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Original Article

Diabetes Mellitus and Cognition- A Non Invasive Study

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Abstract

Background: Diabetes mellitus is increasing worldwide due to improved lifestyle modifications. Particularly more common in developing countries. Peripheral, central and autonomic neuropathy are the most common complications of diabetes mellitus, which if not detected early can lead to early disability. Event related potential P_{300} is a non invasive test to detect one of the higher functions of brain namely cognition. The present study was conducted to evaluate impact of diabetes mellitus and its duration on cognition.

Aims & Objectives: To investigate neurophysiological alterations of higher brain functions in patients with diabetes mellitus.

Materials & Method: Auditory P_{300} event related potentials were recorded in 60 diabetic patients (NIDDM & IDDM) attending medical out patient department of Bapuji & Chigateri hospital, Davangere, who had no evidence of stroke, dementia, or any other neurological illness. The P_{300} wave latencies in diabetic patients were compared with those in neurologically healthy control subjects, with consideration of duration of diabetes and analyzed by using unpaired student T test for comparison between cases and controls and one way ANOVA for multiple group comparisons within diabetics based on duration of diabetes.

Results: Diabetics had significantly longer P_{300} latencies and reduced P_{300} amplitudes than control subjects. There was a positive correlation between prolongation of latencies and duration of diabetes mellitus.

Conclusion: The present study suggests that diabetes does relate significantly to cognitive decline. ERP P300 can be a useful neurophysiological test to detect cognitive decline early in diabetics and also beneficial to the clinician for further management of the patient.

Keywords: *Cognition; Cognitive impairment Diabetes mellitus; Duration of diabetes mellitus & ERP P_{300};; Event related potential (ERP) P_{300}.*

Introduction

Diabetes mellitus is a complex metabolic disease that can have devastating effects on organs in the body. It is associated with slowly progressive end organ damage in the brain. Mild to moderate impairments of cognitive functioning has been reported both in type I diabetes mellitus and in patients with type II diabetes mellitus. Abnormalities in cognitive function mediated by frontal lobe (executive functions), including a number of complex behaviours such as problem solving, planning, organization, insight, reasoning and attention are noted in patients with diabetes[(1)]. Glucose is the primary substrate for brain energy metabolism. When diabetes strikes and insulin signal is ignored by cells, the brain may not get large amount of glucose energy it needs especially for memory. Loss of brain cells and memory

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function result especially in hippocampal region of brain which involves learning and memory.

Brain tissue contains high levels of polyunsaturated fatty acids (PUFA) making it more vulnerable to oxidative insult [(1)]. Morphological and clinical studies have amply documented that diabetes can alter the peripheral nervous system and the CNS. Electrophysiological studies have objectified the peripheral nervous system and more recently the CNS damage caused by diabetes both in diabetic patients and experimental models. The use of electrophysiological methods (multimodal evoked potentials) has also shown that distribution of such abnormalities in diabetic patients is rather patchy, confirming a frequent multifocal CNS involvement and that they can appear at an early stage of the disease and tend to persist over time[(2)].

Chronic hyperglycemia is known to have serious adverse effects on many tissues and organs. Cognitive function has been examined in people with type 2 diabetes in a small number of studies with variable results. The most consistent finding was that verbal memory appears to be impaired in groups with type 2 diabetes when compared with non diabetic controls[3]. Learning and memory dysfunction is widely believed to be a consequence of type 2 diabetes. Case control studies have demonstrated repeatedly that, as a group, older adults with type 2 diabetes remember word lists and stories less efficiently than their nondiabetic peers and large community based epidemiological studies have identified type 2 diabetes as a strong independent predictor of poorer performance on learning and memory tasks[4]. Since the prevalence of type 2 diabetes mellitus increases with age and normal aging is associated with mild deterioration in cognition, the interplay between the aging process and duration and magnitude of hyperglycemia is expected to result in an accelerated cognitive decline[5]. Several reports have indicated that diabetes may cause cognitive dysfunction or alter brain signals related to cognitive function[6].

With the advent and wide application of non invasive, more objective and quantitative evoked potential testing procedure, now it is possible to investigate, quantitatively assessing higher cognitive human brain functions, using endogenous event related evoked potentials[7]. ERP is the external recording of the endogenous electrical activity of the underlying brain structure resulting from a stimulus bound activity. P_{300} is recorded using oddball paradigm, in which subject is attentive and consciously distinguish an acoustic stimulus (target/rare) from a group of other acoustic (nontarget/frequent) stimuli. It consists of a series of positive and negative waves that are generated above the brainstem. P_3 (P_{300}) component of this response has latency of nearly 300- 350ms following the onset of rare stimuli and is of positive polarity. P_{300} latency is an index of processing time required before response generation, so it is a sensitive temporal measure of neural activity underlying the process of attention allocation and immediate memory. P_{300} amplitude vary from 5-20 microvolt but may reach upto 40 microvolts. It is proportional to attention given to a task and high amplitude is associated with superior memory performance P_{300} amplitude can be viewed as measure of CNS activity that reflects the processing of incoming information when it is incorporated into memory representation of stimulus and the context in which the stimulus occurs[8].

