INTEGRITY OF VISUAL PATHWAY IN DIABETES MELLITUS – AN ELECTROPHYSIOLOGY BASED ASSESSMENT

Soundariya K[1], Shanmugappriya S[2]

[1]Professor, Department of Physiology, Sri Manakula Vinayagar Medical College and Hospital, Puducherry - 605107

[1]Final MBBS student, Sri Manakula Vinayagar Medical College and Hospital, Puducherry - 605107

Background: Diabetic retinopathy being a major cause of blindness worldwide, early identification of the functional changes in the retina well before the onset of clinically evident retinopathy, helps to prevent adverse complications in future. Visual evoked potentials (VEP) may serve as a simple, non- invasive effective screening tool in assessing the integrity of visual pathway in diabetic patients and thereby may help in early intervention. Hence the present study aimed to study the integrity of visual pathway in diabetic patients using measurement of visual evoked potentials. **Methods:** About 180 individuals in the age group of 45-60 years were recruited from the patients attending the Ophthalmology and Medicine OPD of our institution. Visual evoked potentials were measured in the diabetic patients with and without retinopathy and the results were compared with the nondiabetics. **Results:** Diabetic patients without clinically evident retinopathy had significantly lesser amplitude and prolonged latency of VEP parameters compared to the nondiabetics. A significant positive correlation was found between the duration of the disease and the VEP parameters. **Interpretation and Conclusion:** Functional alteration as evidenced by prolonged P100 latency may precede well before the onset of vascular changes in the retina, as evidenced by retinopathy. VEP measurement may serve as a simple, non-invasive prognostic marker of the disease, thereby may help to improve patient compliance and prevent overt complications in future. Further duration of the diabetes may significantly contribute to retinal dysfunction.

Key Words: Diabetes, P100 latency, P100 amplitude, Retinopathy, Visual Evoked Potentials

Author for correspondence: Dr. K.Soundariya, Department of Physiology, Sri Manakula Vinayagar Medical College and Hospital, Puducherry – 605107. e- mail: soundariyapriya@yahoo.com

Introduction:

Diabetes Mellitus, a chronic metabolic disorder is expected to be the 7th leading cause of death worldwide by 2030, as projected by WHO[1]. Although the long term complications of diabetes develop gradually, they can later be disabling or life threatening. Diabetic retinopathy, one such complication is a major cause for blindness worldwide. It is traditionally believed that diabetic retinopathy is a micro vascular disease. But diabetic retinopathy may also cause changes in the neural retina. Many studies have reported alteration in neural function and loss of ganglion cells in patients with diabetic retinopathy[2]. Literature search reveals the fact that retinal ganglion cell damage may precede well before the onset of earliest detectable signs of diabetic retinopathy[3]. Early identification of the altered integrity of the visual pathway in diabetic patients before the onset of retinopathy may help to avoid adverse complications in the future.

Visual evoked potentials (VEPs) are electrical potential differences recorded from scalp in response to visual stimuli. They represent the evoked response of the cortical and subcortical areas to the visual stimuli. They provide a sensitive method for documenting the abnormalities in the visual pathways[4]. Measurement of visual evoked potential in diabetic patients, may provide insight into the early neural changes in the retina well before the manifestation of clinically evident signs.

While the peripheral and autonomic neuropathy in diabetes mellitus is well documented, central nervous system dysfunction in diabetes has received less attention. Electrophysiological tests like Visual evoked potentials provide a simple, non-invasive, quick and repeatable measurement of the visual function. Though alteration in VEP parameters in diabetic individuals with retinopathy have been documented [5,6,7], very few studies have focused on the measurement of visual evoked potentials in diabetic patients without retinopathy. Measurement of visual evoked potentials in diabetic patients well before the onset of retinopathy may help to improve their prognosis during treatment. Hence the present study aimed

to measure visual evoked potentials in diabetic patients with and without retinopathy.

