THE STUDY OF VISUAL EVOKED POTENTIAL CHANGES IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

To establish the usefulness of evoked potential testing in the diagnosis of central nervous system disorders in patients with diabetes mellitus, a group of forty diabetic patients (23 males and 17 females, 20 with type 1 and 20 with type 2) were studied They were matched in terms of age and sex with another group of 50 apparently healthy controls (31 males and 19 females). Visual evoked potential test for both diabetic patients and controls and nerve conduction study for diabetics were done. Fasting plasma glucose level was estimated prior to recording of visual evoked potential. The mean P100 latencies were significantly prolonged in diabetic patients with a mean ± standard deviation of (109.87±9.63) as compared with controls (104.08 3.31), (P=0.014). The mean P100 amplitude was (4.63 ± 1.45) in diabetic patients while in controls of (4.78 ± 2.55), (P=0.873). A positive correlation was reported between fasting plasma glucose level and prolonged P 100 latencies but not with the type and duration of diabetes, presence of distal symmetrical polyneuropathy, age and sex of diabetic patients. In conclusions visual evoked potential test enables a diagnosis and objective evaluation of central nervous system disorders in diabetic patients and its abnormality correlates with the level of plasma glucose but not with the type, duration of diabetes, presence of distal symmetrical polyneuropathy, age and sex of patients.

INTRODUCTION

Diabetes mellitus is designated into two broad categories type 1 and type 2.[1] The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy and/or neuropathy. Diabetic neuropathy occurs in approximately 50 percent of individuals with long-standing type 1 and type 2 diabetes mellitus. It may manifest as polyneuropathy, mononeuropathy and/or autonomic neuropathy. As with other complications of diabetes, the development of neuropathy correlates with the duration of diabetes and glycemic control. The most common form of diabetic neuropathy is distal symmetric (sensorimotor) polyneuropathy.[1] Multiple theories have been advanced to describe the aetiological pathway that leads to diabetic neuropathy, but The best-supported mechanisms include metabolic theory and vascular (ischemic-hypoxic) theory. [2-4]

Visual evoked potential (VEP)

These are electrical potential differences recorded from the scalp in response to visual stimuli, it represent a mass response of cortical and possibly subcortical visual areas X.[5] The VEP test the function of the visual pathway from the retina to the occipital cortex, most useful in testing optic nerve function and it is very useful in detecting an anterior visual conduction disturbance. It is also helpful in determining subclinical lesions in the optic nerve, therefore, it is a convenient tool in the diagnosis and follow-up of neurologic disorders.[6] VEP can be recorded to a variety of stimulus types. Those commonly used are pattern reversal, pattern onset-offset and flash stimuli. It may be elicited by stimuli including moving colored, spatially localized, or rapidly changing stimuli.[7,8] The stimulus field size should be expressed in degrees of visual angle, with an indication of field shape.... The location of the fixation point should also be defined in relation to this field; and positioned at the corner of 4 checks when located at the center of the field.[9] The usual waveform is the initial negative peak (Nl or N75), followed by a large positive peak (P 1 or P 100), followed by

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another negative peak (N2 or N145) with peak latency and amplitude (figure 1). VEP peak latency refers to the time from stimulus onset to the maximum positive or negative deflection or excursion. The component of major clinical importance is P 100 response having a latency of approximately 100 ms. Prolongation of P 100 latency is the most common abnormality and usually represents an optic nerve dysfunction. Amplitude may also be measured. Even though published norms are available in the medical literature, each individual laboratory should have its own norms to control for lab-to-lab variability in technique The peak latency of pattern-reversal VEP is a sensitive measure of conduction delay in the optic nerve caused by ischemic disturbances or a demyelination[10], where's atrophy of the optic nerve was correlated with decreased VEP amplitude.[11]

