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RESEARCH ARTICLE

Electrophysiological evaluation in patients with type 2 diabetes mellitus by pattern reversal visual evoked potentials

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ABSTRACT

Background: A more general involvement of the nervous system in diabetes, affecting not only the peripheral but also the central nervous system has been increasingly suggested over the last two decades. Electrophysiological investigations in the form of visual evoked potentials (VEPs) can be very sensitive and valuable method in evaluating central neural conduction in diabetics before the overt manifestations of ophthalmologic involvement. **Aims and Objectives:** This study was planned to detect visual dysfunctions in type 2 diabetics at earlier stages by recording pattern reversal VEPs (PRVEPs). **Materials and Methods:** PRVEP was recorded in 100 subjects (50 patients with type 2 diabetes and 50 controls). Mean latencies of N75, P100 and N145 waves, interocular latency differences (for P100 waves) and N75-P100 amplitude were compared between diabetics and the controls by unpaired *t*-test. $P < 0.05$ was considered as significant. **Results:** A statistically significant increase in mean P100 latency ($P < 0.0001$) and interocular latency difference ($P < 0.001$) along with the reduction in N75-P100 amplitude ($P < 0.0001$) was revealed in diabetics as compared to the controls. Mean N75 and N145 latencies exhibited increase in diabetics but without statistical significance. **Conclusion:** Electrophysiological alterations in the form of abnormal VEPs are registered in type 2 diabetes before clinically detectable ophthalmologic impairment. VEPs should be employed for assessing the visual functions in diabetics to ameliorate the prognosis of the condition.

KEY WORDS: Diabetes Mellitus; Central Nervous System; Visual Evoked Potentials

INTRODUCTION

Type 2 diabetes mellitus has a dramatic increase in its prevalence and incidence globally owing to the behavioral and lifestyle changes in the people in the recent years. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030.[1] Diabetes mellitus is a chronic illness with multiple organ involvement. The complications result in much morbidity and mortality. Metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiologic changes in various organs such as kidneys, retina, and blood vessels. In addition, it is now generally accepted that diabetes can alter central nervous system (CNS) function also and its impact on the nervous system can be another important source of disability. Even in the absence of overt cerebrovascular accidents or repeated hypoglycemic reactions, uncontrolled hyperglycemia has been found to be associated with cognitive and other changes associated with CNS functions.[2-4]

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In the recent years, neurologic symptoms associated with diabetes have gained particular interest for the researchers. The introduction of the concept of diabetic encephalopathy by De Jong, however, dates back to 1950.[5] Various cerebral pathological findings were discussed in diabetes then but in the very advanced stages of the disease. Early CNS damage was yet to be diagnosed. Advances in neurophysiological investigations now provide greater insights into the structural and functional impact of diabetes on the CNS. Electrophysiological techniques make it possible to investigate at initial stages of the disease. Evoked potentials as valuable electrophysiological investigations have now been widely studied and appreciated as sensitive and objective tests to assess subclinical neurological changes in various clinical conditions. The possible deleterious effects of diabetes on CNS can be evaluated by way of these tests in an attempt to reduce the morbidity in these patients with an earlier detection. Greater understanding of CNS involvement could lead to new strategies to prevent or reverse the damage caused by diabetes mellitus.

Visual evoked potentials (VEPs) are the evoked potential tests which assess the functional integrity of the visual pathways by recording electrical potential differences from the scalp in response to visual stimuli. Pattern reversal is the preferred stimulus in most clinical settings. Pattern reversal VEPs (PRVEPs) constitute valuable tool for obtaining important diagnostic informations regarding visual dysfunctions objectively. VEP abnormalities arise before diabetic ocular complications become clinically detectable. Hence, long before the clinically evident structural alterations in the retina and in visual pathways are diagnosed, this objective and noninvasive electrophysiological technique can help detecting the functional alterations in the visual system.[6] Hence, this study was planned to evaluate the patients with type 2 diabetes mellitus before the development of diabetic complications, by PRVEPs. The study aims to detect visual dysfunctions in diabetes mellitus even before the clinical manifestations of ophthalmologic involvement. Evidence of early involvement could contribute to reduce the morbidity of the condition by early and proper management of the patients.

