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COGNITIVE DYSFUNCTION IN NIDDM : P_3 EVENT RELATED EVOKED POTENTIAL STUDY

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Abstract : P3 component of the endogenous cerebral evoked response is a sophisticated, objective and quantitative approach to assess higher functions of the brain. This test was employed using auditory 'odd ball' paradigm to assess cognitive functions in thirty non insulin dependent diabetic patients (NIDDM) aged 43.6 ± 9 yrs with poor blood glucose control. (HbAlc. 9.9 ± 1.0%). The peak latencies of N2, P3 components of event related evoked potentials obtained in these patients were compared with 30 age and sex matched non diabetic healthy controls. Latencies of these potentials were; N2 = 248.0 ± 36.3, P3 = 391.6 ± 49.9 msec in **NIDDM** as compared to 220. **6** ± 26.4, 326.2 ± 26.8 msec in controls and were highly significant (P<0.**001**). The duration of disease, blood glucose level or the physical parameters of height, weight and blood pressure did not show any correlation with N2 or P3 latencies or amplitude. These findings provide an electrophysiological evidence of delayed cognition in poorly controlled NIDDM cases.

Key words : NIDDM, P_3, glycaemic control, HbAlc, event related evoked potential

INTRODUCTION

Nervous system involvement in diabetes mellitus has been amply documented. Electrophysiological studies have objectified the peripheral nervous system (1, 2, 3, 4), and CNS damage caused by diabetes both in patients and experimental models (5, 6). Higher brain functions have not been properly monitored in diabetic patients due to non-availability of biological markers for assessing higher associative brain activity such as message comprehension and mnemonic capacities. Important detectable changes in the higher cognitive functions apppear to occur more frequently in diabetics than commonly believed. The psychometric tests so far employed do show a decreased attention and fine motor skills in diabetic subjects (7, 8, 9) but these tests lack objectivity and may be influenced by a number of psychosocial variables i.e. personality style, self rated depression, behavioral pattern, educational background. Hence, they are unlikely to be related to underlying brain damage (10) and reflect nonspecific effect of living with a chronic life threatening disease (11).

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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. These potentials express the aptitude of the human brain to discriminate, classify, decide and memorise the significance of an exogenous stimulus (or even) purposely presented to the subject being tested (12, 13, 14). Among these endogenous potentials, the P300 (or P3) wave has been identified as a late cortical neurophysiological event, reflecting the activity of cognitive and mnemonic functions in humans. It combines cognition with electrophysiology (15, 16, 17), information processing (18, 19) and appears to be strongly associated with attention and short term memory (16, 17, 20, 21). In the present study attempt has been made to give an insight into the influence of diabetes on higher brain functions in NIDDM patients as increase in P3 latency has already been reported in IDDM cases (22). The specific aim of the study was to investigate as to how the diabetic milieu affects the higher cognitive capabilities of human brain.

METHODS

Thirty NIDDM patients participated in this study alongwith same number of age and sex matched nondiabetic healthy controls. They had duration of diabetes ranging from 2-10 years and the mean ± SD of blood glucose on the morning of the P3 test was 176 ± 58.2 mg% and HbAIc 9.4 ± 1.0%.

The non-diabetic controls were of similar socio-economic and educational background as NIDDM patients. The NIDDM subjects included in the study were carefully screened and those having evidence or history of ketoacidosis, recurrent ketonuria, hyoglycaemic episodes, peripheral nerve dysfunctions, cardiovascular or neurological disorders, taking psychoactive drugs or drug addiction were excluded. These subjects showed blood cholesterol and triglyceride levels within normal range. As most of them were on some antidiabetic regimen, not strickly following it religiously, they did have episodes of hypoglycaemia which were not very frequent or recurrent. Blood glucose was monitored so also the HbAIc and no hypolycaemic episodes or presence of ketoacidosis was recorded at the time of evoked potential testing.

Event Related Evoked Potential : N2 and P3 recordings were obtained on presentation of high pitched infrequent click sound in a train of low pitched frequent and high pitched infrequent click sounds and subject pressing the button on hearing infrequent sound. The bioelectrical signals were recorded by Ag/Agcl electrodes placed at CZ, PZ according to 10-20 internatinal system of EEG electrode placement, referenced to linked ear lobules (A1 + A2). The ground electrode was sited on the forehead. Thirty two evoked responses were averaged and analysed by the Evoked Potential Recorder (Nihon Kohden Japan). Further details of the procedure used are given in our earlier reports (23, 24, 25). Analysis of N2, P3 components was done from CZ recordings which clearly appeared during the execution of button press response on target stimulus.