Factors influencing VEP

The usual VEP is evoked by a checkerboard stimulation and because cells of the visual cortex are maximally sensitive to movement at the edges, a pattern-shift method is used with a frequency of 1-2 Hz. The size of the checks affects the amplitude of the waveform and the latency of the P 100. Prolonged VEP latencies are observed with multiple sclerosis, retrobulbar neuritis, papillitis and ocular causes like glaucoma or conditions affecting conducting media of the eye like cataract, vitreous opacities and retinal diseases [12]. In conditions of refractory errors, the amplitude may be smaller and at a very small check size, the latency may increase. For this reason refraction is an important.[6]

Electrophysiological role in diabetic distal symmetrical polyneuropathy

Electrodiagnostic assessments are sensitive specific and reproducible measures of the presence and severity of peripheral nerve involvement in patients with diabetes mellitus.[13-15] The electromyographic evaluation recording of the electrical activities of the muscles and the peripheral (nerves), includes nerve conduction studies (motor and sensory) and the needle examination of muscle. [16-18]

PATIENTS AND METHODS

This is a case control study. A group of forty diabetic patients (23 males and 17 females, 20 with type 1 and 20 with type 2), age ranged 17-46 years, with a mean age of 35.57 years, admitted to Al-Sadr Teaching Hospital in Basrah and fifty age and sex matched apparently healthy volunteers (controls) who gave no history of diabetes mellitus selected from medical staff working in the same hospital and some from individuals accompanying patients attending the same hospital, (31 males and 19 females), age ranged 16-48 years, with a mean age of 34.62 years were evaluated. Ophthalmologic examination for patients was done by an ophthalmologist, which included visual acuity, recording of ocular tension and fundus examination after full mydriasis, while in controls; visual acuity alone was recorded. Patients and controls with reduced visual acuity non correctable by glasses, patients with retinopathy, cataract, glaucoma and vitreous opacities were excluded from the study. Alcoholics, smoker patients hypertensive and patients with past history of cerebrovascular accidents were also excluded. Fasting plasma glucose of all controls was below 5.6mmol/L. Blood urea and serum creatinine was tested to rule out chronic renal failure.

Patients were stratified according to

Their fasting plasma glucose level [19]:

<5.6 mmol/L, 5.6-6.9 mmol/L, >7 mmol/L
Distal symmetrical polyneuropathy: present or not
Age: < 30 years, 30-39 years, 40-48 years
Duration of diabetes: < 5 years, 5-10 years

Micromed SystemPlus, 8 channel system EMG/ EP machine was used to assess the evidence of distal symmetrical polyneuropathy and evaluation of VEP. All diabetic patients were examined in the electrophysiological

department for evidence of distal symmetrical polyneuropathy by electrophysiological study in the form of motor and sensory nerve conduction of posterior tibial nerve, bilateral common peronial nerves and sural nerve respectively. Visual evoked potential test for both diabetic patients and controls were recorded. Fasting plasma glucose (FPG) level was estimated prior to recording of VEP. VEP was recorded using pattern reversal stimulation. Binocular stimulation was done with checks using a checkerboard. 5 scalp electrodes were sed: one Frontal (FP2), three Occipital (O1, OZ, O2) and one Grounding (G) electrodes. Patients were advised to come without applying oil to their scalp. The distance between the TV screen and each subject was kept at a constant distance of 100 cms; picture (1, A and B). Stimulus rates of 1-2 Hz and an average of 200 sweeps of stimuli was given to each eye per pattern used. The peak P100 latencies in (millisecond) and amplitudes in (rilicrovolt) were recorded. The VEP in diabetic patients was correlated with the age, sex, the presence of distal symmetrical polyneuropathy, the type duration and plasma glucose level. VEP test of diabetic patients were also compared with controls.

All data were analyzed by SPSS version 15.0 for windows (SPSS Inc.,Chicago,IIlinois).

P-value < 0.05 was considered as significant.

