

RESEARCH ARTICLE

Study of visual evoked potentials in patients with type 2 diabetes mellitus and diabetic retinopathy

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a metabolic disorder showing an increasing trend with an increase in complications such as diabetic retinopathy (DR), which can cause blindness. Most patients do not notice vision loss early; hence, it is beneficial to have dysfunction of the retina identified. Patients with T2DM and DR have shown abnormalities in visually evoked potentials (VEPs). **Objectives:** To investigate whether VEPs can be used to detect early changes related to T2DM and DR. **Materials and Methods:** A total of 111 patients, of both sexes and aged 40-70 years, were studied as three groups of 37 each, who were, respectively, patients with T2DM, patients with DR, and normal subjects. For all the groups, VEP recording was done using Medicaid Neurostim EP machine, and retinal examination was done using direct ophthalmoscopy. The latency and amplitude of P100 in VEP of both eyes were, respectively, analyzed using analysis of variance and *post-hoc* test. **Results:** Our results showed significantly prolonged P100 latencies of VEPs in T2DM patients and DR patients when compared to controls. However, there was no significant difference observed in the P100 amplitudes of VEPs in T2DM patients and DR patients when compared to controls. **Conclusion:** The present study has highlighted the importance of VEP as a valuable non-invasive test to detect early neuronal changes in T2DM patients and can be recommended for monitoring early effects of diabetes on visual function.

KEY WORDS: Type 2 Diabetes Mellitus; Diabetic Retinopathy; Central Nervous System; Visual Evoked Potential; P-100 Latency

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder that is characterized by abnormal glucose homeostasis, in the context of insulin resistance and relative insulin deficiency.^[1] T2DM is a global epidemic its prevalence is rapidly increasing all over the globe.^[2] The International Diabetes Federation estimates the total number of diabetic patients to rise to

69.9 million by the year 2025.^[3] With an increasing trend in the incidence of diabetes reported, there is also an increase in complications of T2DM due to damage and dysfunction of the organs such as the eye.^[4]

Diabetes is a major cause of blindness.^[5] Diabetic retinopathy (DR) is a complication of T2DM, which is the sixth common cause of blindness in India,^[6] the overall prevalence being 17.6% in the Indian population.^[7] There is enough evidence to show that at least 90% of these new cases could be reduced if there were proper and vigilant treatment and monitoring of the eyes.^[8] During the initial stage of DR, most people do not notice any change in their vision.^[9] Hence, it is beneficial for the patient to have any changes in the function of the retina identified early enough, to effect early treatment.

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A measure of visual function in patients with diabetes can be performed using visually evoked potentials (VEPs), which are electrical potential differences occurring in the visual areas of the occipital cortex, in response to visual stimuli and are recorded from the scalp.

Patients with T2DM and with DR have shown abnormalities in VEP recordings, relating to increase in implicit time/latency.^[10,11]

With this information, our study makes an attempt to document and interpret the changes in the VEP waveforms such as latency and amplitude of P100, occurring in the patients with T2DM, and in patients having DR.

MATERIALS AND METHODS

This study is an analytical case-control study which was conducted on patients who attended the outpatient of the Department of Ophthalmology of the SRM Medical College Hospital and Research Centre, Kattankulathur - 603 203, India, from September 2011 till August 2012 for 1 year. The study was conducted in accordance with the ethical guidelines for biomedical research on human subjects by the Central Ethics Committee on Human Research and those as contained in the "Declaration of Helsinki". The study was approved by the Institutional Ethical Committee on Human Subjects' Research.

In the present study, a total of 111 patients were studied. They included 17 male and 20 female patients with T2DM of age group 40-70 years grouped as Group A; 37 male and female patients with DR of age group 40-70 years grouped as Group B; healthy male and female controls in the age group 40-70 years grouped as Group C which is the inclusion criteria. Both cases and controls were given an explanatory note, explaining the purpose of the study and the right to deny participation following which due consent on the patient consent form was obtained from each patient before inducting them in the study. Smokers, alcoholics, patients having optic neuropathy, epilepsy, those who had undergone ocular surgery, were excluded from the study.

