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Electro-physiological Changes in the Central Nervous System by Visual Evoked Potential in Diabetic Patients

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ABSTRACT

Background: Increasing sedentary lifestyle in today's world has increased the prevalence of Diabetes Mellitus. Loss of vision due to diabetic retinopathy is a major public health burden. Visual evoked potential identifies the neuronal degenerative changes in chronic metabolic disorders specially Diabetes Mellitus. The study aimed at evaluating changes in visual evoked potential waves in diabetic patients.

Methods: This is a cross sectional comparative study consisting of 90 participants, out of which 60 were diabetic patients and 30 were non-diabetic control group. Among diabetic patients, 30 were without retinopathy, 10 with mild non-proliferative retinopathy, 10 with moderate non-proliferative retinopathy and 10 with severe non-proliferative retinopathy. Visually evoked potential latencies and amplitudes were compared among diabetic patients and the control group and also among individuals with different grades of retinopathy.

Results: Delay in P100 latency and decrease in its amplitude were statistically significant in diabetic patients. The changes in P100 latency, P100 amplitude and N75 latency were also significant in different grades of retinopathy.

Conclusions: There are statistically significant changes in visually evoked potential in diabetes patients. Visual evoked potential is a useful, non-invasive investigation which can establish the central nervous system neuropathy in diabetes at an early stage of the disease. So Diabetic retinopathy can be prevented due to early detection of neuropathy by visual evoked potential test

Keywords: Diabetes mellitus; diabetic retinopathy; visual evoked potential

INTRODUCTION

Prevalence of diabetes mellitus is increasing because of the sedentary life style and obesity.[1] The South East Asia has one fifth of the world's diabetic population. Half of the diabetic cases in the world are undiagnosed.[2] Diabetic retinopathy (DR) is one of the major causes of loss of vision and one of the major public health burden.[3] Recent studies have shown the damage in neural retina and central visual pathway occurs long before any visible damage to the vessels of retina in ophthalmoscopy.[4] Many diabetic patients who show severely slowed conduction in visually evoked potential (VEP) have normal visual acuity showing early sub clinical effects of retina, optic nerve and visual pathway.[4] Considering the evidence of neuronal damage long before any vascular damage, it would be crucial to identify the beginning of neuronal damage in the disease process by VEP.

METHODS

A cross sectional analytical study was conducted in the Retina Clinic, General Eye OPD and the Electrophysiological Lab of B.P. Koirala Lions Centre for Ophthalmic Studies (BPKLCOS), Institute of Medicine, Kathmandu, Nepal. The study participants were selected by convenient sampling from the patients visiting the General and Retina OPD of BPKLCOS. The controls were non-diabetic patients visiting General Eye OPD for eye check up with Random blood sugar <140mg/dl (<7.7mmol/L). All previously diagnosed diabetic patients i.e., the patients who met ADA criteria laid in 2013 i.e., A1C≥6.5 % or Fasting blood glucose ≥126mg/dl (7 mmol/L) or Random plasma glucose ≥200mg/dl (>11mmol/L) were included as cases in the study.[5,6] the aim of the present study was to evaluate optic neuropathy in diabetic patients. We studied visual evoked potentials (VEPs The diagnosis of

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diabetic retinopathy was done by ophthalmologist in the Retina Clinic. Diabetic retinopathy was classified according to American Academy of Ophthalmology's Classification 2003.[7] The patients aged between 35 to 60 years were taken. Patients with reduced visual acuity not corrected by glasses, cataract, glaucoma, optic nerve diseases, proliferative diabetic retinopathy ,macular disease, diabetic macular edema, amblyopia and vitreous opacities, hypertensive retinopathy, past history of cerebro-vascular accidents or seizures, history of chronic renal failure, peripheral nervous system abnormalities not related to diabetes, patients consuming more than 100 ml of alcohol daily, mydriatic or mitotic drug 12 hours before examination, on any sedating drugs were excluded from study.[8-12]

The VEP was recorded in 90 subjects including 60 diabetics and 30 controls after obtaining written consent.[13] VEP was recorded by using Pattern reversal stimulus. VEP consisted of series of wave forms of opposite polarities negative (denoted as N) and positive (denoted as P). The parameters recorded were latencies of various waves namely first negative wave N1 or N75, first positive wave P 100, second negative wave N2 or N 135 in milliseconds and amplitude of P100 wave in millivolts.[8]

Ethical approval was obtained from ethical review committee of Institute of Medicine, Tribhuvan University before conducting the study-107(6-11-E)2/070/071. Statistical Package for Social Sciences (SPSS) version 20 was used for data analysis. The student's t- test and ANOVA were used wherever applicable to statistically analyze and compare the various proportions which were derived in different groups. P-value less than 0.05 and confidence interval of 95% was considered statistically significant.

