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Original Article

Physiology Section

Brainstem Auditory Evoked Potentials in Uncontrolled Diabetes Mellitus with and without Complications

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ABSTRACT

Introduction: Diabetes mellitus is a metabolic disorder known to affect all body systems especially neurons, retina and kidneys. Peripheral neuropathy has been widely studied but the exploration of central neurons is limited.

Aim: To evaluate the magnitude of changes in Brainstem Auditory Evoked Potentials (BAEP) in uncontrolled diabetics with or without complications.

Materials and Methods: Fifty uncontrolled Non-Insulin Dependent Diabetes Mellitus (NIDDM) patients of both sexes including 20 with neuropathy and 10 with retinopathy but having no hearing loss were evaluated for absolute and inter peak latencies by brainstem evoked potentials. This pilot study was conducted in the Department of Physiology, Lala Lajpat Rai Memorial Medical College, Meerut, India, between the periods of November 2016 to July 2017, To evaluate the results, ANOVA, unpaired Student's t-test and Pearson's correlation coefficient was used.

Results: The study revealed that almost all the absolute (AL) and Inter Peak Latencies (IPLs) were increased significantly ($p<0.001$) in patients with complications. Also, the threshold stimulus of median nerve was greater in them. The increase in latencies was not associated with either blood sugar level or duration of illness.

Conclusion: It appears that diabetes mellitus has ototoxic role and regular BAEP test may detect the hearing loss at an early stage.

Keywords: Neuropathy, Retinopathy, Sensorineural hearing loss

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder known to affect all parts of the nervous system. It has been found that there are involvement of occulomotor, trochlear, facial and auditory nerves. Sensorineural hearing loss is a frequent complication of diabetes mellitus. The problem is gradual in onset, slowly progressive and bilateral. Despite the evidence, very little is known about the nature and characteristics of this disability and the specific mechanisms leading to hearing problems in diabetic adults [1]. The pathogenesis of hearing loss in DM is a multifactorial process, having cochlear or retrocochlear or both involvement of cochlear nerve, but not explored fully. It is reported that several structural changes are associated with a deficit in nerve conduction velocities in diabetic patients. It is well reported that there are prolonged absolute and interpeak latencies in diabetics as compared to healthy controls [2]. Therefore, if the glycaemic control is poor and associated with complications as well, there is a greater possibility of delay in nerve conduction in auditory pathways.

BAEP is an objective way of eliciting brainstem potentials in response to audiological click stimuli [3]. The BAEP studies give us an opportunity to evaluate the functional integrity of the auditory pathways from internal ear to the brainstem. Though there are five waves in the recording but practically three waves are commonly evaluated and any abnormality in BAEP is considered as central neuropathy. The possibility of abnormal BAEP is greater in uncontrolled diabetics, more so having associated complications and may have prognostic significance. Therefore, the present study was planned to observe the BAEP changes in uncontrolled diabetics as most of the studies are done in either controlled diabetics or those having no known complication of the disease.

MATERIALS AND METHODS

This pilot study was conducted in the Department of Physiology, Lala Lajpat Rai Memorial Medical College, Meerut, India, between the periods of November 2016 to July 2017, following approval from Institutional Ethical Committee (No./S-I/2018/5431). In this study, 50 non-insulin dependent uncontrolled diabetic patients of both sexes (20 males and 30 females) between 30 to 70 years (mean 50 years) attending Endocrinology and Ophthalmology outpatient department of SVBP hospital were randomly selected. These patients were having the disease from 5 to 12 years (average duration of 8.5 years). The possibility of uncontrolled diabetes is more in them due to non compliance of treatment or ignorance.

Their personal history revealed that all the patients were irregular on treatment and switch to other forms of medical therapies off and on. They were also not following dietary restrictions as per advice of dietician and not getting their blood sugar tested regularly. None of the subjects was having any history of hearing loss, alcohol consumption, cardiac involvement, ototoxic drug intake or family history of deafness. Written and informed consent was taken for the study after explaining the procedure and its significance.

