STUDY ON VEP CHANGES IN PATIENTS WITH TYPE II DIABETES WITHOUT RETINOPATHY

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ABSTRACT

BACKGROUND

In patients with diabetes neurofunctional changes occur much earlier than clinically detectable changes, detection of these changes will help us in early identification of diabetic retinopathy leading to a better management and prognosis.

Aim- The aim and objectives of the study were to observe the pattern reversal VEP in a group of patients with Type 2 Diabetes Mellitus without Retinopathy and to correlate it with duration of Diabetes and HbA1c levels.

MATERIALS AND METHODS

This prospective hospital based cross sectional study was undertaken in 40 patients with type 2 DM referred from the department of diabetology. 40 age and sex matched control subjects were taken from master health check-up attending our hospital. All patients underwent a comprehensive ophthalmic examination, and the pattern VEPs was recorded.

RESULTS

There was a statistically significant difference in p100 latencies. Positive correlation was observed between the duration of diabetes, HbA1c levels and VEP changes.

CONCLUSION

Neurofunctional changes occur in patients with type 2 diabetes earlier than the clinically detectable microvascular changes. So, it is important to screen high risk patients with diabetes both clinically as well as by electrophysiologically.

KEYWORDS

Pattern VEP, Diabetes Mellitus, Electrophysiology, Retinopathy.

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BACKGROUND

Diabetic retinopathy is one of a chronic progressive sight threatening complication of diabetes. It is commonly described as progressive disease of the retinal vasculature with clinical features of increased vascular permeability, vascular occlusion, retinal ischemia. It is diagnosed clinically by the presence of ophthalmoscopically visible lesions in the retinal vasculature and background retina.

Diabetic retinopathy is leading cause of blindness in both developed & developing countries. With increase in the incidence of diabetes in India, diabetic retinopathy has become 6th leading cause of blindness in India. The risk of development and progression of ocular and visual complications of both type 1 and type 2 diabetes are significantly reduced by good metabolic control. It is one of the leading causes of visual impairment and blindness among the working age individuals (30 to 60yrs.) in India and worldwide. The number of people with diabetic retinopathy is estimated to increase from 126 million to 191 million.[1]

The electrophysiological response of the nervous system to different stimuli can be evaluated by a non-invasive method called Evoked potential. The pathways through the optic nerve and brain are examined by visual evoked potential (VEP). In VEP, checker boards are used for visual field stimulation and surface recording electrodes are used for response recording. The stimulus protocols of VEP are of three types-Pattern VEP, Pattern onset/offset VEP and Flash VEP.[2] Since pattern VEP has relatively low variability of waveform and peak latency both with participant and study population, it is the preferred protocol. PVEP has three separate phases in waveform such as, an initial negative feedback, a prominent positive deflection and a later negative deflection. The waves measured are the peak latency and peak-to-peak amplitudes.[3]

Aims and Objectives

The Aim of our study was to observe the pattern reversal VEP in a group of patients with Type 2 Diabetes mellitus without retinopathy with varying duration of diabetes and varying glycemic control of diabetes mellitus.

1. To find whether the PR-VEP latency is altered in diabetes.

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2. To correlate the VEP latencies with duration of diabetes.
3. To correlate the VEP latencies in patients with varying glycemic control of diabetes mellitus.
4. To observe and analyse the patients with prolonged VEP latencies for development of retinopathy changes in the well-controlled and poorly controlled groups.

MATERIALS AND METHODS

This was a hospital based comparative study where latencies of diabetic subjects were compared with age matched normal subjects. This study was done in the outpatient department of Ophthalmology of Stanley medical college, Chennai during the period of April 2015 to December 2016. Informed consent was obtained from all the patients. The study was approved by the hospital ethical committee.

Inclusion Criteria

- Patients with Type 2 diabetes of 30 to 60 years with duration more than one year without any stages of retinopathy changes.
- Age matched Control subjects.

Exclusion Criteria

- Any grading of Diabetic Retinopathy.
- Media opacities.
- Glaucoma.