RESULTS

This study consisted of the total of 90 subjects among whom 60 were diabetics and 30 were non-diabetic control group. Among the diabetics 30 subjects (33%) were without retinopathy and 30 subjects were diabetics with retinopathy among whom 10 patients (11%) had mild NPDR, 10 (11%) had moderate NPDR and 10 (11%) had severe NPDR. 26% of participants were below 40 years, 23% were between 40-50 years and 51% were above 50 years. 61% (n=55) of subjects were male and 39% (n=35) were female. Duration of diabetes among diabetic patients was for 0-9 years for 39%, 10-14 years for 11%, 15-19 years for 11% and 20 years above for 6%. Among total diabetic patients, 55 were under anti- diabetes treatment and 5 were not taking medication. Among 55 patients, 47% (n=26) of patients were receiving only one oral drug, metformin; 29% (n=16) were receiving two or more oral drugs i.e., combined oral drug, metformin combined with other oral drug; 11 % (n=6) were receiving Insulin injections and 13% (n=7) were receiving oral drugs and insulin injections.

Table 1. Mean P100 latency in diabetic patients and controls.

Parameters P100 Latency (msec)	Case (n=60) Mean±SD	Control (n=30) Mean±SD	t value	p value	CI
Right eye 1 degree	111.06 ±10.50	109.53 ±5.30	0.751	.454	(-2.52) -5.58
Left eye 1 degree	112.00 ±10.16	111.40 ±5.61	0.301	.764	(-3.36) -4.56
Right eye 15 min	116.83 ±9.30	111.53 ±5.29	2.890	.005	1.65 -8.94
Left eye 15 min	117.06 ±8.88	113.13 ±6.43	2.155	.034	0.30 -7.55

Similarly, means of N75 latency in diabetics and control groups were also compared. The mean N75 latency was higher in diabetic cases than in controls and statistically significant difference between diabetics and controls was also found. (Right eye 1 degree, P =0.008; Left eye 1 degree, P=0.022, Right eye 15 min, P =0.001 and Left eye 15 min, P = 0.004).

Table 2. Mean P100 latency in diabetic patients without DR and those with different grades of DR.

Parameters P100 Latency (msec)	Diabetic without retinopathy (n=30) Mean±SD	Diabetic with Mild NPDR (n=10) Mean±SD	Diabetic with Moderate NPDR (n=10) Mean±SD	Diabetic with Severe NPDR (n=10) Mean±SD	F value	p value
Right eye 1 degree	109.86±9.46	109.90±12.47	113.70±12.12	113.20±10.65	.564	.454
Left eye 1 degree	112.03±9.44	112.10±11.83	111.10±10.17	112.70±12.02	.090	.764
Right eye 15 min	114.50±7.26	119.60±9.46	118.80±14.32	119.10±8.10	8.354	.005
Left eye 15 min	116.86±7.45	119.40±9.60	114.70±12.00	117.70±9.47	4.646	.034

Table 3. Mean P 100 amplitude in diabetic patients and controls.

Parameters a100 (µm)	Diabetics (n=60)	Control (n=30)	t value	p value	CI
	Mean±SD	Mean±SD			
Right eye 1 degree	8.67 ±3.68	12.98 ±6.07	-4.18	0.000	(-6.36)-(-2.26)
Left eye 1 degree	8.20 ±3.62	12.17 ±5.90	-3.93	0.000	(-5.96)-(-1.96)
Right eye 15 min	7.73 ±4.55	14.77 ±6.07	-6.15	0.000	(-9.29)-(-4.76)
Left eye 15 min	6.88 ±3.84	13.90 ±6.74	-6.29	0.000	(-9.24)-(-4.80)

Table 4. Mean P 100 amplitude in diabetic patients without DR and those with different grades of DR.