Material and Methods:

This cross sectional study was conducted at the research laboratory, department of physiology of our institution from May 2016 to August 2016.Using Open epi version 3.03, taking into account power 80%, 95% CI, mean values of measurements of P100 in diabetics and non-diabetics from a previous study[8], the sample size was estimated to be 178 and rounded off to 180. Inclusion criteria were age group of 45 – 60 years, both genders, patients with diabetes mellitus with duration between 1-15 years, non- proliferative diabetic retinopathy, visual acuity corrected with glasses up to 6/9. Hypertensives, smokers, alcoholics, individuals with presence of cataract, glaucoma, vitreous opacities, multiple sclerosis, optic atrophy, visual acuity < 6/9 with correction, diabetic patients with proliferative diabetic retinopathy were excluded from the study.

The study participants were divided into two groups as follows:

Group I – Non diabetics (60)

Group II – Diabetics (120)

IIa – Diabetic patients without retinopathy

IIb – Diabetic patients with retinopathy

After obtaining permission from the institutional ethics committee, diabetic patients satisfying the inclusion and exclusion criteria were selected from the patients attending the Ophthalmology OPD and Medicine OPD. Informed consent was obtained from all the study participants. After obtaining medical history, a thorough physical examination was performed on all the study participants. All demographic details were recorded through a structured questionnaire. Detailed ophthalmologic examination was done on the diabetic patients for visual acuity measurement, recording of ocular tension and fundus examination by an ophthalmologist. Age and sex matched nondiabetics were selected from the attenders accompanying the patients. The selected study subjects were taken to the research laboratory, department of physiology for the measurement of visual evoked potentials.

Recording of Visual evoked potentials: Subjects were informed about nature of procedure. Informed consent was obtained from all the study participants. Pattern reversal VEPs were recorded using EMG EP MK II equipment (Electromyography, Evoked potential machine, MK II model, Recorders and Medicare System Private Ltd. Chandigarh, India). The subject was asked to sit in front of the checkerboard pattern at an eye screen distance of 100cm. The electrodes were placed based on 10-20 International system. One active electrode was attached in the occiput (Oz), one as ground electrode over the vertex (Cz) and one reference electrode placed at the forehead (F_z).The impedance was kept below 5 K ohms. The subjects were instructed to fix their gaze at red square in the centre of checkerboard pattern. The alteration in the pattern, evoked an electrical response which was recorded using electrodes.

VEPs consisted of waveforms of opposite polarity, negative waveform (N) and a positive waveform (P); followed by the approximate latency in milliseconds. The parameters recorded were the latencies of the waves N75, P100 and N145 (in milliseconds) and the peak to peak amplitudes of the waves N75-P100 and P100-N145 (in microvolts).

The level of significance was compared between normal, diabetic patients with and without retinopathy using one way ANOVA. The correlation between duration of the disease and latency, amplitude of VEP parameters were assessed by Pearson's correlation test. p value < 0.05 was considered statistically significant. SPSS version 20 was used for statistical analysis.

Result:

About 180 study participants were recruited for the present study. About 41.7% were males and 58.3% were females. The mean FBS (fasting blood sugar) and PPBS (postprandial blood sugar) of the diabetic patients were 143.40± 47.10 and 212.80 ± 71.19 respectively. The mean duration of the diabetes was around 7.75 ± 4.27 years.

Table 1 represents the baseline characteristics of the study participants with the mean age around 51.74 ± 5.53.

Table 1: Baseline Characteristics of the study participants

Variables			Values
N			180
Age			51.74 ± 5.53
Latency (msec)	R	N75	79.58 ± 6.30
		P100	109.66 ± 5.77
		N145	147.22 ± 9.47
	L	N75	79.63 ± 6.86
		P100	110.38 ± 5.70
		N145	146.99 ± 8.45
Amplitude (µv)	R	N75 – P100	4.97 ± 2.22
		P100 – N145	6.61 ± 2.65
	L	N75 – P100	5.01 ± 2.20
		P100 – N145	6.64 ± 2.51

Values expressed as mean ± S.D, n – number of study participants, R – Right Eye, L –Left Eye, msec – milliseconds, µv – microvolts

Table 2 and 3 represent the comparison of the VEP parameters between the three groups. Diabetic individuals with retinopathy had significantly increased latencies (N75, P100 and N145) and decreased amplitudes (N75-P100, P100-N145) in both the eyes compared to the non-diabetics and diabetic individuals without retinopathy. Diabetic individuals without retinopathy had significantly prolonged latencies (N75, P100) in both the eyes and decreased amplitude (P100-N145) in both the eyes compared to the nondiabetics.