MATERIALS AND METHODS

The study was conducted on total 100 subjects. Out of 100 subjects, 50 subjects were those who were diagnosed with type 2 diabetes mellitus among the patients attending the Department of Medicine at Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India. 50 subjects were age and sex-matched healthy controls from the area of study (students and staff of the institute). The test was conducted in the electrophysiology laboratory in the department of physiology.

Sample size was estimated on the basis of Pearson's correlation coefficients for P100 latency and duration of diabetes, obtained from previous studies which ranged from 0.570 to 0.790.[7-9] To obtain maximum possible sample size, lower value of correlation coefficient of 0.570 was taken.[7] A sample size of 46 diabetics was calculated accordingly at 5% significance level and power of 99%. 50 diabetic subjects were taken up for the study along with 50 controls for comparison of VEP parameters.

All the patients with type 2 diabetes mellitus (proven by recent blood glucose studies with fasting plasma glucose values exceeding 126 mg/dl, as per the WHO criteria) with normal visual acuity or corrected by glasses and normal fundus examination and without diabetic complications formed the inclusion criteria for the study.[10] The patients with cataract, glaucoma, vitreous opacities or any evidence of optic atrophy, diabetic retinopathy, patients with long standing hypertension as evidenced by fundus appearances, electrocardiogram and clinical examination, patients with past history of cerebrovascular accidents, chronic alcoholics, patients with peripheral nervous system disorders unrelated to diabetes, patients with other endocrine disorders and patients with diabetic complications constituted the exclusion criteria for the study.

Every subject included in the study was examined in details with careful neurological examinations after taking a detailed clinical history. A written informed consent was obtained before the test. Subjects were explained about the test to ensure full cooperation. VEP was performed on Allengers Scorpio - EMG, EP, NCS system in the electrophysiology laboratory with uniform light levels and a quiet environment." (As NCS stands for nerve conduction studies). The method of presentation of the stimuli was a video-monitor and the type of stimuli presented was pattern stimuli with a black and white checker-board pattern reversing alternately at the rate of 2 Hz. The video monitor presented a fixation spot in the center of the screen (mean luminance 50 candela/m^2 and contrast 70%). Subjects were seated comfortably at about 95 cm away from the video-monitor with a 30 cm screen. The checks subtended the visual angle of 54.6 min while the screen subtended a visual angle of 19°. The signals were amplified and filtered with a system band pass filter of 2-200 Hz and 100 responses were averaged. Scalp skin was prepared before the application of electrodes. Standard disc surface electrodes were placed according to the international 10/20 system of electrode placement, with active electrode at Oz, reference electrode at Fz and ground electrode at Fpz.[11] Volunteers were instructed to fix the gaze on a small red square at the center of the screen. Monocular stimulation was done with an eye-patch covering the other eye and recordings for right as well as left eyes in both the groups (cases and controls) were obtained. The latencies of N75, P100 and N145 waves, interocular latency differences (for P100

waves) along with N75-P100 amplitude were the parameters for the study. The data were expressed as mean ± standard deviation (SD). Mean values of the VEP parameters for both right and left eyes (total 100 eyes) were compared between the two groups (cases and controls) by unpaired *t*-tests. The data were analyzed by SPSS (Statistical Package for the Social Sciences) version 20. The statistical analysis was done at significance level of 5%.

RESULTS

Mean age of diabetics was 51.6 ± 9.48 years and that of controls was 51.24 ± 9.55 years with no statistically significant difference ($P > 0.05$). Demographic profile of the study groups revealed that 54% of the subjects belonged to the age-group of 41-60 years in diabetics as well as in controls. Each group (cases) ($n = 50$) and controls ($n = 50$) comprised 25 males and 25 females (Figure 1). Mean duration of the disease in diabetics was 7.54 ± 4.4 years.