These components are representative of higher cognitive level analysis of sensorial stimuli compared with the target stimuli in the memory (13).

N2, P3 latencies in patients were compared with those of controls employing unpaired student 't' test. Various parameters in each group were compared and correlation coefficients worked out.

RESULTS

Various physical parameters recorded in these subjects alongwith N2, P3 latencies and amplitude and blood glucose levels are given in Table I. It is seen that the NIDDM patients had very poor glycaemic control. The N2, P3 peak latencies were significantly higher in the patients as compared to euglycaemic controls. There was no

TABLE 1 : Showing Mean ± S.D. values of P_3 event related evoked potentials in NIDDM and control subjects.

				Latencies (msec) Amp (uv)				
Group	*Age (yrs)*	*BPS (mmHg)*	*BPD (mmhg)*	N_2	P_3	P_3	*Blood glucose (mg/dl)*	*HbAIc (%)*
Control n=30	36.73±13.3	126.2±4.8	76.0±6.8	220.66±26.4	326.27±26.8	14.39±1.6	100.05±27.2	4.3±0.8
NIDDM n=30	43.67±9.0	128.2±3.8	72.9±13.3	248.06±36.3*	391.60±49.7*	13.96±3.2	176.07±58.2*	9.9±1.0*

*P<.001

BPS : blood pressure systolic BPD : blood pressure diastolic

TABLE II : Showing values of correlation coefficients on comparing various parameters with N_2, P_3 latencies and amplitude in NIDDM patients

	Height	*Weight*	*B P S*	*B PD*	*Blood glucose*	*N2 Lat*	*P3 Lat*	*P3 amp*
Height	1.000	.0928	.1095	– .0323	– .4302	.1242	.1148	– .1073
Weight	.0928	1.000	.060	– .0640	– .0941	.1311 –	.1911	.4156
B PS	.1095	.0600	1.000	.0560	– .2492	– .1242	.2824	.1518
B PD	– .0323	– .0640	.0560	1.000	– .0941	.0820	.1115	– .0810
Blood Glucose	– .4702	– .1043	– .2492	– .0941	1.000	.2128	.0155	.0850
N_2 Lat	.0520	– .1030	– .1242	.0820	.2428	1.000	.1206	.2128
P_3 Lat	.1148	– .1911	.2824	.1115	.0155	.1206	1.000	– .3214
P_3 amp	– .1073	.4156	.1518	– .0810	.0850	.2128	– .3214	1.000

significant correlation between latencies of N2 & N3 with other physical parameters of height, weight, BP, Glucose level and duration of the disease (Table II).

DISCUSSION

There have been controversial reports regarding effect of diabetes on cognitive functions. Most of the psychometric studies employing variety of tests, assessing psychomotor speed, selective attention, lexical fluency, auditory verbal learning, showed that scores were lower in diabetics as compared to controls (7, 8, 9).

Even among the two groups of diabetics, scores were much higher in type II as compared to type I (8). These authors also suggest that chronic hyperglycaemia and frequent episodes of hypoglycaemia might have a deleterious effect on cognitive performance. However, recently Lowe et al. (26) have found little evidence that type II diabetes in native Americans is associated with decrement in cognitive functions. The electrophysiological studies using event related evoked potentials have not fully corroborated the findings of the psychometric studies. This might be due to the fact that endogenous electrophysiological analysis highlights neurophysiological changes not detected by psychometric tests.

Our both NIDDM and control group subjects were normotensive (Table I). It is important to record BP not only because of higher incidence of hypertensives amongst diabetics (27) but also, reports have shown that hypertension does affect sensory and cognitive functions (28, 29). In our NIDDM patients, absolute peak latencies of both N2 and P3 components of the endogenous congitive evoked potentials were significantly delayed as compared to controls (Table I). Similar observations have been made by other authors in their IDDM patients (22, 30). These findings suggest that in poorly controlled diabetics, cognitive processes in the brain are slowed down. The blood glucose levels at the time of doing P3 tests were higher being 176.07 ± 87.6 mg% and the HbAlc level was 9.9 ± 1.0%. This would imply that poor glycaemic control seen in these diabetic patients might have resulted in delay in P3 latency. However, it is difficult to specify one factor responsible for this delay in cognition. There are reports suggesting that hypoglycaemia causes delay in P3 latency and the process of decision making (8, 30). Most of our patients did experience occasional hypoglycaemic episodes, but they were showing poor glycaemic control at the time of study. There is multifactoral hypothesis for cognitive impairment in diabetics. The most important factor being glycaemic control, but recent study has shown that improving the metabolic control of patients of IDDM with vigorous and continuous insulin, further deteriorates their cognition (31). Prescott et al., 1990 (32) have shown that glycaemic control had no effect and impairment of cognitive function in diabetes is more likely attributable to the impact of suffering from life-threatening disease rather than organic neurological damage. It has also been reported that in addition to plasma glucose, unknown physiological variables are responsible for triggering cognitive impairments in the diabetics during episode of hypoglycaemia (33). Hence recent study in native Americans has suggested that some of the cognitive impairments