Personal details of all the participants such as name, age, sex, ethnicity, address, and contact phone number, and relevant medical history were entered in a questionnaire from those who agreed to the study.

A retinal examination was done using direct ophthalmoscope after dilatation of pupils, to document absence or presence of DR to group them as Group A and B, respectively.

The Medicaid Neurostim EMG EP machine was used to record VEPs on each patient. The patients were first explained about the test. They were asked to wash the hair with shampoo the

night before the test and not to apply oil on their head. If the patient usually wears glasses, they were asked to be worn during the test. The patients were asked to maintain accurate visual fixation throughout the test.

The test was performed as per the ISCEV guidelines according to the instrument instruction manual. A constant distance of 100 cm was maintained between the TV screen and the patient. VEPs were recorded through pattern-reversal stimulation with mid-size checks (24-32') using a checkerboard. Skin electrodes were used for recording VEPs. These included three scalp electrodes, i.e., Frontal, Occipital, and grounding. The aim was to achieve maximal stimulation of the foveal and parafoveal fibers at 75% contrast and a reversal rate of 1.2 Hz. Uniform illumination was maintained in the laboratory, and the electrode impedance was kept at less than 5 k Ω . An average of 100 sweeps of stimuli was given to each eye. This was repeated twice, and the average of the two was superimposed to demonstrate reproducibility. Any difference of more than 3 m sec in the latencies between trials was not included in the study. The evoked responses were averaged and analyzed by the Medicaid Neurostim EP machine. The peak P100 latencies and amplitudes were recorded, and a printout of the test report was taken.

RESULTS

In our study, three groups were studied, the sample size of each being 37, corresponding to an odds ratio of 4. (Sample size determination by Kelsey-Fleiss/Fleiss with CC Kelsey et al. Methods in Observational Epidemiology, Second Edition Tables 12-15; and Fleiss, statistical methods for rates and proportions, formulas. 3.18 and 3.19, CC=Continuity Correlation Factor). The collected data were entered in the MS Excel spreadsheet. Statistical analysis was done using - analysis of variance (ANOVA) one-way, which included that for latency and amplitude of P100 and multiple comparisons and *post-hoc* test. The descriptive tables for age are given in Table 1, and descriptive tables for gender in Table 2. The mean standard deviation, maximum, minimum, standard error, and confidence bounds for the latency and amplitude of P100 for both eyes of the three groups are given in Tables 3 and 4. The comparative analysis was made using one-way multivariate ANOVA on three groups, and the results are given in Table 5. The *post-hoc* test results are given in Table 6.

It can be seen that the mean value of P100 latency in the group with DR for right eye (RE) is 134.4327 ms (confidence interval [CI]: 133.52, 135.34), and for left eye (LE) is 134.6937 ms (CI: 134.01, 135.37) which indicates maximum increase in the P100 latency among the 3 study groups. The mean value of P100 latency in the control group with RE is 102.5773 ms (CI: 101.10, 103.16), LE-102.4790 ms (CI: 102.0, 102.96 ms). The mean value of P100 latency in the group with T2DM for RE is 124.3817 ms (CI: 123.19, ms)

Table 1: Two-way table for age and groups

Age code	Group			Total
	Patients with type 2 diabetes mellitus	Patients with type 2 diabetic retinopathy	Controls (control group)	
40-50				
Count	4	4	4	12
% within age code	33.3	33.3	33.3	100.0
% within group	10.8	10.8	10.8	10.8
51-60				
Count	7	7	7	21
% within age code	33.3	33.3	33.3	100.0
% within group	18.9	18.9	18.9	18.9
61-70				
Count	21	21	21	63
% within age code	33.3	33.3	33.3	100.0
% within group	56.8	56.8	56.8	56.8
71-80				
Count	5	5	5	15
% within age code	33.3	33.3	33.3	100.0
% within group	13.5	13.5	13.5	13.5
Total				
Count	37	37	37	111
% within age code	33.3	33.3	33.3	100.0
% within group	100.0	100.0	100.0	100.0