RESULTS

The VEP test (the mean P100 latency and amplitude) in comparison between the right and left eyes for 50 control population did not show statistically significant differences (P =0.232) and (P=0.871) for P100 latency and amplitude respectively. The differences were also statistically insignificant in diabetic patients, (P=0.924) and (P=0.820) for P100 latency and amplitude respectively accordingly the P100 latency of (104 millisecond) and the P 100 amplitude of (5 microvolt) was considered as a normal. (Table-1).

Table 1. VEP test (the mean P100 latency and amplitude) of the right and left eyes in diabetic patients and controls.

Examined eye	VEP			
	Controls		Diabetic patients	
	Mean P100 latency +S.D	Mean P100 amplitude +S.D	Mean P100 latency +S.D	Mean P100 amplitude +S.D
Right eye	104.08±3.31	4.78±2.SS	109.87±9.63	4.63±1.45
Left eye	104.38±3.33	4.69±2.96	109.49±10.21	4.80±1.89
P-value	0.232	0.871	0.924	0.820

VEP: visual evoked potential. S.D : standard deviation

Since the VEP test did not show statistically significant differences between right and left eyes in both diabetic patients and controls, therefore the right eye was selected for correlating and comparing the VEP test results in patients and controls. The mean P100 latencies in diabetic patients was significantly prolonged; (table-2) (P =0.014). The mean P 100 amplitudes showed no significant differences, (P=0.873).

Table 2. VEP test (the mean P100 latency and amplitude) of the right eye in diabetic patients and controls .

Examined eye	VEP	Controls 50 (55.6%)	Diabetic patients 40 (44.4%)	P-value
Right eye	Mean P100 latency ±SD	104.08±3.31	109.87±9.63	0.014
	Mean P100 amplitude ±SD	4.78±2.55	4.63±1.45	0.873

The mean P100 latencies did not show statistically significant differences in different age groups; less than 30 years, between 30 and 39 years and between 40 and 48 years, (P =0.902). The mean P 100 amplitudes showed similar results; (P=0.75 1). (Table-3).

Table 3. VEP test (the mean P100 latency and amplitude) of the right eye in (40) diabetic patients in relation to the age.

Examined eye	VEP	Cases No. (%)			
		<30 years 14(35%)	30-39 years 9(22.5%)	40-48 years 17(42.5%)	P-value
Right eye	Mean P100 latency ±SD	110.91±12.04	109.71±5.87	109.33±9.47	0.014
	Mean P100 amplitude ±SD	5.08±1.44	4.57±1.39	4.80±1.53	0.873

The mean P100 latencies did not show statistically significant differences between males and females; (P value = 0.553). The P100 amplitudes showed similar results, (P=0.450). (Table-4)

Table 4. VEP test (the mean P100 latency and amplitude) of the right eye in (40) diabetic patients in relation to the sex.

Examined eye	VEP	Sex No. (%)		
		Males 23(57.5%)	Females 17(42.5%)	P-value
Right eye	Mean P100 latency ±SD	109.08±9.51	110.94±9.97	0.553
	Mean P100 amplitude ±SD	5.00±1.56	4.64±1.32	0.450

The mean P 100 latencies were prolonged as the level of fasting plasma glucose has increased. The mean P 100 latency was (104.40 ±1.5 1) in 5 out of 40 diabetic patients with FPG of less than 5.6 mmol /L. In 15 out of 40 patients with FPG between 5.6 and 6.9 mmol/L the mean P 100 latency was (105.86± 4.61), while the mean P 100 latency was (114.25± 11.55) in 20 out of 40 patients with FPG equal or more than 7 mmol/L; (table-5), (P =0.0 12). The mean P100 amplitudes; did not show statistically significant differences. (P=0.634).

Table 5. VEP test (the mean P100 latency and amplitude) of the right eye in (40) diabetic patients in relation to the level of fasting plasma glucose (FPG) level.