Table 2: Comparison of Latencies of Visual Evoked Potentials between the study groups

Parameters		Latency (milliseconds)		
		N75	**P100**	**N145**
Group I (Non diabetics)	**R**	76.78± 6.65	105.01±3.39	144.06 ± 6.88
	L	77.11± 7.10	106.51±4.41	145.07±5.32
Group IIa (Diabetics without retinopathy)	**R**	79.66±5.65*	110.77±5.48*	147.26±7.51
	L	80.74± 7.18*	110.79±5.20*	145.88±6.29
Group IIb (Diabetics with retinopathy)	**R**	82.29± 5.37$^{\$\#}$	113.21±4.84$^{\$\#}$	150.34±12.1$^{\$\#}$
	L	81.04±5.56$^{\$}$	113.85±4.93$^{\$\#}$	150.02±11.6$^{\$\#}$

Values expressed as mean ± S.D, *$^{\$\#}$ p < 0.05, *- Between group I and IIa, $^{\$}$ - Between group I and IIb, $^{\#}$ - Between group IIa and IIb, R ,L – Right, Left eye

Table 3: Comparison of Amplitude of Visual Evoked Potentials between the groups

		Amplitude (microvolts)	
		N75- P100	**P100-N145**
Group I (Non diabetics)	Right	6.17±1.75	8.15±1.82
	Left	6.18 ± 1.80	8.09± 1.78
Group IIa (Diabetics without retinopathy)	Right	5.65±2.33	7.21±2.94*
	Left	5.29±2.13*	7.01±2.38*
Group IIb (Diabetics with retinopathy)	Right	3.10±1.61$^{\$\#}$	4.47±1.40$^{\$\#}$
	Left	3.54±1.81$^{\$\#}$	4.82±2.14$^{\$\#}$

Values expressed as mean ± S.D, *$^{\$\#}$ p < 0.05, *- Between group I and IIa, $^{\$}$ - Between group I and IIb, $^{\#}$ - Between group IIa and IIb, R ,L – Right, Left eye

Table 4 shows the baseline characteristics of the diabetic patients based on their duration of the disease (A = 1-5 years, B = 6 – 10 Years, C = 11-15 years).

Table 4: Baseline characteristics of the diabetics based on the duration of the disease

Parameters	1-5 years (A)	6-10 years (B)	11-15 years (C)
n	45	40	35
Age	50.86 ±5.76	51.05±6.08	53.51±5.89
Duration	3.37±1.82	7.97±1.49	13.11±1.43
FBS	129.71±39.08	146.82±50.16	157.11±49.47
PPBS	195.60±74.11	220.80±73.19	225.80±61.99

Values expressed as mean ± SD, n- number of study participants, FBS – Fasting blood sugar, PPBS – Postprandial blood sugar

Table 5 and 6 shows the comparison of the VEP parameters in subgroups classified based on the duration of the disease (A = 1-5 years, B = 6 – 10 Years, C = 11- 15 years). Diabetics with duration of disease less than 5 years had significantly lower latencies and higher amplitude of VEP parameters than diabetics with greater duration of disease. -

However there was no significant difference between individuals with duration between 6-10 years and individuals with duration between 11-15 years.

Table 5: Comparison of latencies of Visual Evoked Potentials among diabetics based on the duration of the disease

		Latency (milliseconds)		
		N75	P100	N145
1-5 years (A) n - 45	R	79.55 ± 5.82	109.58 ± 4.89	144.75±7.9
	L	79.02±6.23	109.96±4.75	144.5±5.8
6 -10 years (B) n - 40	R	81.64±4.47	112.81±4.91*	150.04±11.6*
	L	81.08±5.41	113.62±4.54*	148.5±10.33*
11-15 years (C) n - 35	R	82.06±6.36	114.14±5.12$	152.59±9.41$
	L	83.09±7.06	113.87±5.71$	151.67±10.9$

Values expressed as mean ± S.D, *$ p < 0.05, *- Between group A and B, $ - Between group A and C, n= number of study participants, R – Right eye, L – left eye