Table 2: Two-way table for gender and different groups

Group	Gender		Total
	Male	Female	
Patients with type 2 diabetes mellitus			
Count	17	20	37
% within group	45.9	54.1	100.0
% within gender	32.1	34.5	33.3
Patients with diabetic retinopathy			
Count	18	19	37
% within group	48.6	51.4	100.0
% within gender	34.0	32.8	33.3
Controls (control group)			
Count	18	19	37
% within group	48.6	51.4	100.0
% within gender	34.0	32.8	33.3

DISCUSSION

We have found in our study that the P100 latencies of VEP were significantly prolonged in patients with T2DM when compared to the control group indicating that neuronal damage occurs before any visible changes in the retina are seen. The P100 latencies were significantly prolonged in T2DM patients with DR when compared with the patients with T2DM without DR indicating that the magnitude of neuronal damage is more in T2DM patients having DR than those who did not. However, the P100 amplitudes were not affected significantly in T2DM or the DR groups.

Earlier studies of VEPs in diabetic patients have established the prevalence of abnormalities in VEPs of diabetic patients of both sexes in comparison with a control population.^[12-14] Studies with pattern-reversal VEPs have shown abnormalities as an increase in latency of P100 in patients with T2DM with and without retinopathy.^[15-17] There is prolonged P100 latency reported in patients with diabetes some of whom had DR.^[13] Prolongation of latency has also been reported in diabetic patients who did not have retinopathy.^[18,19] It has also been reported that the VEP abnormalities did not correlate with the level of retinopathy.^[20] It has been shown that VEP can detect early retinal dysfunction in diabetics having no features of retinopathy and so it can be a method to detect early alterations reflecting preclinical microvascular or neurodegenerative changes inside or upstream the retina in patients without DR.^[21]

and for LE is 125.7677 ms (CI: 124.89, 126.64 ms). The mean value of P100 amplitude in the three groups is the same, that is, for RE is 10.6333 mV (CI: 10.45, 10.48 mV) and for LE is 10.3667 mV (CI: 10.18, 10.54 mV). Since the p values of all combinations are <0.05, the latency values of both eyes of all three groups are different. It is maximum in Group B and minimum in Group C. The insignificant p values (p>0.05) establish that the P100 amplitude values of both eyes do not differ from one another (Table 7).

Table 3: The descriptive statistics for amplitude of RE and LE of P100 for three groups

Variable	N	Mean	Standard deviation	Standard error	95% confidence interval for mean		Minimum	Maximum
					Lower bound	Upper bound		
Amplitude RE								
Group A	37	10.6333	0.49013	0.08949	10.4503	10.8164	10.00	11.00
Group B	37	10.6333	0.49013	0.08949	10.4503	10.8164	10.00	11.00
Control	37	10.6333	0.49013	0.08949	10.4503	10.8164	10.00	11.00
Total	111	10.6333	0.48459	0.05108	10.5318	10.7348	10.00	11.00
Amplitude LE								
Group A	37	10.3667	0.49013	0.08949	10.1836	10.5497	10.00	11.00
Group B	37	10.3667	0.49013	0.08949	10.1836	10.5497	10.00	11.00
Control	37	10.3667	0.49013	0.08949	10.1836	10.5497	10.00	11.00
Total	111	10.3667	0.48459	0.05108	10.2652	10.4682	10.00	11.00

RE: Right eye, LE: Left eye

Table 4: The descriptive statistics of latency of RE and LE of P100 for three groups