Examined eye	VEP	FPG in mmol/L No. (%)			
		<5.6 5(12.5%)	5.6-6.9 15(37.5%)	≥ 7 20(50%)	P-value
Right eye	Mean P100 latency ±SD	104.40±1.51	105.86±4.61	114.25±11.55	0.012
	Mean P100 amplitude ±SD	5.40±1.14	4.66±1.39	4.85±1.59	0.634

The mean P100 latency in 18 diabetic patients without evidence of distal symmetrical peripheral neuropathy was (108.38+6.40); which was statistically insignificant in comparison to the mean P100 latency of (111.09±11.64) in 22 patients with evidence of distal symmetrical polyneuropathy; the mean P 100 latencies were prolonged in diabetic patients with or without evidence of distal symmetrical polyneuropathy, (P=0.380). The mean P100 amplitudes also showed insignificant results, (P =0.622). (Table-6)

Table 6. VEP test (the mean P100 latency and amplitude) of the right eye in (40) diabetic patients in relation to the present of distal symmetrical polyneuropathy (PN).

Examined eye	VEP	PN No. (%)		
		Present 22 (55%)	Not present 18(45%)	P-value
Right eye	Mean P100 latency ±SD	111.09±11.64	108.38±6.40	0.380
	Mean P100 amplitude ±SD	4.95±1.49	4.44±1.43	0.622

The mean P 100 latencies in diabetic patients with type 1 showed statistically insignificant differences in comparison to type 2; (P=0.854). Similar results were found in the mean P100 amplitudes; (P=0.393). (Table-7).

Table 7. VEP test (the mean P100 latency and amplitude) of the right eye in (40) diabetic patients in relation to the type of diabetes mellitus (DM).

Examined eye	VEP	DM No. (%)		
		Type 1 20(50%)	Type 2 20(50%)	P-value
Right eye	Mean P100 latency ±SD	110.15±9.86	109.60±9.64	0.854
	Mean P100 amplitude ±SD	5.05±1.53	4.65±1.38	0.393

The mean P100 latencies in 25 diabetic patients with duration of less than 5 years did not' show statistically significant differences from those 15 patients with duration between 5 and 10 years, (P= 0.162). The mean P 100 amplitudes showed similar results, (P =0.70 1). (Table-8)

Table 8. VEP test (the mean P100 latency and amplitude) of the right eye in (40) diabetic patients in relation to the duration of diabetes mellitus (DM).

Examined eye	VEP	Duration No. (%)		
		<5 years 25 (62.5%)	5-10 years 15(37.5%)	P-value
Right eye	Mean P100 latency ±SD	108.24±9.10	112.60±10.18	0.162
	Mean P100 amplitude ±SD	4.92±1.57	4.73±1.27	0.701

The mean P 100 latencies showed statistically significant differences in diabetic patients versus controls with the same age the mean P 100 amplitudes did not show significant differences. (Table- 9)

Table 9. VEP test in relation to the age of diabetic patients and controls.

	Age No.					
	< 30 years 30		30-39 years 22		40-48 years 38	
VEP / Cases	Mean P100 latency ±SD	Mean P100 amplitude ±SD	Mean P100 latency ±SD	Mean P100 amplitude ± SD	Mean P100 latency ±SD	Mean P100 amplitude ±SD
Diabetic Patients 40	14		9		17	
	110.91±12.04	5.08 ±.44	109.71±5.87	4.57±1.39	109.33±9.47	4.80±1.53
Controls 50	16		13		21	
	104.0±3.45	4.81±2.50	103.23±2.68	5.15±3:02	104.56±3.58	4.52±2.37
P-value	0.034	0.741	0.003	0.633	0.039	0.646

The mean P100 latencies showed statistically significant differences in diabetic patients versus controls with the same sex the mean P100 amplitudes did not show significant differences. (Table- 10)

***Table 10. VEP test in relation to the sex of diabetic patients and control*.**

	Sex No.			
	Males 54		Female	
VEP / Cases	Mean P100 latency ±SD	Mean P100 amplitude ±SD	Mean P100 latency ±SD	Mean P100 amplitude ± SD
Diabetic Patients 40	23		17	
	110.08±9.51	5.00 ±1.56	110.94±9.97	4.64±1.32
Controls 50	31		19	
	103.45±3.13	4.64±2.75	105.05±3.40	5.05±2.27
P-value	0.003	0.582	0.021	0.524

The mean P 100 latencies and amplitudes showed statistically insignificant differences in diabetic patients versus controls with the same level of FBS. (Table-11)

Table 11. VEP test in relation to fasting blood glucose level in diabetic and controls.