All of the patients were subjected to a comprehensive ophthalmic examination, including medical history review, refraction, best-corrected visual acuity (BCVA), intraocular pressure (IOP) measured by the Goldmann applanation tonometer, and anterior and fundus examinations. Age, sex, duration of diabetes, and HbA1c levels were recorded.

Diabetic patients were divided into groups depending on the duration of diabetes.

Group 1- Diabetic patients without retinopathy.

Group 1A- Duration of DM 1-3 years.

Group 1B- Duration of DM 4-7 years.

Group 1C-Duration of DM 8-10years.

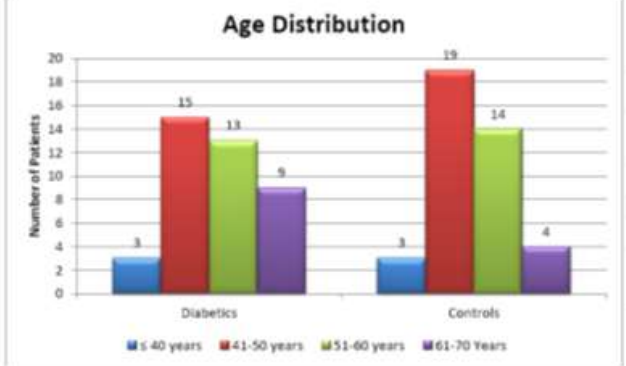
Group 2- Age Matched Control subjects.

Statistical Analysis

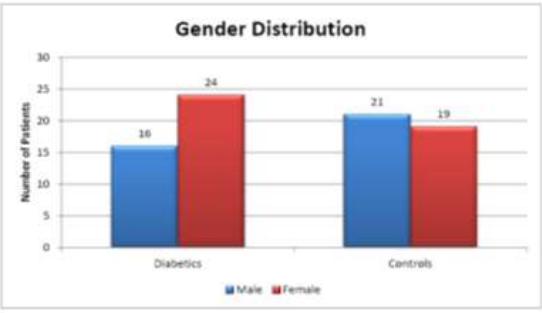
All the data were analysed by descriptive statistics and reported in means of mean values and percentage. Statistical tests for comparison were done. Unpaired t test and ANOVA test were used for analysing continuous variables. Pearson's product–moment correlation coefficients were used to analyse the correlation coefficients. $P<0.05$ was taken as statistically significant. Analysis of data was done using SPSS version 16 and Microsoft Excel 2007.

RESULTS

This study included 40 patients with type 2 diabetes (16 males and 24 females) and 40 control subjects (21 males and 19 females). The mean age distribution between diabetics and controls were 52.60and 50.55 respectively. Data on the age and gender of the subjects are presented below.

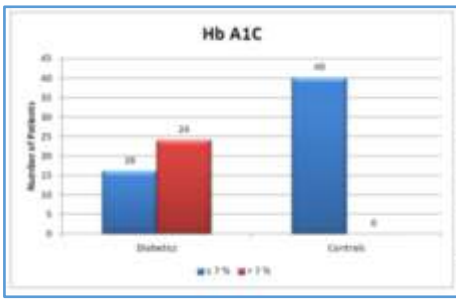


Age Distribution	Diabetics	Controls
N	40	40
Mean	52.60	50.55
SD	8.08	6.94
P value Unpaired t Test		0.2270



Gender Distribution	Diabetics	%	Controls	%
Male	16	40	21	52.5
Female	24	60	19	47.5
Total	40	100	40	100
P value Fishers exact Test			0.2740	

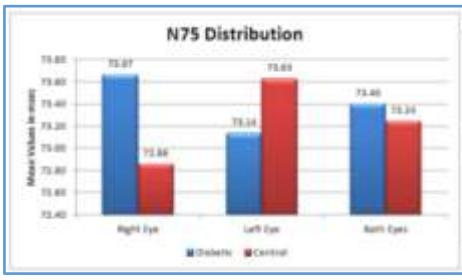
Comparison of HbA1c Levels between Diabetes and Control Group



Hb A1C	Diabetics	Controls
N	40	40
Mean	7.06	5.65
SD	1.24	0.58
P value Unpaired t Test		0.0000

The mean HbA1c levels between the diabetes and control group is 7.06 ± 1.24 and 5.65 ± 0.58 respectively which is statistically significant.