Each patient was subjected to thorough clinical examination including fundus and otoscopic examination to exclude any medical problem and to prevent confounding of results. Height and weight of the subjects were also recorded. On the basis of history and clinical examination, the diabetic subjects were divided into three groups: (a) without any complication; (b) with neuropathy; and (c) with retinopathy.

Random blood sugar estimation: It was done prior to BAEP and Motor Nerve Conduction Velocity (MNCV) to know their sugar level on the day of test by Glucose Oxidase method [4].

Direct ophthalmoscopy: It was done to confirm the findings of retinopathy. The light source from the batteries was reflected at 90° using the mirror placed in the head portion at 45° angle. The retina was examined by looking through a hole in the mirror that is through the light.

MNCV: The MNCV of median nerve was done to test peripheral neuropathy in all subjects, using software Neurostim NS-4 (Medicaid,

Chandigarh). The subject was made to sit comfortably and explained the procedure. Then the electrodes were suitably placed after the application of jelly. The recording electrode (black) was placed close to the motor point of abductor pollicis brevis and Reference Electrode (red) was placed 3 cm distal to the first metacarpophalangeal joint. The ground electrode (green) was placed between the two stimulation points. Connection of the electrodes through the pre-amplifier to the Cathode Ray Oscilloscope (CRO) was done. Repetitive stimuli through the hand-held probe were given. Supramaximal stimuli were first given at the wrist position (3 cm proximal to the distal wrist crease) and then moved to the elbow position (near the volar crease of the brachial pulse). The stimulus current was initially set at 20 mA and then gradually increased till a stable response was assured [5].

BAEP: The BAEP was done with patient lying supine comfortably and in a relaxed state on a wooden couch using the software Neurostim NS 4 (Medicaid, Chandigarh). The electrodes were placed behind each of the earlobes (Ai and Ac). Grounding was done by placing an electrode on subject's forehead. Reference electrode was placed on vertex (Cz). All electrodes were finally placed/plugged into the electrode box and the appropriate channels were switched on. Skin to electrode impedance was maintained below 5 Ω. The signals were then picked up by these electrodes from the scalp after standard click stimuli and were then filtered, amplified, averaged and displayed on the screen of Neurostim-NS4 Evoked Potential Recorder. For recording of the BAEPs, 2000 (minimum) click stimuli having intensity 30-40 dB above threshold were given to the right ear independently at the rate of 11/second and duration of 1 millisecond. During testing of right ear, the left ear was masked with a white noise of 40 dB and vice versa. These clicks were generated by passing one millisecond squared pulses through shielded headphones with alternating polarity. After filtration (100 Hz and 10 kHz), amplification and averaging the waves in the first 10 millisecond of latency were considered for AL I, III, V and IPL I-III, III-V and I-V. The changes in these latencies were exhibiting difference between two ears. Therefore, the mean value of all absolute and interpeak latencies of both ears was taken to draw the inference [5].

STATISTICAL ANALYSIS

The results are expressed as mean and standard deviation. Unpaired students t-test was used for intergroup and ANOVA for intragroup comparisons. Pearson's coefficient was used to see the correlation. p-value<0.05 was considered as significant.

RESULTS

The mean demographic data and random blood sugar, taken on the day of the test, of the three groups of uncontrolled diabetic subjects are shown in [Table/Fig-1]. The demographic data was comparable in the three groups with a significant difference in age, BMI and duration of diabetes. The [Table/Fig-2] shows the mean interaural absolute and interpeak latencies in uncontrolled diabetics having either neuropathy or retinopathy. The average median nerve conduction velocity was found 54.08 millisecond at stimulus level of 44.25 mA in patients with peripheral neuropathy while it was 53.30 millisecond with stimulus level 31.75 mA with retinopathy. The table also shows that the absolute and interpeak latencies were greater in retinopathic than neuropathic diabetic subjects but the median nerve MNCV was low.

The [Table/Fig-3] compares the mean interaural absolute and interpeak latencies between uncontrolled diabetics with or without complications. It is evident that there is increased absolute and IPLs in diabetic subjects with complications. The subjects having complications need significantly higher stimulus ($p < 0.01$) to stimulate the median nerve than with patients having no complications. The [Table/Fig-4] shows that there was no correlation between the BAEP parameters and random blood sugar in patients of all the three groups except in ALI and IPL I-III in patients having diabetic retinopathy. It seems that the diabetic related changes in BAEP were independent of the glycaemic level. The [Table/Fig-5] correlates the different BAEP parameters with the duration of illness in the diabetic subjects of all the three groups. It also revealed that no correlation exists between the BAEP changes with duration of illness.