Parameters a 100(µm)	Diabetic without retinopathy (n=30)	Diabetic with Mild NPDR (n=10)	Diabetic with Moderate NPDR (n=10)	Diabetic with Severe NPDR (n=10)	F value	p value
	Mean±SD	Mean±SD	Mean±SD	Mean±SD		
Right eye 1 degree	10.54 ±3.52	6.48 ±2.67	7.39 ±2.14	6.51 ±3.61	17.51	0.000
Left eye 1 degree	9.54 ±3.65	6.06 ±3.12	7.48 ±3.03	7.02 ±3.30	15.50	0.000
Right eye 15 min	9.96 ±4.77	6.12 ±2.75	5.21 ±2.43	5.20 ±3.94	37.93	0.000
Left eye 15 min	8.42 ±4.21	5.01 ±2.41	4.67 ±2.40	6.34 ±3.28	39.57	0.000

The means of N75 latency showed fluctuations in mean values with respect to both the subtended angles in both eyes, hence it cannot be said that latency increases with grades of increasing severity of DR but there is statistically significant difference in diabetic patients without retinopathy and those with different groups of NPDR (Right eye 1 degree, P = 0.008; Left eye 1 degree, P =0.022; Right eye 15 min, P =0.001 and Left eye 15 min, P =0.004).

DISCUSSION

In this study P100 latency which is considered the most important parameter of VEP showed statistically significant delays in diabetics than control group which is consistent to many studies done previously by Gayatri V et al., Bhanu R et al. and Mariani et al., where they showed increase in P100 latency in diabetics than normal controls.[14-16] Furthermore, we have taken parameters in two angles i.e. 1 degree and 15 minutes. 15 minutes was found to be more sensitive to detect subtle changes in VEP which is again consistent with the findings of D J Creel in which he has mentioned that 15 minute angles are more sensitive in detecting minor abnormalities in visual pathway.[8] This study also showed significant difference in P100 latency with different severity of retinopathy with P-values 0.005 for right eye and 0.034 for left eye. Visual evoked potential P100 latency delay may be contributed by two factors: The first related to the innermost retinal dysfunction as suggested by abnormal Pattern Electroretinogram (PERG), and second related to impaired neural conduction at post retinal levels as indicated by the delay Retino Cortical Time (RCT) and Latency window. There is independent contribution of innermost retinal layers and post retinal structures in VEP P100 delay.[17]

In this study, there was highly significant decrease in P100 amplitude in diabetics than in controls (P =0.000). This is consistent with study done by Gayatri V et al.[14] Furthermore, in this study there was highly significant decrease in P100 amplitude in groups of different grades of retinopathy. The study done by Heravian et al., also found significant difference in P100 amplitude among diabetic patients without NPDR, patients with NPDR and control group (P <0.001).[12]

The metabolic alterations in diabetes mellitus leading to neuro-inflammation, apoptosis, glutamate toxicity, deficiency of neuro-protective factors lead to early neuro-degeneration.[17] In fact retinal neurons particularly ganglion cells begin to die within weeks of beginning of diabetes.[18] A study done by Yaltkaya et al., correlates very well with our work which suggested that delay in P100 latency in diabetic patients was due to retro-chiasmal involvement.[19] Some confounding factors might affect the results of VEP such as age of person, influence of refractive error, fixation and cooperation of patient. Such problems were taken into account and tried to minimize such errors by excluding patients above 60 years of age in whom VEP wave latency increase rapidly due to aging process, or correcting visual acuity with suitable glasses.[20]

Our study did not show any statistically significant relation between duration of diabetes and alteration in VEP parameters. The study done by Gayatri V et al., had shown increase in P100 latency with increased duration

of DM.[14] The study done by Heravian J et al., Rajewski et al., and Comi G et al., have not shown any correlation between latency delays with increase in duration of DM.[12,21,22]

There has been study done by Simo et al. on therapeutic implication of prevention and management of neuropathy. The study concluded that from clinical point of view identification of those patients in whom neurodegenerative changes have started will be crucial for implementing treatment of neuro-protective drugs especially neuro-protective eye drops rather than aggressive intra-vitreous injections in early stages of DR.[23,24] The treatment of neuropathy at very early stage of the disease before significant damage might bring new perspective in treatment of diabetic retinopathy.

There are some limitations to this study. As it was conducted in a single centre and hence cannot be generalized. Selection bias may have occurred as cases and control were selected conveniently. Another limitation was glycated haemoglobin level (HbA1c) was not done. The evaluation of time that elapses between the appearance of the first detectable pathologic changes in VEP and the first detectable retinal changes in ophthalmoscopy could not be found by this study.

CONCLUSIONS

Diabetic patients with central neuropathy demonstrate VEP changes which are not seen in normal people. VEP is a useful non-invasive method of investigation in establishing the central nervous system neuropathy in diabetic patients who have not yet developed diabetic retinopathy. Therefore, visual evoked potential investigation of diabetic patients can be a useful tool for the treating physicians in order to prevent the progress of diabetic retinopathy which may not be detected on routine retinal fundoscopy. Diabetic retinopathy is a preventable condition and its progression can be slowed down in diabetic patients if managed properly with correct management of disease in time.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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