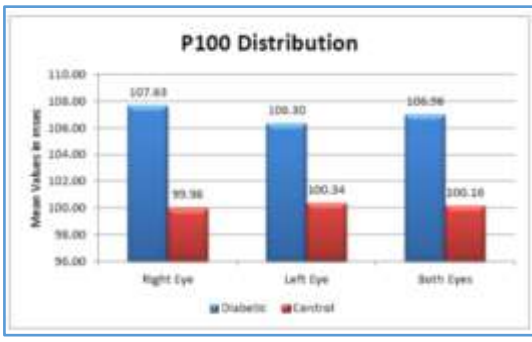
Comparison of N 75 Latency between Diabetes and Control Group



N75 Latency Distribution in ms	Diabetic		Control		P value Unpaired t Test
	Mean (in sec)	SD (in sec)	Mean (in sec)	SD (in sec)	
N75 - Right Eye	73.67	6.49	72.86	5.91	0.5624
N75 - Left Eye	73.14	5.90	73.63	5.82	0.7079
N75 - Mean	73.40	5.60	73.24	5.66	0.9008

The N 75 latencies in diabetic patients is prolonged when compared to control group but statistically insignificant. (p>0.05).

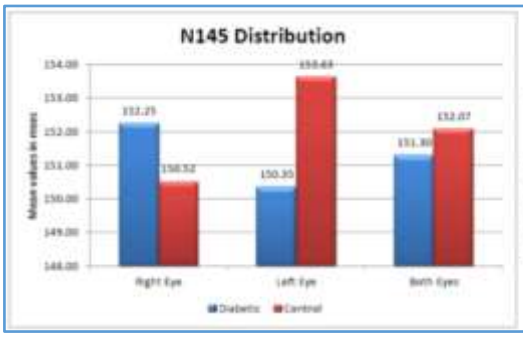
Comparison of P 100 Latencies between Diabetes and Control Group



P100 Latency Distribution in ms	Diabetic		Control		P value Unpaired t Test
	Mean (in sec)	SD (in sec)	Mean (in sec)	SD (in sec)	
P100 - Right Eye	107.63	6.17	99.98	1.90	0.0000
P100 - Left Eye	106.30	6.99	100.34	2.30	0.0000
P100 – Mean	106.96	6.34	100.16	1.57	0.0000

The mean P 100 latencies between the diabetes and control group is 106.96 and 100.16 respectively. Results shows statistically significant correlation between the diabetes and control group. (P value <0.05).

Comparison of n145 latencies between Diabetes and Control Group



N145 Latency Distribution in msec	Diabetic		Control		P value Unpaired t Test
	Mean (in sec)	SD (in sec)	Mean (in sec)	SD (in sec)	
N145 - Right Eye	152.25	12.06	150.52	11.73	0.5173
N145 - Left Eye	150.35	11.43	153.63	11.10	0.1956
N145 – Mean	151.30	10.38	152.07	10.49	0.7395

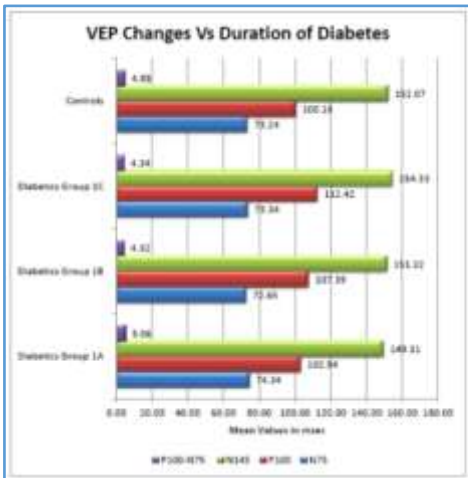
The mean N 145 latencies in the diabetes and control group were151.30 and 152.07 msec respectively group.