Parameters	Diabetics without complications (n=20)	Diabetics with neuropathy (n=20)	Diabetics with retinopathy (n=10)	F-ratio	p-value
Age (years)	59.1±6.52	63.2±3.99	65.10±4.18	5.43	0.007
Height (m)	1.60±0.06	1.60±0.04	1.60±0.06	0.275	0.761
Weight (kg)	75.75±8.43	78.6±6.24	80.80±5.51	3.021	0.059
BMI (kg/m^2)	29.68±3.63	30.78±2.20	31.71±3.56	3.555	0.036
Random blood sugar (mg/dL)	205±42.43	296±41.01	334±175.36	2.001	0.147
Duration of diabetes (years)	6±2.67	8±3.84	10±5.65	50.692	0.001

[Table/Fig-1]: Demographic data and random blood sugar of uncontrolled diabetics. The parameters are expressed in mean±SD; Statistical test is applied at 5% level of significance

Parameter	Diabetic neuropathy n=20	Diabetic retinopathy n=10	p-value
AL I (ms)	1.09±0.13	1.50±0.70	0.016
AL III (ms)	3.12±0.16	3.94±0.07	0.0001
AL V (ms)	5.49±0.30	5.92±0.10	0.0002
IPL I-III (ms)	2.03±0.04	2.45±0.63	0.005
IPL III-V (ms)	2.65±0.24	2.35±0.35	0.010
IPL I-V (ms)	4.41±0.18	4.43±0.08	0.742
MNCV of median nerve (m/s)	54.08±1.72	53.30±4.67	0.508
MNCV threshold stimulus level (mA)	44.25±6.01	31.75±5.30	0.0001

[Table/Fig-2]: Various parameters in uncontrolled diabetics with complications.
The parameters are expressed in mean±SD
AL: Absolute latency; IPL: Interpeak latency; MNCV: Motor nerve conduction velocity
Statistical test is applied at 5% level of significance

Parameter	Diabetics without complication n=20	Diabetic neuropathy n=20	p-value	Diabetic retinopathy n=10	p-value
AL I (ms)	1.00±0.36	1.09±0.13	0.0145	1.50±0.70	0.2996
AL III (ms)	3.00±0.00	3.12±0.16	0.0001	3.94±0.07	0.0018
AL V (ms)	5.05±0.07	5.49±0.30	0.0001	5.92±0.10	0.0001
IPL I-III (ms)	2.06±0.57	2.03±0.04	0.0989	2.45±0.63	0.8156
IPL III-V (ms)	2.17±0.06	2.65±0.24	0.0309	2.35±0.35	0.0001
IPL I-V (ms)	4.37±0.06	4.41±0.18	0.7373	4.43±0.08	0.3602
MNCV of median nerve (m/s)	56.36±6.85	54.08±1.72	0.1570	53.30±4.67	0.2154
MNCV threshold stimulus (mA)	27.00±2.83	44.25±6.01	0.0001	31.75±5.30	0.003

[Table/Fig-3]: Comparison of various parameters in uncontrolled diabetics with and without complications.
The parameters are expressed in mean±SD; Statistical test is applied at 5% level of significance

Parameters	Diabetics Without Complication		Diabetic Neuropathy		Diabetic Retinopathy	
	r-value	p-value	r-value	p-value	r-value	p-value
AL I (ms)	-0.003	0.99	0.23	0.33	-0.7020	0.02
AL III (ms)	-0.295	0.21	0.11	0.64	0.137	0.71
AL V (ms)	-0.086	0.72	-0.03	0.90	-0.038	0.92
IPL I-III (ms)	-0.16	10.50	-0.11	0.66	0.732	0.02
IPL III-V (ms)	0.049	0.84	-0.07	0.76	-0.155	0.67
IPL I-V (ms)	-0.231	0.33	-0.19	0.43	0.585	0.08

[Table/Fig-4]: Correlation between BAEP parameters and random blood sugar.
Statistical test is applied at 5% level of significance.

