0.05$) respectively. The latency difference of wave I in study and control group in all the three intensities were not highly significant, suggesting that the 8th nerve transmission till the level of the cochlear nucleus was not greatly altered in diabetics. ABR recordings based on the study by Durmus et al to measure the delays in neural conduction along the auditory pathway was done in 43 diabetes patients.[6] The recordings from their study shown that the absolute latencies of waves I, III, and V were significantly delayed in the diabetes group compared to the control group ($p<0.05$).

Kurien et al did pure tone audiometry in 30 diabetic patients and 30 controls and found that diabetics had poorer hearing threshold than non-diabetics. All diabetic age groups showed significant high frequency hearing loss as compared to control population.[7]

In type 2 diabetic patients, latencies of waves I, II, III, IV and V and interpeak latencies IIII, I-V and III-V were significantly delayed. There was no statistically significant difference in latency delay between type 1 and type 2 DM. No relation was found with the duration of DM. Among individuals with long standing type 1 and type 2 DM, almost 50% develop neuropathic complications 88. The pathophysiology of neuronal degeneration in diabetes is unsure. Recently it has been proposed that in addition to compromised cell survival metabolism and neuronal plasticity, Insulin resistance in type-2 DM also increases oxidative stress and neuronal apoptosis89. As far as CNS involvement is concerned, a rise in ceramide generation and its preceding increase across the blood brain barrier encourages further insulin resistance and neurodegenerative changes in type-2DM patients. All diabetic patients should be screened for neuropathy of any kind annually as suggested by the American diabetes association.

At present the screening tool for diabetic neuropathy widely in practice is the nerve conduction study. Utilizing BERA/ABR in this scenario as a screening tool would be of great benefit.

In our study, we concluded that diabetes and BERA abnormalities are significantly associated which has also been substantiated by numerous preceding studies.

The global prevalence of diabetes keeps profoundly increasing day by day which directs us to investigate its complications and screen them from affecting the quality of life of the patient. Therefore, it is highly beneficial to include BERA/ABR in the investigative battery of tests in the long-standing diabetic population.

Limitations

The results can be precisely framed by adding more audiological and neurological tests, which can also be used to exclude other pathologies pertaining to specific sites, for example tests to include hair cell damage or neuronal damage in brain parenchyma.

Diabetes in the long run produces these complications, so it would be better if our research work targets the preventive aspect, i.e., in this case, to detect at the earliest for the society to be benefited as a whole.

CONCLUSION

Central acoustic neuropathy can be identified early with the help of BERA even if there is no clinically evident hearing loss. Thus, the results of BERA/ABR can assist the treating clinician for watchful control of the blood glucose level if it is not adequately controlled. BERA/ABR testing can be done on an annual basis which will help the physician to update their diabetic patient's hearing status so that necessary guidance can be given to control it. Also helps to prevent the further progression of neuropathy is highly recommended. More similar studies are necessary and helpful not only for the standardization of BERA results in diabetics but also for detecting the association between BERA abnormalities and severity of diabetes with greater accuracy.

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