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Original Article

Obstetrics and Gynaecology Section

Role of Visual Evoked Potential as a Screening Tool for Subclinical Optic Neuropathy in Patients with Diabetes Mellitus: A Cross-sectional Study

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ABSTRACT

Introduction: Diabetes poses a major health challenge in India, with rising cases leading to serious complications like optic neuropathy and vision loss. These conditions often remain silent in the early stages, making timely detection crucial. Visual Evoked Potentials (VEPs), a simple non-invasive test, offer promise in identifying early optic nerve changes in diabetic patients and may improve outcomes through earlier intervention.

Aim: To assess P_{100} latency and N_{75}-P_{100} amplitude of VEP as a screening tool for detecting subclinical optic neuropathy in patients with Diabetes Mellitus (DM).

Materials and Methods: This hospital-based cross-sectional study was conducted in the Department of Physiology in collaboration with the Department of Medicine at Shaheed Hasan Khan Mewati Government (SHKM) Government Medical College, Nalhar, Nuh, Haryana, India, from November 2022 to October 2023. A total of 240 subjects aged 18 to 60 years were enrolled, comprising 80 individuals with Type 1 Diabetes Mellitus (DM), 80 with Type 2 DM (case group) and 80 non diabetic individuals (control group). Participants were selected using a systematic random sampling method. The VEP test was performed and VEP parameters were compared between the case and control groups.

Results: The mean age of the Type 1 DM, Type 2 DM and control groups was 26.61±6.71 years, 43.32±11.09 years and 30.7±11.23 years, respectively. Gender distribution showed that males comprised 53.75% of the Type 1 DM group, 60% of the Type 2 DM group and 70% of the control group. Females accounted for 46.25%, 40% and 30%, respectively. Analysis revealed a significant increase in P_{100} latency in both Type 1 diabetics (105.30±4.79 msec; $p<0.001$) and Type 2 diabetics (102.69±6.94 msec; $p<0.001$) compared with healthy controls. The N_{75}-P_{100} amplitude was significantly reduced in Type 1 diabetics (5.73±1.98 µV; $p=0.04$) and Type 2 diabetics (5.87±2.89 µV; $p>0.05$) compared with controls; however, the difference reached statistical significance only in Type 1 diabetics.

Conclusion: This study revealed that P_{100} latency was prolonged and N_{75}-P_{100} amplitude was reduced in both Type 1 and Type 2 diabetic patients compared with healthy controls. These results suggest structural changes in the optic nerve, including demyelination and axonal loss. The study recommends incorporating VEP testing into screening protocols for early detection of neurological complications in diabetic patients.

Keywords: Demyelination, Diabetics, Optic nerves

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterised by chronic hyperglycaemia resulting from inadequate insulin secretion, insulin resistance, or both. Long-standing metabolic derangements are associated with functional and structural changes in multiple organs, particularly the vascular system, leading to the clinical complications of diabetes [1].

Diabetes affects 11.4% of India's population—approximately 101 million people—making it the second-largest diabetic population globally. Additionally, 15.3% (around 136 million individuals) are prediabetic. Diabetes-related complications, such as blindness due to optic neuropathy, significantly contribute to the national disease burden, resulting in increased morbidity, mortality and economic strain on the healthcare system [2]. The prevalence of diabetic retinopathy is 12.5%, of which 4% represents vision-threatening diabetic retinopathy [3]. There is an urgent need for effective interventions at both individual and population levels to slow the diabetes epidemic and reduce associated complications [4]. Early detection is crucial, as these complications are often asymptomatic in their initial stages.

The VEP is a sensitive and non invasive method that evaluates the electrophysiological response of the nervous system to a visual stimulus. Pattern-reversal VEPs (PRVEPs), compared with other VEP types, have relatively low inter- and intra-subject variability and allow contrast variations at constant average luminance, making them preferred for clinical use [5]. Normal cortical responses are recorded only when the entire visual pathway is intact; disturbances anywhere along the visual system can produce abnormal VEPs [6]. Prolonged P_{100} latency and reduced amplitude indicate structural impairment of optic nerve fibres [5]. VEPs can help identify early signs of optic neuropathy in diabetic patients, thereby improving outcomes through prevention of disease progression [4,7]. Over the past two decades, advancements in neurophysiological techniques have enhanced the understanding of normal visual function and the neuropathic complications associated with diabetes.

