Original Article

Physiology Section

A Study of Visual Evoked Potentials in Patients of Type-2 Diabetes Mellitus

DEEPIKA CHOPRA, MRIDU GUPTA, K.C. MANCHANDA, RAM SARUP SHARMA, RAJINDER SINGH SIDHU

ABSTRACT

Introduction: Type-2 diabetes mellitus (DM) is one of the most serious challenges to healthcare, primarily because of the increase in the prevalence of sedentary life styles and obesity. Neuropathies are the common complications of type-2 DM. Abnormalities within the peripheral nervous system are well documented, but however, changes in the central nervous system and particularly their correlation with visual function, have received much less attention. Visual Evoked Potentials (VEPs) can be used to evaluate the disturbances in the CNS with a simple, sensitive and non-invasive methodology.

Aims And Objectives: To compare the visual evoked potentials in type-2 DM patients with that of healthy controls and to find out any possible correlation with the duration of the disease.

Material And Methods: The present study was conducted on three groups (30 patients each) of type 2 DM (different durations of disease) and one group of 30 healthy age and sex matched controls. The patients with reduced visual acuity which was not correctable with lenses or with retinopathy were excluded. VEP was recorded by using pattern reversal stimulation with A PC Based 2ch. RMS EMG EP Mark II Machine. The peak latencies N70, P100 and N155 and the peak to peak amplitudes N70-P100 and P100-N155 of the waves were measured.

Results: Our results showed significantly prolonged N70 and P100 latencies in diabetic patients and also a significant correlation between the delay in the P100 latency and the duration of the disease.

Conclusion: Abnormalities in the VEP response occur in diabetic patients before the development of overt retinopathy. So, VEP measurements can be used for the early diagnosis of central neuropathy to offer an early opportunity for proper management.

Key Words: Type-2 Diabetes Mellitus, Central Nervous system, Visual evoked potential, P-100 Latency

INTRODUCTION

Type-2 diabetes mellitus (DM) is one of the most serious challenges to healthcare, primarily because of the increase in the prevalence of sedentary life styles and obesity [1]. Chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction and the failure of various organs, especially the eyes, kidneys, nerves, the heart and the blood vessels [2]. It is well known that patients with diabetes develop peripheral and autonomic neuropathy. Recent reviews have suggested that they may also suffer from central neuropathy or the degeneration of the higher nervous system. The significance of these changes has proved to be difficult to be investigated, as for many years, electroencephalography (EEG) was the only technique available to study the electrophysiological activity of the brain. However, the information which is provided by this method is limited, particularly in the assessment of the deeper brain structures. The advent of advanced electro-neurophysiological techniques to assess cerebral function, such as the measurement of electrical evoked potentials like the visual evoked potentials (VEPs), have increased our understanding of the normal visual function and the possible effects that diabetes may exert [3]. VEPs are electrophysiological signals which are extracted from the EEG activity in the visual cortex in response to visual stimuli and these are recorded from the overlying scalp. The pattern reversal VEP is the preferred stimulus because of less variability in the waveform and the timing than the VEPs elicited by other stimuli. VEP represents a resultant response of cortical as well as subcortical areas to photostimulation and it depends on the functional integrity of the central vision at any level of the visual pathway [4].

The present study was conducted with an aim to observe whether there was any involvement of the CNS in the type-2 DM patients as compared to the healthy controls, by recording VEP. If there was any involvement, it was aimed to check whether it showed any probable relationship with the duration of diabetes or not.

MATERIAL AND METHOD

Three groups (30 patients each) of type-2 DM with different durations of disease and 30 age and sex matched healthy controls were taken. All the cases of DM were taken from the diabetic clinic of Guru Nanak Dev Hospital, Amritsar and the controls were taken from general population. The tests were conducted in the Department of Physiology. The groups were divided as:

Group 1 → 30 controls, age and sex matched healthy individuals.
Group 2 → 30 patients of type-2 DM with a duration of <10 years.
Group 3 → 30 patients of type-2 DM with a duration of 10-15 years.
Group 4 → 30 patients of type-2 DM with a duration of >15 years.

The ethical committee clearance and an informed consent of the subjects were taken. A detailed clinical history of all the subjects was taken and a thorough physical examination was performed. Visual acuity with Snellen's chart and ophthalmoscopy were done to rule out any visual disorder.