	FPG No.			
	<5.6 mmol/L 52		5.6-6.9 mmol/L 18	
VEP / Cases	Mean P100 latency ±SD	Mean P100 amplitude ±S.D	Mean P100 latency ±S.D	Mean P100 amplitude ± S.D
Diabetic Patients ٢٥	5		15	
	104.04±1.51	5.40 ±1.14	105.86±4.61	4.64±1.39
Controls 50	47		3	
	102.81±3.47	4.56±2.70	103.57±1.27	5.71±1.11
P-value	0.003	0.562	0.871	0.093

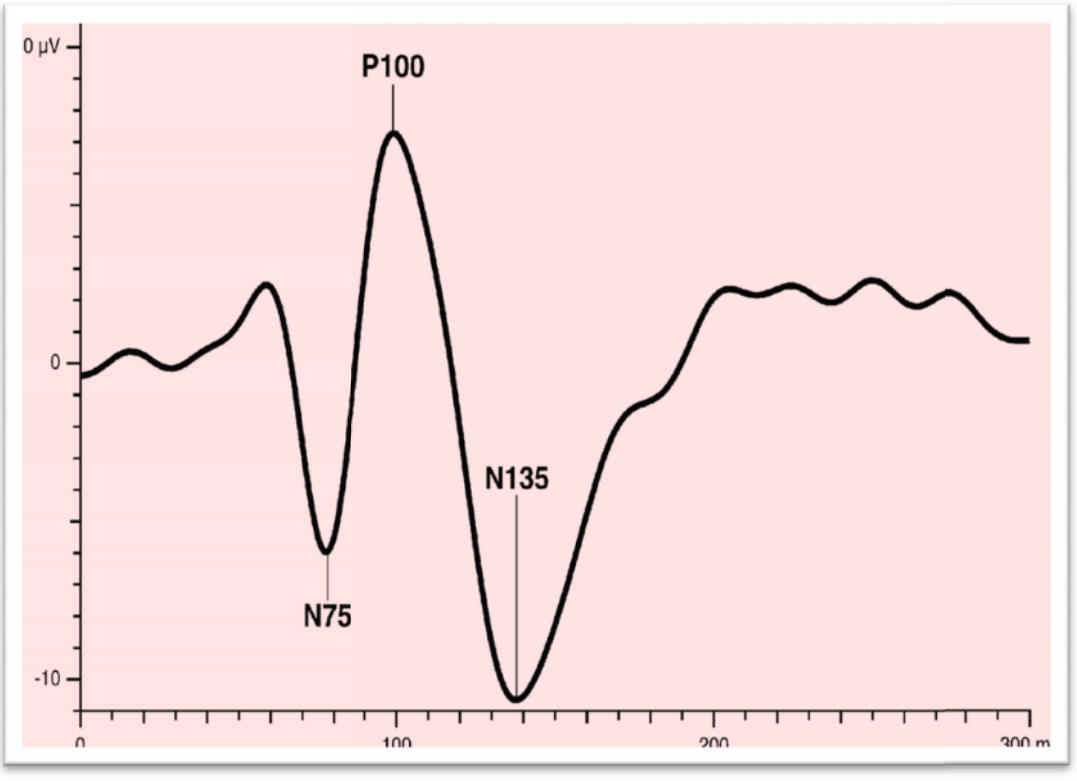

Fig 1. A normal pattern reversal VEP wave.