Several studies using PRVEP have shown altered VEP responses—such as prolonged P_{100} latency and reduced N_{75}-P_{100} amplitude—in diabetic patients, even during subclinical stages [7-9]. VEP can therefore serve as a valuable diagnostic and prognostic tool for detecting visual impairment in diabetic individuals. However, prior research [8,9] has often been limited by small sample sizes. To enhance the robustness of evidence, the present study included both Type 1 and Type 2 diabetic participants with a substantially larger sample size.

Therefore, the aim of the present study was to compare the PRVEP responses in diabetic cases (both Type 1 and Type 2) with those of healthy controls.

MATERIALS AND METHODS

This hospital-based cross-sectional study was conducted in the Department of Physiology, in coordination with the Department of Medicine, at Shaheed Hasan Khan Mewati Government Medical College, Nuh, Haryana, India, from November 2022 to October 2023. The study protocol was approved by the Institutional Ethics Committee (SHKM/IEC/2022/84). Participants were explained about the nature and purpose of the study, and written informed consent was obtained. Patients attending the outpatient department of General Medicine were screened using the following eligibility criteria.

Inclusion and Exclusion criteria: Diagnosed cases of Diabetes Mellitus (Type 1 DM and Type 2 DM) of either sex, within the age group of 18-60 years, who were willing to participate, were included in the study group. Apparently healthy individuals aged 18-60 years were recruited as controls. Subjects with pre-existing neuropathy, cataract, glaucoma, optic atrophy, diabetic retinopathy, alcoholism, or those using drugs such as chloroquine, isoniazid, or disulfiram, as well as those who were morbidly obese, were excluded from the study.

Sample size calculation: A total of 240 subjects were included in the study, as determined using the sample size formula:

$$n= 2(Z_{1-\alpha/2}+Z_{1-\beta})^2\sigma2/ \Delta^2 \quad [10]$$

Where,

n=sample size per group

σ=standard deviation= 2.7μV (from previous study) [11]

Δ=mean difference= 1.2 μV

α=type I error

β=type II error

z=z score, Z1−α/2=1.96, Z1−β=0.842

$$n=2(Z_{1-\alpha/2}+Z_{1-\beta})^2\sigma2/ \Delta^2$$
$$=2 ((2.802)2\ \sigma2/ \Delta^2$$
$$=5.70\ (2.7)^2/ (1.2)^2$$
$$= 15.70\times7.29/1.44$$
$$=114.5/1.44$$
$$=79.5 \text{ per group}$$

Group 1- 80 cases of Type 1 DM

Group 2- 80 cases of Type 2 DM

Group 3- 80 healthy controls

Participants were explained about the nature and purpose of the study and written informed consent was obtained. The study protocol was approved by the Institutional Ethics Committee (SHKM/IEC/2022/84).

Study Procedure

Anthropometric measurements and demographic information (age and gender) were recorded for each participant. Blood glucose levels {fasting blood sugar, Glycated Haemoglobin (HbA1c)} and blood pressure were measured. Although fundus examination and visual acuity assessment were performed during evaluation, their data were not included in the current analysis. The Michigan Neuropathy Screening Instrument was used to exclude participants with pre-existing neuropathy [12].

Procedure of recording PRVEP: Recordings of PRVEP were carried out in a calm and comfortable environment in the departmental electrophysiology laboratory using the Evoked Potentials (EP) Nerve Conduction Velocity (NCV) Electromyography (EMG) machine (Allengers Scorpio Inc., Chandigarh). After cleaning the skin, electrodes were gently applied to the scalp according to the International 10/20 system [13]. The active electrode was placed over the visual cortex at Oz, the reference electrode at Fpz and the ground electrode at Cz. A linked-ear reference was also used as a non cephalic reference. Electrode impedance was kept below 5 kΩ. A two-channel montage, as recommended by the International Federation of Clinical Neurophysiology (IFCN), was used [6]:

Channel 1: Oz-Fpz

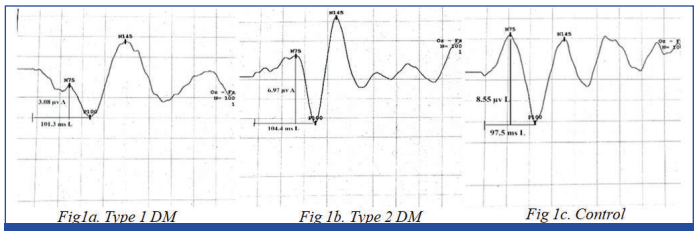
Channel 2: Oz- linked ear

Ground: Cz

IFCN-recommended parameters were used to record the PRVEP [14]:

- Stimulus: Black-and-white checkerboard
- Size of pattern element: 16´
- Frequency: 1 Hz
- Full-field size: 8°
- Mean luminance: 100 cd/m^2
- Contrast: 60%

Participants were seated comfortably in front of the checkerboard pattern at a viewing distance of 100 cm and instructed to fixate on a red dot at the centre of the screen. Each eye was stimulated separately. A total of 100 epochs were obtained and averaged. The P_{100} latency and N_{75}-P_{100} amplitude were measured for each eye [Table/Fig-1].



[Table/Fig-1]: (a-c) Pattern-Reversal Visual Evoked Potential (PRVEP) waveforms are shown.

STATISTICAL ANALYSIS

Data were compiled and analysed using the Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Inc., Chicago, USA). Means and standard deviations were used for summarising continuous variables and categorical variables were expressed as frequencies and percentages. Gender distribution among groups was assessed using the Chi-square test. Independent samples t-test was used to compare primary outcome variables (P_{100} latency and amplitude). A p-value <0.05 was considered statistically significant.

RESULTS

Most subjects with Type 1 DM were within the 18-28-year age range (68.75%; mean age 26.61±6.71 years), whereas the majority of Type 2 DM participants were within the 40-50 years age range (41.25%; mean age 43.32±11.09 years). The control group showed a non uniform age distribution, with a higher proportion (48.75%) in the 18-28-year age range (mean age 30.7±11.23 years) [Table/Fig-2].

Age group	Type 1 DM (n=80)	Type 2 DM (n=80)	Control group (n=80)
18-28 years	55 (68.75)	10 (12.5)	39 (48.75)
29-39 years	21 (26.25)	16 (20)	30 (37.5)
40-50 years	4 (5)	33 (41.25)	3 (3.75)
51-60 years	00 (0)	21 (26.25)	8 (10)

[Table/Fig-2]: Age-wise distribution in Type 1 DM, Type 2 DM and control groups, respectively.
*Data presented as frequency (percentage)

Most participants across all three groups (Type 1 DM, Type 2 DM and controls) were males. The Chi-square test showed no statistically significant difference in gender distribution among the groups (χ^2=4.53, df=2, p=0.104) [Table/Fig-3].

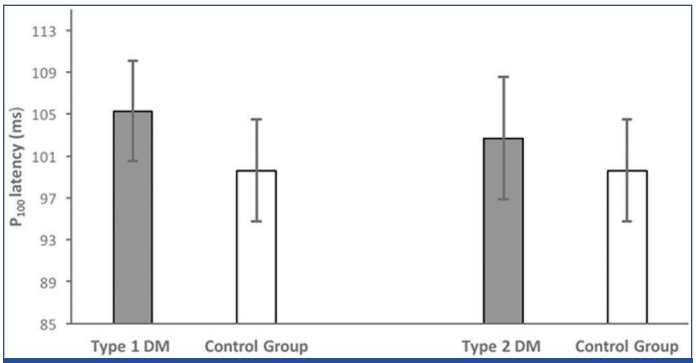
The P_{100} latency was significantly prolonged in both Type 1 diabetics (105.30±4.79 msec) and Type 2 diabetics (102.69±6.94 msec) when compared with healthy controls (p<0.001). Mean P_{100} latency was increased in both diabetic groups [Table/Fig-4,5].