VEP P100 latency, N75 latency, N145 latency, and N75-P100 and amplitudes compared between right and left eyes for both cases and controls were not statistically significantly different ($P > 0.05$). Regarding the comparisons of VEP parameters between the cases and the controls, mean P100 latencies (in ms ± SD) increased in the cases for both the eyes (right eye: 113.51 ± 6.50, left eye: 113.0 ± 6.58 and mean of both eyes: 113.28 ± 6.44) as compared to the controls (right eye: 100.29 ± 5.42, left eye: 99.94 ± 5.65 and mean of both eyes: 100.13 ± 5.44) with a statistically significant difference ($P < 0.0001$) (Table 1). Furthermore, mean N75-P100 amplitudes (in μv ± SD) were found to be decreased for both the eyes (right eye: 4.6 ± 1.51, left eye: 4.99 ± 1.73 and mean of both eyes: 4.8 ± 1.54) among diabetics as compared to the controls (right eye: 6.34 ± 1.72, left eye: 6.83 ± 2.13 and mean of both eyes: 6.59 ± 1.74) with a statistically significant difference ($P < 0.0001$) (Table 1). Comparison of mean interocular latency differences (P100 wave) also revealed a statistically significant increase in diabetics with $P < 0.001$ (Table 1).

Mean N75 latencies exhibited increase among the cases but without statistical significance ($P = 0.073$, $P = 0.085$ and $P = 0.068$) for right eye, left eye and mean of both the eyes, respectively (Table 2). Similar results were obtained for the comparison of mean N145 latencies with $P = 0.07$, $P = 0.08$ and $P = 0.058$ for right eye, left eye and mean of both the eyes respectively (Table 2).

DISCUSSION

The deleterious effects of metabolic derangements in diabetes have been increasingly suggested to involve CNS functions also. VEPs which evaluate the visual path from retinal ganglion cells to the visual cortex can prove to be a sensitive tool to study the possible effects that diabetes may exert on the visual system. The visual system in diabetics undergoes subtle functional changes long before the clinically evident structural alterations in the retina and in visual pathways. In this study, affection of the visual functions was detected

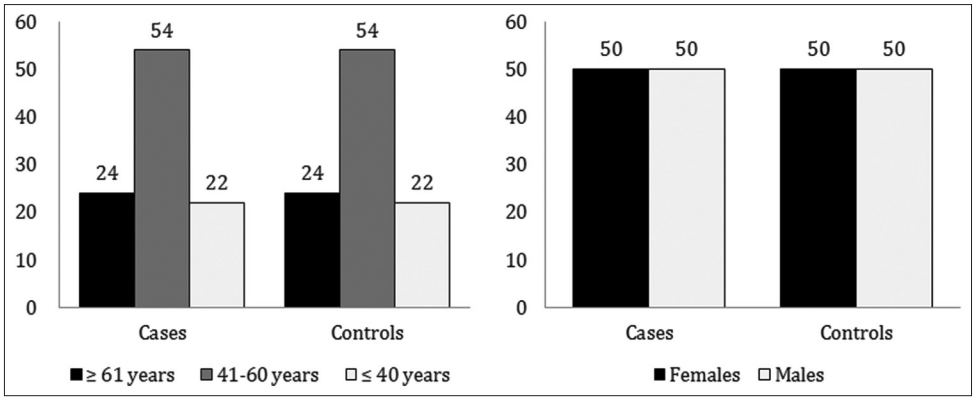

Figure 1: Demographic profile of the subjects in the two groups

Table 1: Comparison of mean values of P100 wave latency, interocular latency difference and N75-P100 amplitude in cases and controls