Aims & Objectives

To analyse event related potential P300 using odd ball paradigm and compare the response between diabetics and age matched controls for latencies of P2, N2, P3 and amplitude of P_{300}. To compare ERP P_{300} parameters between diabetics of different duration.

Materials & Method

The study was conducted in the department of Physiology, J.J.M. medical college, Davangere. In this study, diabetics (total 60) between 25 to 55years attending medical outpatient department of Bapuji hospital and Chigateri General hospital attached to J.J.M. medical college were selected and 60 normal age matched subjects were selected randomly from the general population. Inclusion criteria: Patients who are biochemically proved diabetes mellitus. Patients of type I and type II diabetes mellitus. Normal healthy age matched controls between 25-55 years. Subjects were divided into 4 groups: Group 1→ 60 controls, age matched healthy individuals, Group 2→ 20 diabetics with duration less than 10 years, Group 3→ 20 diabetics with duration 10-15 years, Group 4→ 20 diabetics with duration more than 15 years. Age group below 25 years and above 55 years, Patients with acute complication of diabetes like, diabetic ketoacidosis, recurrent ketonuria ,non ketotic hyper- osmolar coma and hypoglycaemia, Patients taking psychoactive drugs

or drug addiction, H/O Hypertension, anaemia, stroke, dementia, Smokers, Alcoholics, H/O cardiovascular or neurological disorders were excluded from the study. Written and informed consent were taken for the study after explaining the procedure and its significance in their vernacular language. The ethical committee clearance was taken. A brief personal history was taken and a clinical examination of all the systems was done to exclude medical problems and to prevent confounding of results. ERP P_{300} was recorded using PC based, 2 channel, RMS EMG. EP MARK II machine manufactured by RMS RECORDERS and MEDICARE SYSTEM, Chandigarh. Procedure in brief: Recording was carried out in a quiet and dimly lit room. Subjects were asked to come without applying oil to scalp and to shampoo hair and make it dry.

The subject was made to lie down comfortably and relaxed in a soundproof room with closed eyes. Rare tone (2KHz) and frequent tone (1KHz) were applied on both ears together in 20% and 80% in frequency in random through headphones. Total 300 stimuli were applied at the rate of 1stimuli/second. Band pass filter was 0.2-100Hz to filter out undesirable frequencies in the surroundings. The volume conducted evoked responses (Bioelectric signals) were picked up from the scalp using silver-silver chloride electrodes. The recording sites on the scalp were cleaned with spirit swab. After applying electrode paste on the recording surface of electrodes, one active electrode was placed on the vertex (Cz), one as ground electrode to forehead (Fz) and two reference electrodes to right and left mastoid (A1 and A2). All electrodes were plugged to a junction box keeping skin to electrode impedance below 5KΩ. Subjects were asked to avoid sleep and identify the rare stimulus, counting mentally. The signals picked up by electrodes, were filtered, amplified, averaged and displayed on the screen. Parameter studied: Latencies of waves P_2, N_2, P_3 in milliseconds (ms) and amplitude of P_{300} in microvolts (μv) were measured from the recording for comparison among diabetics and controls as well as diabetics with different duration.

Results

TABLE 1: COMPARISON OF ERP P_{300} PARAMETERS BETWEEN DIABETICS AND HEALTHY CONTROLS.

ERP P_{300}(ms)	Cases (N=60)		Controls (N=60)		Unpaired t Test	
	Mean	Std. Deviation	Mean	Std. Deviation	t Value	P Value
P_2	170.60	10.19	169.36	10.07	0.67	0.53, NS
N_2	249.79	11.83	225.06	29.03	6.11	P<0.001
P_3	370.33	21.50	339.98	13.72	9.22	P<0.001
Amplitude P_{300}(μv)	3.61	1.49	7.88	1.33	-16.53	P<0.001

ERP P300: Event related potential P300. Analysis done by student's unpaired t- test. Values are expressed as mean±SD. P<0.05, **P<0.01, ***P<0.001

TABLE 2: COMPARISON OF ERP P_{300} PARAMETERS AND DURATION OF DIABETES MELLITUS.

ERP P_{300}(ms)	DURATION			ANOVA	
	<10 (N =20)	10-15 (N=20)	>15 (N=20)	F Value	P Value
P_2	172.9± 9.8	169.0 ± 10.26	169.89 ±10.5	0.79	0.45
N_2	238.69 ±9.03	250.77 ± 8.22	260.39± 6.4	36.19	P<0.001
P_3	349.3 ±14.7	373.36 ± 14.3	388.97 ± 13.7	38.24	P<0.001
Amplitude P_{300}(μv)	5.17 ± 0.79	3.46 ±0.96	2.12 ±0.74	63.8	P<0.001