Gender	Type 1 DM (n=80)	Type 2 DM (n=80)	Control group (n=80)
Male	43 (53.75)	48 (60)	56 (70)
Female	37 (46.25)	32 (40)	24 (30)

[Table/Fig-3]: Gender-wise distribution of subjects in Type 1 DM, Type 2 DM and control groups, respectively.
*Data presented as frequency (percentage)

Group	P_{100} latency Mean±SD (msec)	Mean difference vs controls (msec)	95% CI (Lower-Upper)	t (df)	p-value
Type 1 DM (n=80)	105.30±4.79	5.69	5.32-6.07	7.47 (158)	<0.001**
Type 2 DM (n=80)	102.69±6.94	3.08	2.66-4.22	3.61 (158)	<0.001**
Control (n=80)	99.61±3.45	-	-	-	-

[Table/Fig-4]: Comparison of P_{100} latency between diabetic and control groups.
*Data are presented as mean±standard deviation; ǂStatistical comparison was done using an unpaired t-test; 95% confidence intervals are reported for mean differences.



[Table/Fig-5]: Comparison of P_{100} latency between diabetic cases and healthy controls.
*Data are presented as mean (±1 standard deviation error bars).

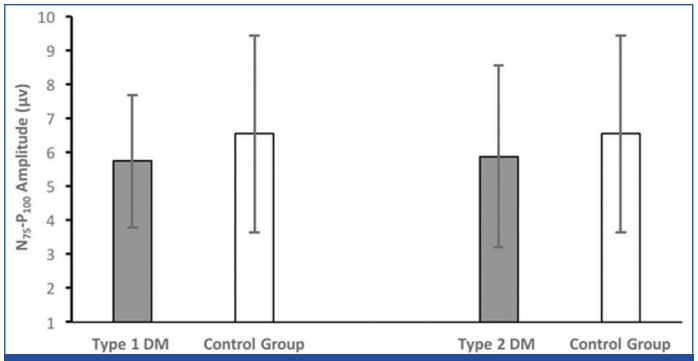
The N_{75}-P_{100} amplitude was reduced in both diabetic groups compared with healthy controls [Table/Fig-6,7]. In Type 1 diabetics, the mean amplitude was 5.73±1.98 µV, significantly lower than the control mean of 6.65±3.31 µV, with a mean difference of -0.92 µV (p=0.04). In Type 2 diabetics, the mean amplitude was 5.87±2.89 µV, also lower than controls, with a mean difference of -0.78 µV; however, this difference did not reach statistical significance (p>0.05). Type 1 and Type 2 DM groups were not compared with each other.

Group	N_{75}-P_{100} amplitude Mean±SD (µV)	Mean difference vs controls (µV)	95% CI (Lower-Upper)	t (df)	p-value
Type 1 DM (n=80)	5.73±1.98	-0.92	-1.77-0.07	-2.14 (158)	0.04*
Type 2 DM (n=80)	5.87±2.89	-0.78	-1.75-0.19	-1.59 (158)	>0.05
Control (n=80)	6.65±3.31	-	-	-	-

[Table/Fig-6]: Comparison of N_{75}-P_{100} amplitude between diabetic cases and healthy controls.
*Data are presented as mean±standard deviation; †Statistical comparison was done using unpaired t-test; 95% confidence intervals are reported for mean differences.

DISCUSSION

The Visual Evoked Potential (VEP) is a non invasive and sensitive screening tool for early neurological involvement in DM [15]. Vascular and metabolic abnormalities contribute to visual dysfunction in diabetic patients [16]. Peripheral and central neuropathy result from microvascular damage triggered by the polyol pathway and diabetes-induced oxidative stress [16,17]. Neuropathy is prevalent across diabetes-related complications, even at subclinical or



[Table/Fig-7]: Comparison of N_{75}-P_{100} amplitude between diabetic cases and healthy controls.
*Data are presented as mean (±1 standard deviation error bars).

clinically apparent stages [16]. Visual pathway abnormalities, as part of central nervous system involvement, provide insight into electrophysiological effects associated with diabetes.