previously attributed to diabetes may be related, at least in part to the influence of other risk factors (26). Sex may be one of them as women are less cognitively impaired than men with IDDM during hypoglycaemia (34) and hyperinsulinaemia in non-diabetic individuals is associated with cognitive impairment (35). Our electrophysiological observation of delayed N2 and P3 latencies in NIDDM cases suggest that whatever be the multifactoral etiology of malcognitive functions, the diabetic milieu interacts with generators of N2 and P3 in the cerebral cortex so as to cause delay in cognitive processes. There are reports indicating that P3 generators are located in hippocampal area (HPC) of limbic system (36). As HPC is known to be involved in learning and memory the delayed P3 in NIDDM therefore, reflects inhibition or possible damage of this area.

We did not find and significant correlation between blood glucose level, duration of diabetes or physical parameters of weight, Height, BP with latencies of N2 and P3 waves of event related evoked potentials. To summerise, our findings, therefore, suggest that significant impairment occurs in higher brain functions during diabetes particularly in the higher associative brain activity such as message comprehension and mnemonic capacities. This is important because detectable changes in the higher cognitive functions in diabetic appear to occur more frequently than is commonly believed.

REFERENCES

1. Hansen S, Ballyntyne JP. Azonal dysfunction in the neuropathy of diabetes mellitus : a quantitative electro-physiological study : *J Neurol Neurosurg Psychiat* 1977; 40 : 555–564.
2. Tachmann W, Lehmann HJ. Conduction of electrically elicited impulses in peripheral nerves of diabetic patients. *Eur Neurol* 1980; 19 : 20–29.
3. Halar EM, Graf RJ, Halter JB, Brozovich FV, Soine TL. Diabetic neuropathy : a clinical laboratory and electro-diagnostic study. *Arch Phys Med Rehabil* 1982; 63 : 298–303.
4. Ward JD. Diabetic neuropathy. *Br Med Bull* 1989; 45 : 111–126.
5. Buller N, Laurian N, Shvili I, Laurian L. Delayed brainstem auditory evoked responses in experimental diabetes mellitus. *J Laryngol Otol* 1986; 100 : 888–891.
6. Carsten RE, Whalen LR, Ishii, DN. Impairment of spinal cord conduction velocity in diabetic rats. *Diabetes* 1989; 38 : 730–736.
7. Reaven GM, Thompson LW, Nahum D, Haskins E. Relationship between hyperglycaemia and cognitive function in older NIDDM patients. *Diabetes Care* 1990; 13 : 16–21.
8. Sachon C, Grimaldi A, Digy JP, Pillon B, Dubois B, Thervet F. Cognitive function, insulin dependent diabetes and hypoglycaemia. *J Intern Med* 1992; 231 : 471–475.
9. Worral G. Moulton N, Briffett E. Effect of type II diabetes mellitus on cognitive function. *J Fam Pract* 1993; 36 : 639–643.
10. Ryan CM. Neurobehavioural complication of type I diabetes examination of possible risk factors. *Diabetes Care* 1988; 11 : 86–93.
11. Moordian AD. Diabetic complications of the cental nervous system. *Endocr Rev* 1988; 9 : 346–356.
12. Dochin E, Ritter W, Mccallum WC. Cognitive psychophysiology : the endogenous components of ERP. In Event related Brain Potentials in Man. Callaway E, Tueting P, Kaslow S, (eds.) Academic Press, New York 1978; 349–411.
13. Hillyard SA, Picton TW, Regan D. Sensation perception and attention analysis using ERPs. In Event Related Brain Potentials in Man. Callaway E, Tueting P, Kaslow S, (eds.) Academic Press, New York 1978; 223–321.

14. Start A, Barrett G. Disordered auditory short term memory in man and event related potentials. *Brain* 1987; 100 : 935–959.