Exclusion criteria

Subjects having a history of any disorder which could influence the interpretation of the results, like demyelinating disorders such as multiple sclerosis, retinopathy, cataract, glaucoma and vitreous

opacities, or those having any evidence of optic atrophy and a visual acuity < 6/18 even with corrective lenses, were excluded from the study.

Recording Techniques

VEPs were recorded with a PC based, 2 channel, RMS EMG EP mark II machine and standard silver-silver chloride disc electrodes. A VEP monitor displaying checker board was used to give the pattern reversal stimulus.

A montage consisting of one channel was used for the VEP recording. The subject was asked to sit comfortably in front of the checkerboard pattern at an eye screen distance of 100cm. An amplification which ranged between 20,000 and 1,00,000 was used to record the VEPs. The electrode impedance was kept below 5KΩ. The recordings were performed in a dark and sound attenuated room. Uniocular stimulation was given to both the eyes separately with black and white checks that changed phase (i.e., black to white and white to black) abruptly and repeatedly at a specified number of reversals per second, by using a checkerboard.

The usual glasses (if any) were allowed to be put on during the test. The subject was instructed to avoid the usage of meiotic or mydriatics drugs, 12 hrs before the test. The electrodes were placed with an electrode paste after cleaning the site with spirit swab. The scalp electrodes were placed relative to bony landmarks, in proportion to the size of the head, according to the International 10/20 system, to ensure the reproducible electrodes placement in the serial studies. The anterior/posterior midline measurements were based on the distance between the nasion and the inion over the vertex. The active electrode was placed in the middle of the variation zone of the calcarine fissure at Oz, which is the highest point on the occiput. The reference electrode was placed at Fz or 12cm above the inion. The ground electrode was placed over the vertex or the forehead at Cz [Table/Fig-1].

VEPs consist of a series of waveforms of opposite polarity, a negative waveform (denoted as N) and a positive waveform (denoted as P); which is followed by the approximate latency in milliseconds [Table/Fig-2]. The parameters which were recorded were; the latencies of the waves N70, P100 and N155 (in milliseconds) and the peak to peak amplitudes of the waves N70-P100 and P100-N155 (in microvolts).

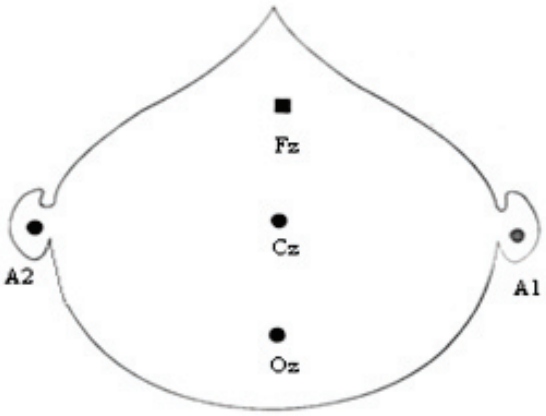
The Student's t-test was used to statistically analyze and compare the various proportions which were derived in the different groups and the p-values were obtained. A p-value which was >0.05 was considered as non-significant, while a p value which was <0.05 was considered as significant and a p value which was <0.001was considered to be highly significant.

RESULTS

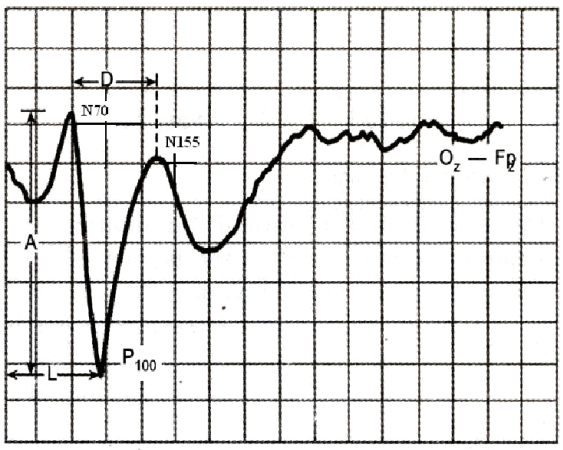
The mean value ± standard deviations of the VEP parameters of the left and right eyes in the control group as well as in the diabetic patients of variable duration (group 2, 3, and 4), are shown in [Table/Fig-3]. We statistically analyzed the mean values of the VEP parameters of the left and right eyes in all the study groups [Table/Fig-4] and did not find any statistically significant difference in the present study. Therefore, for further intergroup analysis [Table/Fig-5], we confined our observations and discussion to the mean values of the left eye parameters only.