Picture 1. A and B; VEP test

DISCUSSION

It is evident that diabetes mellitus has an effect on the nervous system. Peripheral neuropathy in diabetes is well studied and correlated with the duration of diabetes and glycemic control. Optic nerve affection in diabetes as a part of the central nervous system involvement can expand the knowledge of electrophysiological effect of diabetes on the nervous system. VEP abnormality had been described in diabetes mellitus, but the proportion of patients with increased P100 latencies is variable. [20-23] Such variability could be explained by several factors, such as variability of plasma glucose levels, the presence of retinopathy and differences in stimulus recording conditions, or differences in study populations and methodologies. In this study, a significantly prolonged P 100 wave latencies were found in diabetic patients as compared with 50 control subjects. Prolonged latencies were found in 25 of 40 diabetic patients (62.5%). Similar results were found by other authors[20,21] who reported prolongation of P100 latencies in most of their diabetic patients that do not have retinopathy. Others reported prolongation of P100 latencies in few of their diabetics with retinopathy. [24,25] The delayed P100 latencies in the studied diabetic patients by treatment with aldose reductase inhibitors. The prolongation of P100 latencies is thus an expression of structural damage at the level of the optic nerve fibers.

In this study, significant correlations were demonstrated between prolonged P100 latencies and increasing level of FPG in diabetic patients; the more increasing in the FPG levels were recorded, the more prolongation in the P100 latencies were found. Similar results observed by Raman et al.[21] However, these significant differences were not demonstrated between diabetic patients and controls" with the same level of FPG. This explains that the VEP test can be affected by the level of plasma glucose. The mean P 100 amplitudes of diabetic patients showed no significant difference from the which were recorded in the absence of cataract, glaucoma, vitriol abnormality and retinopathy are indicative of visual pathway affection in diabetes at the level of the optic nerve fibers, but it was impossible to determine the site of optic nerve dysfunction; although normal fundus examination does not exclude the presence of retinopathy and a more sensitive results can be obtained by fluorescein angiography or optical coherence tomography. The above result was supported by the results of other authors; Parisi et al. [26] who had shown an impaired pattern-electroretinogram not related to the presence of retinopathy, they suggested that the innermost retinal layers are early and selectively affected by diabetes mellitus and the prolongation of P100 latency at the level of the optic nerve in diabetic patients is probably caused by ischemic changes. Kamijo et al.[27] have demonstrated from animal studies that axonal dysfunction was the structural lesion that occurs in optic neuropathy of diabetes which was similar to the lesions of diabetic peripheral neuropathy, and these changes were responsible for the changes in latency of optic nerve responses and were probably related to polyol pathway. These authors also demonstrated that axoglial dysfunction was completely prevented controls, similar results were observed by the same authors.

In this study, no significant correlations were found between P 100 latencies and amplitudes with the duration type sex and age of diabetic patients. Rajew[29] also observed no correlation, except a correlation of the P 100 amplitude with increasing age of diabetic patients. This could be related to age differences in both studies.

The evidence for an association between changes in peripheral and central neurophysiological function is conflicting. In this study, no significant differences were demonstrated between P 100 latencies and amplitude and the presence or absence of distal symmetrical polyneuropathy. Some patients with delayed latency showed evidence of distal

symmetrical polyneuropathy and some did not, although higher incidence of delayed P 100 latency were seen in patients with polyneuropathy. Similar changes were also seen in other studies. [30,31] This may be because of different pathogenetic mechanisms operating behind peripheral nerve involvement and optic pathway affection. Some authors have also pointed to the early appearance of VEP pathologies in young diabetic patients without other signs of nervous system damage which can be explained by insufficient metabolic control and the high incidence of hypoglycaemic episodes, which impair the energy metabolism of the brain.[32,33] In contrast; Puvanendran K et al.[34] and Mariani E et al.[21] reported positive correlations between abnormalities in peripheral nerve conduction and changes in VEP test.

In this study, significant correlations were demonstrated in the P100 latencies but not with the P 100 amplitude between diabetic patients and controls of the same age and sex, this explains that VEP abnormality could be due to diabetes mellitus itself as shown in table 9 and 10.

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