15. Syndulko K, Cohen SN, Tourtellotle WW, Potwin, AR. Endogenous event related potentials, Prospective application in neuro-physiology and behaviour. *Neurology Bull Los Angel Neurol Soc* 1982; 47 : 124–140.

16. Polich J, Howard L, Starr A. P300 latency correlated with digit span. *Psychphysiology* 1983; 20 : 665–69.

17. Surwillo WW. P300 latency and digit span. Psychophysiology 1982; 21 : 708–709.

18. Desmedt JE. Scalp-recorded cerebral event related potential in man as point of entry into the analysis of cognitive processing. In the organisation of the cerebral cortex. Schmitt FO, Worden FG, Addman G, Dennis SG (eds). MIT Press, Cambridges MA, 1981; 14–29.

19. Hillyard SA, Kutas M. Electrophysiology of cognitive processing. *Ann Rev Psychol* 1983; 34 : 33–61.

20. Polich J, Starr A. Evoked potential in aging. In clinical Neurology of ageing. Alport ML, (ed.) Oxford Univ Press, New York. 1984; 149–177.

21. Neshige R, Barrett G, Stribasakitt. Auditory long latency, event related potential in Alzheimers disease and multi infarct dementia. *J Neurol Neurosurg Psychiatry* 1988; 51 : 1120–1125.

22. Pozzessere G, Valle E, Crignis, SD, Cordischi VM, Fattapposta F, Rizzo PA, Pietravalle P, Cristina G, Morano S, Mario UD. Abnormalities of cognitive functions in IDDM revealed by P300 event related potential analysis-comparison with short latency evoked potentials and psychometric tests. *Diabetes* 1991; 40 : 952–958.

23. Tandon OP. P3 event related evoked potential in young adults. *Indian J Physiol Pharmacol* 1990; 34 : 191–194.

24. Tandon OP, Kumar S. P3 even related evoked potential in chronic pain patients. *Indian J Physiol Pharmacol* 1993; 37 : 51–55.

25. Tandon OP, Bhatia R, Goel N. P3 event related evoked potential in pregnancy. *Indian J Physiol Pharmacol* 1996; 40 : 345–349.

26. Lowe LP, Tranel D, Wallace RB, Wetty TK. Type II diabetes and cognitive functions – A population based study of native Americans. *Diabetes Care* 1994; 17 : 891–896.

27. Barnes AJ, Locke P, Seudder PR, Dormandy TL. Dormandy JA, Slack J. Is hyperviscosity a treatment component of diabetic microcirculatory disease ? *Lancet* 1977; 2 : 789–791.

28. Tandon OP, Ram D, Awasthi R. Brainstem auditory evoked responses in primary hypertension. *Indian J Med Res* 1996; 104 : 311–315.

29. Tandon OP, Joon K. Event related evoked potential (P300) in hypertensive subjects. *Indian J Physiol Pharmacol* 1997; 41(1) : 79–82.

30. Blackman JD, Towle VL, Sturis J, Lewis GF, Spire JP, Polonsky KS, Hypoglycemic thresholds for cognitive functions in IDDM. *Diabetes* 1992; 41 : 392–399.

31. Connis RT, Taylor TR, Gordon MJ, Mecklenburg RS, Liljenguist JE, Stephens JW, Baker MS. Changes in cognitive and social functioning of diabetic patients following initiation of insulin infusion therapy. *Exp Aging Res* 1989; 15 : 51–60.

32. Prescott JH, Richardson JT, Gillespie CR. Cognitive functions in diabetes mellitus : the effect of duration of illness and glycaemic control. *Br J Clin Psychol* 1990; 29 : 167–175.

33. Ryan CM, Atchison J, Puczynski S, Puczynski M, Arslawan S, Becker D. Mild hypoglycaemia associated with deterioration of mental efficiency in children with insulin-dependent diabetes mellitus. *J Pediatr* 1990; 117 : 32–38.

34. Dralos MT, Jacobson AM, Weinger K, Widom B, Ryan CM, Finkelstein DM, Simonson DC. Cognitive functions in patients with insulin dependent diabetes mellitus during hyperglycaemia and hypoglycaemia. *Am J Med* 1995; 98 : 135–144.

35. Kalmijn S, Feskens EJ, Launer LJ, Stijnen T, Kromhout D. Glucose inolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 1995; 38 : 1096–1102.

36. Okada YC, Kaufman L, Williamson SJ. The hypocampal formation as a source of the slow endogenous potential. *Electroencephalogr Clin Neurophysiol* 1983; 55 : 417–426.