Parameters	Diabetics Without Complication		Diabetic Neuropathy		Diabetic Retinopathy	
	r-value	p-value	r-value	p-value	r-value	p-value
AL I (ms)	-0.093	0.70	0.186	0.43	-0.359	0.31
AL III (ms)	0.189	0.42	0.015	0.95	0.251	0.48
AL V (ms)	0.280	0.23	0.192	0.42	0.334	0.35
IPL I-III (ms)	-0.008	0.97	-0.143	0.55	0.521	0.12
IPL III-V (ms)	0.002	0.99	0.103	0.67	-0.248	0.49
IPL I-V (ms)	0.200	0.40	-0.033	0.89	0.325	0.36

[Table/Fig-5]: Correlation between BAEP parameters and duration of diabetes.
Statistical test is applied at 5% level of significance

DISCUSSION

The study revealed that though median nerve conduction velocities were having no significant difference in all the three groups of diabetic patients but the threshold stimulus required for nerve stimulation was significantly less in uncontrolled diabetics without any complications that with it. Moreover, it was highest in patients with known neuropathy than retinopathy. Therefore, the patients with retinopathy, though having no clinical evidence of neuropathy, the required threshold stimulus was more, suggestive of the subclinical involvement of peripheral nerves in them. The study shows that diabetic retinopathy appears at later age with persistently high blood sugar levels and exhibits significant delay (p <0.01-0.002) in all absolute and interpeak latencies except IPL I-V than patients with neuropathy.

This work also shows that all the absolute and interpeak latencies were greater in uncontrolled diabetic subjects with complications than without it. However, the delay in absolute latencies was significant but the IPLs show a variable pattern as evident from results. Moreover, the patients with retinopathy were having greater delay in these latencies than neuropathic group and they were also having subclinical neuropathy as stated above. Most studies compared the AL and IPLs in diabetics and healthy controls and found variable results. Some observed that all ALs and IPLs are prolonged in diabetics [6,7] while others observed that some ALs or IPLs are delayed in one or both the ears [8,9].

The authors found only one study comparing the BAEP responses in uncontrolled diabetics with and without complications [10]. Therefore, such an aspect in DM is not fully explored. It appears that with the development of diabetic complications, there might be greater involvement of auditory pathways-both at the nuclear level or along the conducting pathway and this may lead to sensorineural hearing loss commonly observed in diabetes. Since, all the subjects in the study were not having hearing loss, it might be possible that there is variation in clinical evidence of hearing loss with the involvement for auditory tracts for which no conclusive reason could be ascribed. As the delay in ALI, IPL I-III and I-V were not found significant between the uncontrolled diabetic patients with and without complications; it suggests that the involvement of auditory pathways is more central than peripheral in the disease. The probable reason for abnormal BAEP in diabetes is microangiopathies. Such changes are common histopathological findings of inner ear in diabetic subjects [10]. It has been reported that brain stem neuropathy is worse in diabetic with complications than without it [7].

Authors also tried to observe a correlation between BAEP parameters with either random blood sugar [Table/Fig-4] or duration of illness [Table/Fig-5]. However, no definite correlation was observed in either of them. It suggests that the alterations in BAEP latencies are independent of both. Similar findings were observed by some other workers [10-12], but other suggests the existence of a relationship [13]. Therefore, it is also debatable and needs further exploration.

LIMITATION

To assess the control of blood sugar level, HbA1c should have been done. However, the said facility was not available with us. Therefore, we could not do it. In spite of great load of diabetic patients, the total number of cases is less but we needed only uncontrolled diabetics with or without complications with their consent.

CONCLUSION

The study revealed that though diabetes mellitus is associated with delaying the impulse transmission in auditory pathways. However, it is more pronounced in patients having poor glycaemic control and with associated complications. The delay in auditory transmission is independent of blood sugar level and duration of the disease. It may lead to early hearing loss, though the reason is still unclear. Therefore, BAEP testing can be used as prognostic tool in early detection of auditory pathways involvement in diabetes mellitus.

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