A Comparative Study of Color Pattern Reversal Visual Evoked Potential in Type 2 Diabetics and Normal Individuals

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ABSTRACT

Introduction: *Diabetes Mellitus (DM) is a globally present metabolic syndrome characterized by macro vascular and micro vascular damage. Commonest micro vascular complication is diabetic retinopathy (DR) which can cause visual impairment and sometimes also lead to blindness. It is observed that even before the onset of the micro vascular lesions of DR, the neural retina of the diabetic eye undergoes subtle functional changes, like the color vision. Electro physiologic techniques have served to detect early neuroretinal functional changes that occur in Type 2 Diabetes mellitus (T2DM). The color pattern reversal visual evoked potential (Color PRVEP) is a useful electro physiologic indicator of early color vision changes in DM.*

Materials and Methods: *The cross sectional case control study consisted of 30 subjects, 15 as Cases with newly diagnosed T2DM in the age group 35 to 40 years and 15 age and sex matched subjects without T2DM as Controls. PRVEP and color PRVEP were recorded from all subjects and the HbA1c was determined. An informed written consent to participate in the study was taken from the subjects. There was no financial burden on the subjects. The study protocol was approved by the Institutional Ethical Committee. All the quantitative data such as age, latency, duration of the diseases, HbA1c, P wave latency and amplitude were summarized and statistically analyzed.*

Results: *The basic characteristics with respect to age did not show any significant difference between the diabetics as compared to non diabetics ($p<0.05$). The HbA1c of diabetics was significantly increased as compared to non diabetics ($p<0.05$). The P100 latency after PRVEP and color PRVEP was significantly delayed (increased) in diabetics as compared to non diabetics ($p<0.05$). Pearson Correlation of HbA1c with P100 latencies in diabetics was statistically significant for Black / White PRVEP ($p<0.05$).*

Conclusions: *There is a delayed P100 latency observed in T2DM as compared to non diabetics. This delay could be of various possibilities and importantly due to demyelination which is the mainframe of the abnormal PRVEP. HbA1c does not correlate well with the PRVEP parameters in these newly detected diabetics. This warrants the possibilities of worsening scenario in long standing, chronic diabetes.*

Key words: *Color PRVEP, Color Vision, Diabetic Retinopathy, P100, T2DM*

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INTRODUCTION

Diabetes Mellitus (DM) is one of the most common metabolic syndromes occurring worldwide in which is characterized by a person having high blood sugar. Type 2 Diabetes mellitus (T2DM) is one of the most serious challenges to healthcare primarily because of the increase in prevalence of sedentary life style and obesity. DM affects many major organs like heart, blood vessels (macro vascular and micro vascular systems), nerves, eyes and kidney. Micro vascular damage is a known complication of diabetes. Commonest micro vascular complications occurring in the eye is diabetic retinopathy (DR) which can cause visual impairment and sometimes also lead to blindness.

Ocular manifestations due to micro vascular damage of diabetes include Diabetic Retinopathy (DR), early onset senile immature cataract and frequent eye lid infections. Retinopathy is a condition in which retina in the eye becomes damaged. The two primary abnormalities that occur are a weakening of the blood vessels in the retina and the obstruction in the capillaries. The early and more common type is the non proliferative type and the other is the proliferative type. DR being the commonest among these ocular manifestations can cause serious impairment of vision and sometimes blindness. Studies have reported that the future risk of DR can be avoided by maintaining blood glucose levels in a near normal range. Yet it is being observed that even before the onset of the micro vascular lesions of DR, the neural retina of the diabetic eye undergoes subtle functional changes that are undetectable by fund us examination and photography.[1,2,3] However, electro physiologic techniques have served to detect early neuroretinal functional changes that occur in T2DM. One of the functional changes to precede the

appearance of overt retinopathy and may reflect early neuroretinal dysfunction in T2DM, is a change in color vision[3,4] Color vision is a central or foveal function that may be impaired by any retinal disease that affects the neural retina 6 or the neural pathway to the visual cortex.[3,4,7]

There are three kinds of colour-discriminating receptor cells, called cone cells, in the human retina. The three cone types have broadly overlapping ranges of sensitivity, and are designated L, M and S according to the location of their peak sensitivities in the long, medium and short wave length parts of the spectrum respectively. The L, M and S cones have also been described as red, green, and blue sensitive cones respectively. Studies show deficits or changes specifically in pathways of particular wave length which is responsible for color discrimination. One such study has suggested deficit in short wave length chromatic pathway responsible for blue-yellow color discrimination in adults and adolescents with diabetes mellitus. These deficits were attributed to elevated blood glucose levels at the time of color vision testing.

The color pattern reversal visual evoked potential (Color PRVEP) assesses the integrity of the retina and neural pathways responsible for color vision. It is a useful electro physiologic indicator of early color vision changes in DM.[7,8] There are not many studies which have used color PRVEP as a method of color vision testing which is sensitive than other color vision tests in detecting early deficits. This advantage of color PRVEP emphasizes its use as a tool to detect subtle DR in diabetes mellitus.

This study intends to assess the color vision by Color PRVEP in T2DM who are on treatment as this would provide further information of the retinal function in T2DM. The present study is based on the hypothesis "there is a change in the visual processing for different colors in diabetics when compared to non diabetics".