Comparison of P100-N75 Amplitudes between Diabetes and Control Group.

P100-N75 Amplitude Distribution in microvolt	Diabetic		Control		P value Unpaired t Test
	Mean (μV)	SD (μV)	Mean (μV)	SD (μV)	
P100-N75 - Right Eye	4.46	1.65	4.84	1.09	0.2293
P100-N75 - Left Eye	4.71	1.40	4.91	1.20	0.4926
P100-N75 – Mean	4.59	1.36	4.88	0.99	0.2790

Though the amplitude is decreased in diabetes when compared to control group, p values are not statistically significant. (p value >0.05).

Correlation of VEP Changes with Duration of Diabetes



VEP Changes Vs Duration of Diabetes	Diabetics Group 1A (n=14) 1-5 YRS	Diabetics Group 1B (n=17) 4-7YRS	Diabetics Group 1C (n=9) 8-10YRS	Controls (n=40)	P value One-way ANOVA
N75 (in sec)	74.34±5.63	72.65±4.63	73.34±7.45	73.24±5.89	0.8738
P100 (in sec)	102.94±6.83	107.38±5.25	113.42±1.67	100.16±1.57	0.0000
N145 (in sec)	148.31±8.88	151.32±11.47	154.31±10.81	152.07±10.49	0.7346
P100-N75 (μV)	5.06±1.44	4.32±1.29	4.34±1.32	4.88±0.99	0.2893

One-way ANOVA test shows significant correlation between P 100 latencies and duration of diabetes. As the duration increases the P100 latency is more prolonged.

Correlation Analysis - VEP Changes Vs Duration of Diabetes	Duration of Diabetes	
	Correlation Coefficient	P value
N75 - Mean	0.972722	0.3267
P100 - Mean	**0.903882**	**0.0000**
N145 - Mean	0.946902	0.5108
P100-N75 - Mean	0.928023	0.3376

There is a positive correlation between VEP changes and duration of diabetes. (p value <0.05)

Correlation Analysis - VEP Changes Vs Hb A1C Levels	**Hb A1C**	
	Correlation Coefficient	**P value**
N75 - Mean	0.869707	0.4112
P100 - Mean	**0.952864**	**0.0000**
N145 - Mean	0.911879	0.1977
P100-N75 - Mean	0.932844	0.0725

Statistically significant correlation was found between HbA1c levels and VEP changes.

DISCUSSION

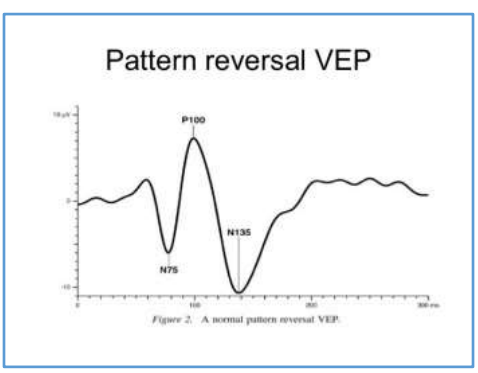
Visual Evoked Potential

Visual evoked potential helps in subclinical detection of lesions in the anterior visual pathway. The visual evoked potential (VEP) is a in vivo non-invasive tool to study the functional integrity of visual pathways from the retina to the visual cortex. VEP are primarily the reflection of activity originating from the central3 to 6-degree field of vision which are relayed in the occipital cortex.[4] Low voltage electrical response (1-20 V) time-locked to a visual stimulus is recorded, and signals are averaged from electro encephalographic activity (60-100V).

Reversal checker board pattern is commonly used which is generated on a Visual display unit. RMS EMG EP MK2 was used for VEP evaluation. An average of 100 sweeps of stimuli were given to each eye.3 components are recorded in the mid occipital region. N75, P100, N145.The Latency of P100 potential is universally accepted as the most useful measure for interpreting the pattern VEP.[5] P100 latency P100 response is a part of VEP wave. It is highly consistent and reproducible wave form generated in the striate and parastriate areas of visual cortex.