The data revealed that:

1. The mean value of the N70 latency increased in all the diabetic groups as compared to that of the healthy subjects [Table/Fig-6].



[Table/Fig-1]: Position of recording electrodes
Oz - active, Fz- reference electrode, Cz- ground electrode
(The subscript z indicates a midline position)



[Table/Fig-2]: Normal tracing of VEP waveform

PARAMETERS		GROUP-1 Mean ± SD		GROUP-2 Mean ± SD		GROUP-3 Mean ± SD		GROUP-4 Mean ± SD	
		Left	Right	Left	Right	Left	Right	Left	Right
Latency (ms)	N70	65.59 ± 3.35	65.72 ± 3.30	68.78 ± 3.07	68.11± 2.54	68.58 ± 3.54	68.14± 3.63	69.57 ± 6.84	69.34 ± 7.25
	P100	95.28 ± 3.16	95.03 ± 3.33	97.54 ± 2.45	97.34± 2.81	98.37 ± 2.77	98.46 ± 2.73	101.70 ± 5.29	101.57 ± 5.61
	N155	134.03 ± 11.17	134.71± 11.33	135.07 ± 7.72	134.56 ± 8.89	134.36 ± 8.01	134.28 ± 7.38	138.07 ± 8.12	137.77± 8.26
Amplitude (µv)	N70-P100	5.42 ± 2.00	5.33 ± 1.73	5.28 ± 1.97	5.34 ± 2.25	4.38 ± 1.38	4.53± 1.53	4.21 ± 1.41	4.00 ± 1.35
	P100-N155	7.62 ± 2.73	7.65± 2.59	7.42 ± 2.23	7.66 ± 2.68	5.90 ± 1.76	6.12± 1.60	5.86 ± 2.02	6.02± 1.76

[Table/Fig-3]: VEP Parameters of both eyes in all the study groups

PARAMETERS		GROUP 1	GROUP 2	GROUP 3	GROUP 4
Latency P-value	N70	.666NS	.091NS	.188NS	.538NS
	P100	.666NS	.552NS	.830NS	.713NS
	N155	.274NS	.813NS	.937NS	.680NS
Amplitude P-value	N70-P100	.680NS	.754NS	.483NS	.133NS
	P100-N155	.887NS	.272NS	.265NS	.406NS

[Table/Fig-4]: comparison of VEP parameters of both the eyes in all study groups

P- Value (>0. 05 NS – Not significant; <0.05 S- significant; <0.001 S*- Highly significant)

PARAMETERS		Gp-2 vs. Gp-1	Gp-3 vs. Gp-1	Gp-4 vs. Gp-1	Gp-3 vs. Gp-2	Gp-4 vs. Gp-2	Gp-4 vs. Gp-3
Latency	N70	<.001s*	.001s	.006	.821	.564	.484
	P100	.003s	<.001s*	<.001s*	.222	<.001s*	.003s
	N155	.665	.874	.114	.740	.156	.085
Amplitude	N70-P100	.794	.023s	.009s	.045s	.018	.630
	P100-N155	.760	.005s	.006s	.005s	.006	.942

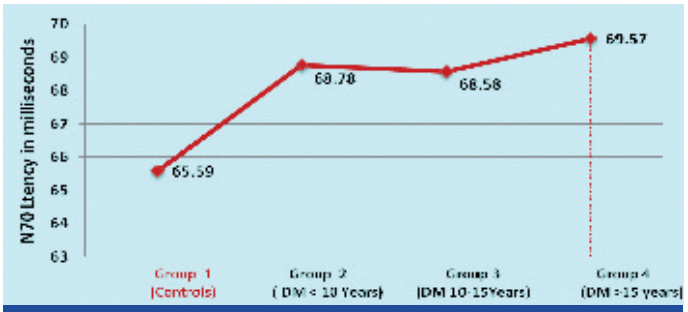
[Table/Fig-5]: P –value (Intergroup comparison of left eye VEP parameters) P- Value (>0. 05 NS – Not significant; <0.05 S- significant; <0.001 S*- Highly significant)