Cont... **TABLE 2: COMPARISON OF ERP P_{300} PARAMETERS AND DURATION OF DIABETES MELLITUS.**

Tukey's Post Hoc multiple Comparison			
LATENCIES(ms)	< 10 vs 10-15	< 10 Vs > 15	10-15 vs > 15
N_2	P<0.001	P<0.001	P<0.001
P_3	P<0.001	P<0.001	P<0.001
AMPLITUDE(μv) P_{300}	P<0.001	P<0.001	P<0.001

ERP P300: Event related potential P300. Analysis done using one way ANOVA for multiple group comparison; Post Hoc Tukey's test for subgroup comparison. Values are expressed as mean±SD. P<0.05, **P<0.01, ***P<0.001

Discussion

Averaged evoked potentials have been widely used to record the changes in electrical potential that occur within nervous system in response to an external stimulus. A distinct class of evoked potential: the "endogenous" or "event related" potentials (ERPs) that can be recorded in response to an external stimulus or event. These potential changes occur only when the subject is selectively attentive to the stimulus and elicited only in circumstances in which the subject is required to distinguish one stimulus (target) from a group of other stimuli (the nontargets). ERPs seem to be related to some aspect of cognitive events associated with distinction of target from nontarget stimuli[9]. The response to frequent stimulus consists of a series of waves (the stimulus related components) that relates to sensory modality stimulated. The neural generators of long latency (greater than 50msec) responses are uncertain, although probably reflect overlapping neural activity from multiple neocortical and limbic regions. The long latency response to the rare auditory stimulus is considerably different and consists of a negative (N1)- positive (apparent P2)- negative (N2)- positive (P3) complex. The neural generators of this P3 response are unknown, although, some evidence has suggested multiple neocortical and subcortical locations[9] .Long latency evoked potentials (Eps) are related to cognitive processing and are referred to as cognitive evoked potentials, event related potential (ERP), P3, P_{300} and endogenous EP[10].

In our study, we found prolongation of N2, P3 latencies and reduced amplitude of P300 in diabetics compared to controls. The N2 component is related to unexpectedness of the stimulus and is regarded as a measure of the time of early stimulus processing, engaging orientation and attention. P_{300} is considered as reflection of memory storage operations that are initiated in the hippocampus, claimed to be the P_{300} generator. P_{300} latency is regarded as measure of stimulus classification speed, reflecting the allocation of attentional resources for memory operations, P_{300} amplitude represents on line updating of working memory and attentional processes involved in working memory. Therefore, prolongation of N_{200} latency might be associated with decline in attention and early stimulus processing and P_{300} abnormalities with difficulties in stimulus classification speed and working memory[5] . Similar findings were reported in Singh M et al[8], Kvizom et al[11]. P2 did not show any significant difference in diabetics compared to controls.

The latencies of N_2 and P_3 were significantly prolonged in diabetics with duration of illness between 10-15years and more than 15 years compared to duration of less than 10 years (p<0.001, p<0.001) and there was a significant reduction in amplitude of P_{300} in diabetics of longer duration (p<0.001) respectively. Similar findings were reported in Mohammadkhani G et al[6]. Diabetes mellitus duration is important in pathogenesis of cognitive impairment. It is possible that metabolic imbalances and other factors could interact, either directly or indirectly and result in altered central nervous system function and impaired cognition. The deleterious effects of chronic hyperglycemia are mediated through the polyol pathway forming sorbitol and fructose, oxidative stress and non enzymatic glycation of biomolecules[12]. Both chronic hyperglycemia and consequent occurrence of diabetes complications as well as recurrent episodes of severe hypoglycaemia are thought to be associated with cognitive dysfunction in patients with type I diabetes[13].

Intensified insulin therapy which can achieve strict glycemic control is associated with a threefold higher incidence of severe hypoglycaemia. Protracted severe hypoglycaemia is uncommon but may cause permanent neurological and cognitive deficits. Long duration of type I diabetes complicated by retinopathy has been shown to be associated with impaired cerebrovascular responsiveness[14]. Subtle but definite differences in brain structure and modest differences in specific intellectual and information processing abilities are common in adults who develop type I diabetes before their seventh birthday[15].

Conclusion

The study was conducted to investigate cognitive impairment in diabetes mellitus and evaluate the role of relevant factor i.e., duration of diabetes mellitus. The following conclusions can be drawn from the study: Latencies of N2, P3 were prolonged and amplitude of P300 was reduced in diabetics with duration of illness 10-15years and more than 15 years when compared to duration of illness less than 10 years. Latencies of N2, P3 were delayed and amplitude of P_{300} was reduced in diabetics when compared to controls.

Cognitive impairment can be considered as one of the complications of diabetes with neuropathy, retinopathy and nephropathy. ERP P_{300} is a non invasive test which has to be performed along with other tests on a regular basis in diabetics for early detection of cognitive deterioration which could help the physician to update record of cognitive status of the patients and also use the results to give necessary guidance in control of diabetes and its related complications.

Limitations:

For better interpretation of results number of cases and controls included could have been more.

Conflict of Interest: NIL

Source of Funding: Self

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