Variable	N	Mean	Standard deviation	Standard error	95% confidence interval for mean		Minimum	Maximum
					Lower bound	Upper bound		
Latency RE								
Group A	37	124.3817	3.18702	0.58187	123.1916	125.5717	120.14	129.88
Group B	37	134.4327	2.43577	0.44471	133.5231	135.3422	130.08	139.57
Control	37	102.5773	1.55789	0.28443	101.9956	103.1591	100.05	104.98
Total	111	120.4639	13.59491	1.43303	117.6165	123.3113	100.05	139.57
Latency LE								
Group A	37	125.7677	2.34555	0.42824	124.8918	126.6435	121.24	129.92
Group B	37	134.6937	1.82535	0.33326	134.0121	135.3753	130.29	138.74
Control	37	102.4790	1.28157	0.23398	102.0005	102.9575	100.01	104.58
Total	111	120.9801	13.78079	1.45262	118.0938	123.8664	100.01	138.74

RE: Right eye, LE: Left eye

Table 5: Analysis of variance table for latency values of RE and LE

Variable	Sum of squares	Df	Mean square	F	Significant
Latency RE					
Between groups	15912.138	2	7956.069	1288.987	0.000
Within groups	536.994	87	6.172		
Total	16449.132	89			
Latency LE					
Between groups	16598.202	2	8299.101	2376.619	0.000
Within groups	303.802	87	3.492		
Total	16902.004	89			

RE: Right eye, LE: Left eye

The limitation of our study is that since the study groups were a section of the patients and patients who came to the outpatient in the Department of Ophthalmology, they do not truly reflect the exact prevalence in the community. Hence, a larger study sample has to be studied for better understanding and validation of the test. Further follow-up study is required, to throw more light on the time taken for the T2DM patients to manifest the earliest detectable neurophysiological variations.

CONCLUSION

DR is a serious sight-threatening complication of T2DM and early detection of changes in the visual function using electrophysiology before the florid manifestation of DR is useful to detect and treat this otherwise irreversible blindness.

VEP is a useful tool in detecting early dysfunction due to retinal ganglion cell damage in diabetics before signs of DR

Table 6: The results of *post-hoc* tests for latency values of both eyes

Dependent variable	(I) Group	(J) Group	Mean difference (I-J)	Standard error	Significant	95% confidence interval	
						Lower bound	Upper bound
Latency RE	Group A	Group B	-10.05100*	0.64147	0.000	-11.6486	-8.4534
		Control	21.80433*	0.64147	0.000	20.2067	23.4019
	Group B	Group A	10.05100*	0.64147	0.000	8.4534	11.6486
		Control	31.85533*	0.64147	0.000	30.2577	33.4529
	Control	Group A	-21.80433*	0.64147	0.000	-23.4019	-20.2067
		Group B	-31.85533*	0.64147	0.000	-33.4529	-30.2577
Latency LE	Group A	Group B	-8.92600*	0.48249	0.000	-10.1276	-7.7244
		Control	23.28867*	0.48249	0.000	22.0870	24.4903
	Group B	Group A	8.92600*	0.48249	0.000	7.7244	10.1276
		Control	32.21467*	0.48249	0.000	31.0130	33.4163
	Control	Group A	-23.28867*	0.48249	0.000	-24.4903	-22.0870
		Group B	-32.21467*	0.48249	0.000	-33.4163	-31.0130

RE: Right eye, LE: Left eye, *: < 0.05

Table 7: Analysis of variance table for amplitude values of RE and LE

Variable	Sum of squares	Df	Mean square	F	Significant
Amplitude RE					
Between groups	0.000	2	0.000	0.000	1.000
Within groups	20.900	87	0.240		
Total	20.900	89			
Amplitude LE					
Between groups	0.000	2	0.000	0.000	1.000
Within groups	20.900	87	0.240		
Total	20.900	89			

RE: Right eye, LE: Left eye

are actually detected in the patients. The ideal parameter of VEP is latency of P100. The present study has shown that P100 latency was significantly prolonged in patients with T2DM and patients with DR, when compared to controls and highlighted the importance of VEP as a valuable non-invasive test to detect early neuronal changes in the pre-retinopathy stage in T2DM patients. Thus, VEP can be recommended as an early investigation in T2DM before the occurrence of retinopathy to monitor the early effects of diabetes on visual function thus helping to prevent blindness.

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