2. The P100 latency was delayed in all diabetic groups as compared to that in the healthy subjects [Table/Fig-7]. The delay in the P100 latency is highly significant in the diabetic groups 3 and 4 [Table/Fig-5].
3. The intergroup comparison of the diabetic patients showed a significant delay [Table/Fig-5] in the P100 latency in the patients of group 4 as compared to that of the patients of groups 2 and 3.
4. There was no significant prolongation of the absolute latency of N155 in the diabetic patients as compared to that of the healthy subjects [Table/Fig-5 and 8]
5. The mean values of the N70-P100 and the N70-P100 amplitudes showed a significant decrease in all the patients with a disease duration >10 years as compared to that of the healthy controls [Table/Fig-5, 9 and 10]

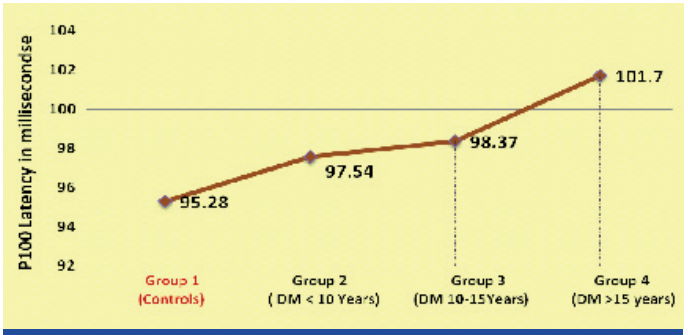
DISCUSSION

The P100 wave form is generated in the striate and peristriate occipital cortex due to the activation of the primary visual cortex and also due to the discharge of the thalamocortical fibers. N70 reflects the activity of the fovea and the primary visual cortex while N155 reflects the activity of the visual association area. The P100 is a prominent peak that shows relatively little variation between the subjects, minimal within-subject interocular difference, and minimal variation with repeated measurements over time [4]. Therefore, this paper focused more on the correlation P100 latency values among the groups which were examined.

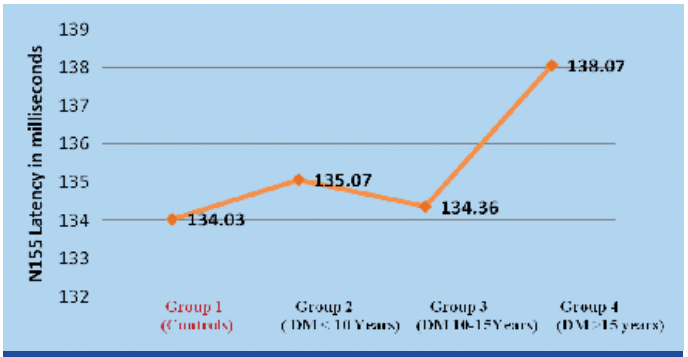
In our study, a delay in the P100 latencies in all the diabetic groups as compared to the controls, was consistent with the observations of Varkonyi T et al [5], Dolu H et al [6], Azal O et al [7], Szabela D et al [8] and Li P et al [9], who reported similar changes in their study. A significant correlation of the delay in the P100 latency with the increased duration of diabetes, corroborated with the findings of Dolu H et al, Azal O et al and Li P et al, but not with the findings of



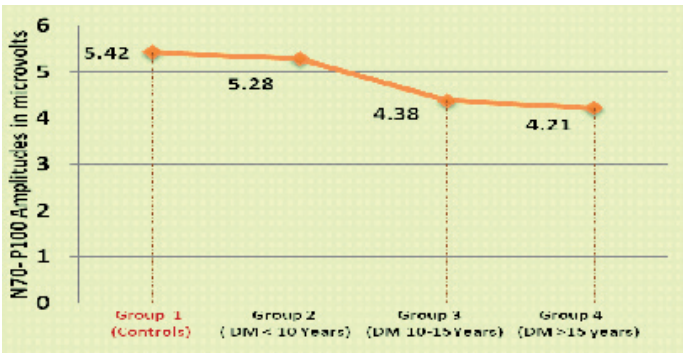
[Table/Fig-6]: Mean value of N70 Latency in various study groups