Study groups	Mean P100 latency (ms±SD)			N75-P100 amplitude (μv±SD)			Interocular latency difference (P100 wave) (ms±SD)*
	Right eye**	Left eye**	Mean of both eyes**	Right eye**	Left eye**	Mean of both eyes**	
Cases	113.51±6.50	113.0±6.58	113.28±6.44	4.6±1.51	4.99±1.73	4.8±1.54	1.79±1.39
Controls	100.29±5.42	99.94±5.65	100.13±5.44	6.34±1.72	6.83±2.13	6.59±1.74	0.95±0.9

**Increase in mean P100 latency and reduction in N75-P100 amplitude (for right eye, left eye and mean of both eyes) among the cases (diabetics) was statistically significant with $P<0.0001$. *Mean interocular latency difference increased in the cases with $P<0.001$ ($P=0.0005$). SD: Standard deviation

Table 2: Comparison of mean values of N75 and N145 wave latencies in cases and controls

Study groups	Mean N75 latency (ms±SD)			Mean N145 latency (ms±SD)		
	Right eye	Left eye	Mean of both eyes	Right eye	Left eye	Mean of both eyes
Cases	70.8±6.39	70.45±6.85	70.65±6.33	146.72±11.31	146.95±11.75	146.86±11.05
Controls	68.58±5.8	68.33±5.2	68.47±5.41	142.58±11.57	142.52±11.64	142.57±11.32

Mean N75 latency and mean N145 latency increased in the cases with nonsignificant statistical difference (P>0.05) (for right eye, left eye and mean of both the eyes). SD: Standard deviation

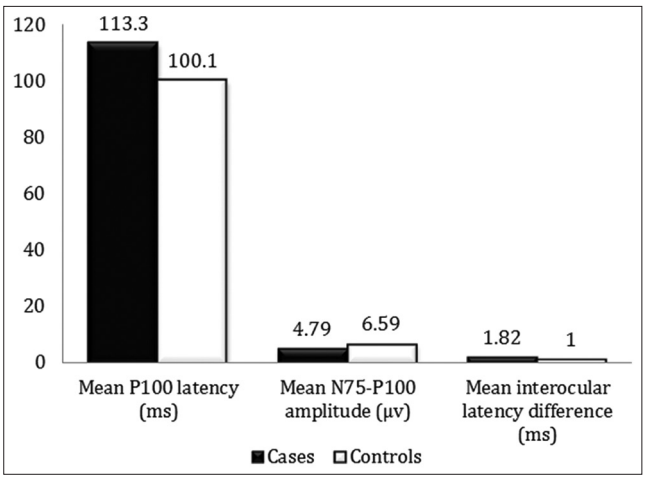

Figure 2: Mean visual evoked potential P100 latency, N75-P100 amplitude and interocular latency difference (mean of both the eyes) compared in cases and controls

by recording VEPs in patients with type 2 diabetes mellitus without chronic complications and in healthy controls and comparing the records in the two groups.

Mean VEP P100 latency and interocular latency differences (for P100 waves) demonstrated a statistically significant increase and mean N75-P100 amplitude exhibited decrease in the patients with diabetes as compared to the healthy controls studied (Figure 2). Mean P100 latency among the control group was 100.13 ± 5.44 ms while that among diabetics was 113.28 ± 6.44 ms. Abnormal P100 latency prolongation (>2 SD) was found in 66% of diabetic subjects (>111.01 ms) in our study. The results comply with some similar studies in the past. Puvanendran et al. stated an abnormal latency prolongation in 62.5% of diabetics in their study.[12] Pozzessere et al. found a pathologic increase in the latency of the P100 wave in 21.4% of type 2 diabetic patients.[13] Abnormal latency values were found in 28% of diabetics in a study by Algan et al.[14] Another study by Heravian et al. states abnormal latencies in 60% of diabetic patients.[15] The variability in the proportion of patients with increased P100 latency ranges from 9% to 77% in various studies.[12-16] This high variability could be explained by differences in the criteria for inclusion or diagnosis, the presence of retinopathy or peripheral neuropathies and differences in stimulus and recording conditions.