Subtle functional changes occur in the neural retina of diabetic individuals before the appearance of microvascular lesions characteristic of diabetic retinopathy and these early changes cannot be detected by fundoscopy [9]. PRVEP therefore serves as a valuable tool for identifying early electrophysiological alterations in the visual pathway in diabetic patients.

At the subclinical stage, PRVEP parameter analysis provides early evidence of visual dysfunction and helps prevent further progression of the disease through timely glycaemic control. VEP can therefore serve as an effective electrophysiological tool for both the diagnosis and prognosis of central neuropathy, even at subclinical stages [9].

In the present study, P_{100} latency and N_{75}-P_{100} amplitude were measured in 80 Type 1 and 80 Type 2 diabetic patients and compared with 80 healthy controls. P_{100} latency was significantly prolonged in both Type 1 and Type 2 diabetics when compared with the controls. However, the N_{75}-P_{100} amplitude was significantly reduced only in Type 1 diabetics. These findings are consistent with previous studies conducted on Type 1, Type 2, or mixed diabetic populations without retinopathy.

Al-Najjar RS et al., recorded PRVEP P_{100} latency and N_{75}-P_{100} amplitude in 50 cases of Type 2 DM without retinopathy, 50 cases of Type 2 DM with retinopathy and 50 controls. They reported significant prolongation of P_{100} latency and reduction in N_{75}-P_{100} amplitude [8]. Gupta S et al., studied VEP in 64 Type 2 diabetics without retinopathy and compared findings with 52 controls; they found a statistically significant prolongation in P_{100} latency [9]. Balakrishnan P et al., observed significantly prolonged P_{100} latency using PRVEP in 50 diabetics compared with 50 controls [15]. Cheema N et al., evaluated VEP in 20 Type 2 diabetics and 20 controls and found significant P_{100} latency prolongation, but no significant reduction in N_{75}-P_{100} amplitude [16]. Ashok K et al., reported significantly prolonged P_{100} latency and reduced N_{75}-P_{100} amplitude in their comparative study of 75 diabetic patients and 75 controls [18].

Notably, the innermost retinal layer is the first to exhibit dysfunction in the retina, macula and visual pathways in diabetes—even before the appearance of diabetic retinopathy [19]. Although the exact mechanism underlying diabetic neuropathy remains unclear, several studies suggest that activation of the polyol pathway and diabetes-induced oxidative stress play a significant role in damaging the myelinated optic nerve. This damage leads to reduced conduction velocity, resulting in prolonged P_{100} latency. Axonal injury contributes to a decrease in the N_{75}-P_{100} amplitude [17,20,21].

In the present study, the authors observed significant prolongation of P_{100} latency and a reduction in N_{75}-P_{100} amplitude in diabetic patients without clinical manifestations of diabetic retinopathy. These findings suggest underlying structural damage, potentially attributable to demyelination and/or axonal loss within the optic nerve.

Limitation(s)

The present study has certain limitations. As a single-centre, cross-sectional study, the findings cannot be generalised to larger populations and do not allow causal inferences. Key variables like duration of diabetes and glycaemic control (HbA1c) were not analysed in detail, which might have strengthened associations between diabetes severity and VEP changes. Excluding patients with diabetic retinopathy further restricted evaluation across the full spectrum of diabetic ocular complications. Although standardised protocols were followed, VEP measurements remain susceptible to variations in patient cooperation and minor technical inconsistencies. Additionally, the absence of complementary diagnostic modalities such as Optical Coherence Tomography (OCT) or Electroretinography (ERG) limited the ability to establish more comprehensive structural and functional correlations in the visual pathway.

CONCLUSION(S)

The findings of the present study revealed significant changes in PRVEP parameters (P_{100} latency and N_{75}-P_{100} amplitude) in both Type 1 and Type 2 diabetic patients compared with healthy controls. Thus, the authors propose that VEP testing should be incorporated into routine screening protocols for early detection of neurological involvement in diabetic patients whenever feasible. Early identification of subclinical visual pathway dysfunction can contribute to more effective management of diabetic complications, reducing diabetes-related morbidity and the burden on the healthcare system.

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