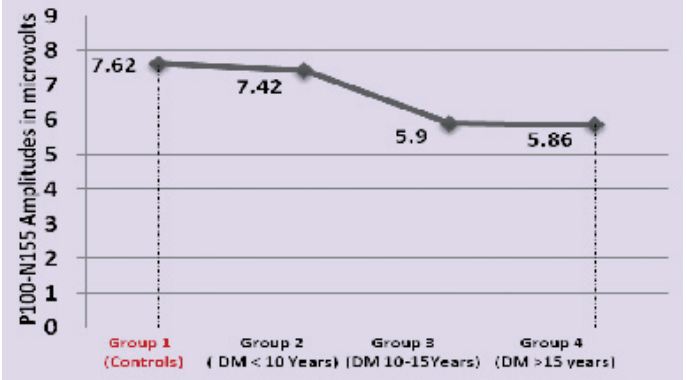
[Table/Fig-7]: Mean value of P100 Latency in various study groups



[Table/Fig-8]: Mean value of N155 Latency in various study groups



[Table/Fig-9]: Mean value of N70-P100 Amplitude in various study groups



[Table/Fig-10]: Mean value of P100-N155 Amplitude in various study groups

Szabela D et al, who observed that the delay in the P100 latency was stable in long standing diabetics.

Our findings signify that there is a definite neurological deficit in type 2 diabetes mellitus, which can involve the central nervous system at a much earlier stage and increases with an increased duration of the disease.

The exact pathophysiology of the central nervous dysfunction is not clear, but it seems to be multifactorial, involving metabolic and vascular factors, which is similar to the pathogenesis of diabetic peripheral neuropathy. Ischaemia, reduced protein synthesis, depleted myoinositol, and high sorbitol levels have been demonstrated in patients with diabetes and these may result in nerve fibre loss in the peripheral nerves. Hence, it is possible that the optic nerve fibers may also suffer from these diabetes induced changes. Neuropoietic cytokines including interleukin-1 (IL-1), IL-6, leukaemia inhibitory factor (LIF), ciliary neuro-trophic factor (CNTF), tumour necrosis factor alpha (TNF-alpha), and transforming growth factor-beta (TGF-beta), exhibit pleiotropic effects on the homeostasis of the glia and on the neurons in the central, peripheral, and the autonomic nervous systems. These cytokines are produced locally by the resident and infiltrating macrophages, lymphocytes, mast cells, SC, fibroblasts, and sensory neurons [10].

The accumulation of these mediators probably delays the conduction in the visual pathway, which can be the probable cause of the delay in the latencies, which is found in diabetics as compared to the healthy controls. With the increase in duration of diabetes, the accumulation of these mediators also increases, which can cause further delay in the latencies in diabetics with more duration of the disease as compared to diabetics with a lesser duration of the disease.

CONCLUSION

Thus, from the present study, it can be concluded that the changes in the VEP response occur in diabetic patients much before the development of overt retinopathy or clinically apparent sensory neuropathy and these changes are positively correlated with the duration of the disease. So, VEP measurement which is a highly sensitive, reliable, noninvasive and reproducible method for detecting the early alterations in the central optic pathways in diabetics, should be recommended whenever possible and these must be added to the list of screening tools for a more complete and early assessment of the neurological involvement of the diabetic patients to advise them for an early and proper management of the disease.

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AUTHOR(S):

1. Dr. Deepika Chopra
2. Dr. Mridu Gupta
3. Dr. K.C. Manchanda
4. Dr. Ram Sarup Sharma
5. Dr. Rajinder Singh Sidhu

NAME OF DEPARTMENT(S)/INSTITUTION(S) TO WHICH THE WORK IS ATTRIBUTED:

Department of Physiology, Government Medical College, Amritsar, Punjab, India.

NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Deepika Chopra
Department of Physiology,
Government Medical College,
Amritsar, Punjab, India.
Phone: +91-9888460834.
E-mail: doc.deepika01@gmail.com

DECLARATION ON COMPETING INTERESTS:

No competing Interests.

Date of Submission: **Mar 10, 2011**
Date of Peer Review: **Mar 19, 2011**
Date of Acceptance: **Mar 25, 2011**
Date of Publishing: **Jun 13, 2011**