A statistically significant prolongation of P100 latency in type 2 diabetics has been reported in the present study. The finding is consistent with many previous similar studies including that by Bhanu et al. who studied 20 type 2 diabetics without complications and obtained mean value of P100 latency as 110.14 ± 5.30 ms as compared to that in controls as 100.17 ± 0.75 ms with $P < 0.001$.[9] Another study by Gayathri et al. reports a significant prolongation of P100 latency in 40 type 2 diabetics (101.24 ± 5.7 ms) when compared to that in the controls (93.81 ± 3.27 ms).[17] Similar significant prolongations are reported by a study by Gupta et al. (who compared 64 diabetics with 52 healthy controls). They reported mean P100 latency in diabetics as 105.34 ± 7.11 ms while that in controls as 98.21 ± 0.96 ms.[18] Heravian et al. and Algan et al. in their studies also report a significant prolongation with $P < 0.001$ for the comparison of mean P100 latency in diabetics and controls.[14,15] This study also obtained a statistically significant reduction in mean N75-P100 amplitude among diabetics which conforms to the findings by some previous similar studies.[15,17,18] However, when compared to P100 latency prolongation in diabetics, reduction in N75-P100 amplitude has been a less consistent finding.[19,20] We also obtained increase in the mean interocular latency difference in diabetics which conforms to the studies by Gupta et al. and Raman et al.[18,19]

N75 latency in this study was found to be increased but without statistical significance ($P > 0.05$) which conforms to many previous similar studies.[15,19] A similar result was obtained for N145 latency studied in both the groups which comply with a study by Chopra et al.[21]

In an attempt to search for the pathogenetic mechanisms underlying the VEP abnormalities in diabetics, the studies in the past have concluded that an early involvement of the innermost retinal layers or a delayed neural conduction in the post-retinal visual pathways could independently influence the VEP responses in diabetics without retinopathy.[22] Abnormal VEP responses observed in diabetics hence could be the expression of structural damage at the level of myelinated optic nerve fibers or retinal ganglion cell damage before the development of overt retinopathy.

A multifactorial pathophysiology of CNS dysfunctions involving metabolic and vascular factors similar to the pathogenesis of diabetic peripheral neuropathy has been implicated. Hyperglycemic milieu in diabetics results in the shunting of excess glucose into the polyol pathway and is converted to sorbitol and fructose. Sorbitol and fructose

tend to accumulate within the nerve owing to the relative impermeability of the nerve cell membrane for the same. Osmotically active sorbitol and fructose increase the water content in the nerves. An associated depletion of nerve myo-inositol also has been suggested. The above changes decrease the activity of Na+K+ATP-ase (sodium potassium ATP-ase) thought to be located primarily in the nodal and paranodal regions of large myelinated nerve fibers resulting in increased intra-axonal Na+ concentration, reduced nodal Na+ permeability causing diminished conduction velocity.[23,24] Ischemic neuronal and other retinal structural damage caused by microvascular abnormalities in diabetes has also been implicated.[25] Animal models of diabetic neuropathy have demonstrated that the neuropathy is accompanied by reduced endoneurial blood flow, increased endoneurial vascular resistance, and reduced oxygen tension.[26] Ischemia may result in nerve fiber loss in peripheral nerves. It has been suggested that optic nerve fibers may also undergo similar ischemic changes in diabetes.

CONCLUSION

VEPs demonstrate electrophysiological alterations in diabetics. Abnormal VEP changes may be detected before the clinical manifestations of the ophthalmic involvement in diabetes. This electrophysiological evidence of visual dysfunctions in diabetics may be the beginning of the retinal ganglion cell damage which precedes the detectable signs of diabetic retinopathy or due to the preclinical changes in the post-retinal visual pathways. Regular electrophysiological screening in diabetic patients in the form of VEP tests which are noninvasive, sensitive and objective investigations should receive more attention for better ophthalmological care and for optimizing the management of the condition.

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