Table 6: Comparison of amplitude of Visual Evoked Potentials among diabetics based on the duration of the disease

		Amplitude (microvolts)	
		N75- P100	P100-N145
1 – 5 years (A)	Right	5.56 ±2.04	7.27±3.30
	Left	5.56±2.29	7.16 ± 2.67
6 – 10 years (B)	Right	3.72±1.44*	4.95±1.90*
	Left	3.75±1.75*	5.18±2.13*
11 – 15 years (C)	Right	3.59±4.38$	5.02±1.60$
	Left	3.72±1.79$	5.15 ± 2.07$

Values expressed as mean ± S.D, *$ p < 0.05, *- Between group A and B, $ - Between group A and C, n= number of study participants

Table 7 shows the correlation of the duration of the diabetes with the VEP parameters. There was a significant positive correlation between the latency and the duration of diabetes and a significant negative correlation between the amplitude and duration of diabetes.

Table 7: Correlation of the VEP parameters with the duration of diabetes

Parameters (Both eyes)	Latency (N75, P100, N145)	Amplitude (N 75-100, P100-N145)	p Value
Duration of Diabetes	Positive	Negative	<0.05

Discussion:

Visual evoked potentials represent a simple, non - invasive means of assessment of visual function. The P100 wave form is generated in the striate and peristriate occipital cortex due to the activation of the primary visual cortex. N75 reflects the activity of the fovea and the primary visual cortex while N145 reflects the activity of the visual association areas.

In our study diabetic individuals had significantly prolonged N75, P100 and N145 latencies compared to the nondiabetic individuals. These findings are consistent with the findings of other studies[3,5,9]. The prolonged latencies are a sign of delayed optic nerve conduction and this may indicate the existence of subtle neural dysfunction in the diabetic individuals[10]. These results also suggest the existing retinal ganglion cell damage in the diabetic individuals[3,8]. These changes also reflect the decrease in the processing efficiency of the visual cortex[9]. The diabetic individuals also showed a significant reduction in amplitude of the VEP parameters compared to the nondiabetic individuals. The reduction in amplitude could also be explained by the age related changes. Similar results were observed by Gupta and his colleagues[11].These results could be explained by the toxicity of the products formed by non enzymatic glycosylation in diabetes and also the role of oxidative stress in causing the retinal damage[3]. Thus these factors could contribute to the results observed in diabetic individuals with retinopathy.

However in our study prolonged P100 latency and reduced amplitude was also observed in diabetic

individuals even without retinopathy. But N75 and N145 did not show a significant difference compared to the normal. But since P100 is considered to be the most reliable measure owing to its less variability, these results suggest that retinal damage begins well before the onset of vascular changes in the retina as evidenced by fundus examination. Similar results were observed by other studies[3,9,12,13]. However Collier et al did not observe significant differences in the parameters in the diabetic individuals without retinopathy[14], but this could be explained by their low sample size. Thus neural damage may well precede the onset of diabetic retinopathy in diabetic individuals.

Diabetic individuals with the duration between 11-15 years had significantly prolonged latencies and reduced amplitudes compared to the diabetics < 6 years duration. This shows that central neurological deficit may progress with the increase in the duration of the disease. The accumulation of metabolites progressively increases with the increase in the duration of the disease, as shown by the results of the present study. Similar results were observed by other studies[12, 15-17]. Further a significant positive correlation was observed between the VEP latencies and the duration of the disease. Thus visual evoked potentials may serve as a noninvasive tool in assessing the prognosis of the disease. However Heravian J did not observe a significant correlation between the measurements and the duration of diabetes[8]. So more studies with large sample size need to come up, as inconclusive results exist in relation with the duration of diabetes.

Conclusion:

Diabetic individuals may develop neural changes in the retina, well before the obvious vascular changes, as evidenced by the alteration in the VEP parameters even before the development of overt retinopathy. Further duration of diabetes may significantly influence the VEP parameters. Hence Visual evoked potential measurement may serve as an effective screening tool to assess the prognosis of the disease at least in the earlier stages of the disease. This may help to improve patient compliance to treatment and prevent overt complications in future.

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