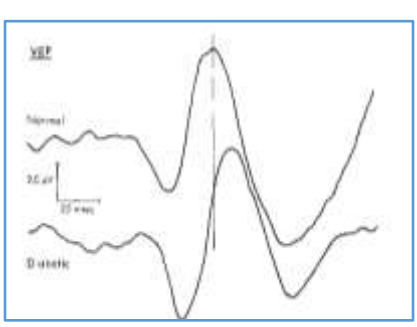
Pattern Reversal VEP can be used as a simple, non-invasive, screening tool for early detection of changes in the Diabetic retinopathy.[6]

Normal VEP Curve



VEP Changes in Diabetes Mellitus

In diabetes there will be significant prolongation of the mean P100 latency and interocular latency difference. There will also be a significant reduction of mean N75-P100 amplitude in the diabetic patients even before the development of diabetic retinopathy



P 100 Latency

Mean P 100 latency in the study group was 106.16 msec and in the control group it was 100.06 msec. The difference between the two is statistically significant. (p value <0.000). Results show that the P100 latencies are prolonged in diabetes when compared to study group which indicates that some amount of damage to retinal ganglion cell occurs even before retinopathy has become clinically evident.[7]

Mechanism of damage to retinal ganglion cell in Diabetes[8]

1. Extracellular glutamate accumulation.
2. Oxidative stress due to increase in free radical and oxidant production or decrease in antioxidant metabolism.
3. Activation of polyol pathway.

In our study latencies and amplitude of VEP were correlated with duration of diabetes which showed statistically significant changes (p value <0.000). This could be explained by poor metabolic control, long exposure of retinal ganglion cell to toxic metabolites.

Glycaemic Control

In our study long term metabolic control was assessed by HbA1c levels. VEP changes were correlated with glycosylated Hb levels which also showed significant correlation with prolongation of latencies in patients with HbA1c levels >7. The mean age between the study and control group is 52.60 ± 8.08 and 50.55 ± 6.94. Gender distribution between study and control groups were comparable by Fishers exact test.

Amplitude

The mean P 100-N 75 amplitude between the study and control was 4.59 ± 1.36 and 4.88±0.99 respectively. Although amplitude of PR-VEP in diabetics is decreased when compared to control group, it does not show any significant correlation. (p value >0.05).

Results of our study correlates with that of many of the studies.[9]

- Karlica et al. showed prolonged P100 latencies in patients with type 1 DM without retinopathy. They concluded it as a direct sign of RGC death
- Haeverian et al. found that VEP helps in identifying the signs of retinal ganglion cell damage even before the onset of retinopathy clinically.
- Wolff et al. showed significant mf VEP implicit time difference between controls and patients with or without retinopathy.
- Algan et al. found prolongation of P 100 in 50 diabetic patients out of which 44 had retinopathy and six patients did not have retinopathy.
- Mariani et al. found prolongation of P 100 latency in 35 diabetic patients without retinopathy
- Timothy et al, in his study suggested retinal ganglion cell die due to inflammation, excitotoxicity and oxidative stress. In diabetes there is a tendency of

ischemia in the neural and other retinal structures which could cause generation of microangiopathy, resulting in VEP latency prolongation.[10]

CONCLUSION

Diabetic retinopathy is a major complication of diabetes. Several physiological and biochemical changes occur in the retina long before structural alterations may become clinically detected. Neuro functional changes occur in patients with type 2 diabetes earlier than clinically detectable microvascular changes occur. So, it is important to screen high risk patients with diabetes both clinically as well as by electrophysiologically. Hence VEP can be used as a safe, non-invasive, objective method for preclinical evaluation and screening of high-risk patients for development of retinopathy in diabetics. In future, it can be used as a screening tool for early detection of probable candidates who might develop retinopathy early and hence needing closer observation and stricter metabolic control.

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