MATERIALS & METHODS

The aim of the study was to asses color vision by Color PRVEP and PRVEP in T2DM, and compare with normal individuals and to correlate Color PRVEP and PRVEP with the HbA1c values. A cross sectional case control study design was adapted and the duration was 6 months. The study consisted of 30 subjects, 15 as Cases with newly diagnosed T2DM in the age group 35 to 40 years and 15 age and sex matched subjects without T2DM as Controls. Subjects with pre-existing retinal complications / with refractive errors / color blindness and those on drugs which can have an effect / interfere with color vision (drugs like ethambutol, digoxin, chloroquin, clofazimine, amiodarone) were excluded from the study.

METHODOLOGY

The study was conducted at the department of physiology M.S Ramaiah Medical College, Bangalore, INDIA. Study subjects who meet the inclusion criteria were chosen from those attending the endocrinology OPD at M S Ramaiah Medical College and Hospital. Subjects were examined at the Ophthalmology dept, M S Ramaiah Medical College to rule out any pre-existing retinal complications / with refractive errors / color blindness. An informed written consent to participate in the study was taken from the subjects. There was no financial burden on the subjects. The study protocol was approved by the Institutional Ethical Committee.

Rationale for Sample Size: Existing literature[8] reveals that in the right eye the mean VEP amongst the diabetes and non diabetics to be 95.21+/-2.66 and 100.15+/-5.00 respectively. In order to obtain a statistically significant difference in the VEP between the 2 groups at a power of 80% and alpha error of 5% it is estimated that nearly 15 persons in each group need to be studied.

PROCEDURES

PRVEP: Visual stimuli were recorded by reversing the checker boxes (32 X32) generated by a widely used board and displayed on a color monitor. Chromatic visual stimuli were white-black equiluminant reversing checker boxes. PRVEP was recorded form the right and left eyes separately. P wave latency (ms) and amplitude (μV) were measured.

Color PRVEP: Visual stimuli were recorded by reversing the checker boxes (32 X32) generated by a widely used board and displayed on a color monitor. Chromatic visual stimuli were red-black, green-black, blue-black equiluminant reversing checker boxes. Color PRVEP was recorded form the right and left eyes separately for each of the color combinations. P wave latency (ms) and amplitude (μV) were measured. Chromatic visual stimulations for both eyes were done under constant mesopicillumination.

The subjects under examination for PRVEP and Color PRVEP were seated in a semi-dark, acoustically isolated room in front of the display. Prior to the experiment, each subject was adapted to the ambient room light for 10 min. Two traces were obtained for each stimulating pattern to ensure response consistency and reproducibility.

HbA1c: 5ml of venous blood was collected from all subjects in the fasting state and was analyzed for HbA1c by chromatography.

STATISTICAL ANALYSIS

All the quantitative data such as age, latency, duration of the diseases, HbA1c, P wave

latency and amplitude were summarized through descriptive statistics in terms of mean, median and standard deviation. In order to test for differences in latencies or in mean latencies between diabetic and non-diabetic, students T test / appropriate non parametric test (if the data do not follow normal distribution) were employed. Significance level of $p<0.05$ was considered.

OBSERVATIONS AND RESULTS

- This cross sectional case control study of color pattern visual evoked potentials was done with 15 diabetics and 15 controls.
- The basic characteristics with respect to age did not show any significant difference between the diabetics as compared to non diabetics. ($p<0.05$) [TABLE 1].
- The HbA1c of diabetics was significantly increased as compared to non diabetics. ($p<0.05$) [TABLE 1].
- The P100 latency after White / Black PRVEP was significantly delayed (increased) indiabetics as compared to non diabetics ($p<0.05$) [TABLE 2].
- The P100 latency after Red / Black PRVEP was significantly delayed (increased) indiabetics as compared to non diabetics ($p<0.05$) [TABLE 2].
- The P100 latency after Blue / Black PRVEP was significantly delayed (increased) indiabetics as compared to non diabetics ($p<0.05$) [TABLE 2].
- The P100 latency after Green / Black PRVEP was significantly delayed (increased) indiabetics as compared to non diabetics ($p<0.05$) [TABLE 2].
- There was no significant difference in P100 latency between right and left eye within the same group - diabetics / non diabetics after Black / White, Red / Black, Blue / Black, Green / Black PRVEP [TABLE 2].
- Pearson Correlation of HbA1c with P100 latencies in diabetics was statistically significant for Black / White PRVEP ($p<0.05$) [TABLE 3].
- Pearson Correlation of HbA1c with P100 latencies in diabetics was not significant for Red / Black, Blue / Black, Green / Black PRVEP ($p<0.05$) [TABLE 3].

Table 1: Basic characteristics of the study

Basic characteristics (Mean ± SD)	Diabetics (n=15)	Non Diabetics (n=15)	P value
Age (years)	38.50±2.28	37.95±1.67	0.654
HbA1c (%)	7.16±1.99	5.76±0.55	0.004*

Table 2: Comparison of Mean Pattern of P 100 Latency on PRVEP stimulation between the Diabetics and Non Diabetics

PRVEP Stimulation Type	Eye	P 100 Latency Diabetics	P 100 Latency Non Diabetics	P value
White / Black	Right	109.59±1.75[a]	104.69±1.76[b]	0.000*
	Left	109.40±1.29[a]	105.40±1.89[b]	0.000*
Red / Black	Right	108.45±1.73[a]	105.96±2.12[b]	0.010*
	Left	110.10±1.68[a]	106.92±2.19[b]	0.001*
Blue / Black	Right	108.20±1.76[a]	105.98±1.34[b]	0.005*
	Left	109.06±2.18[a]	106.20±1.94[b]	0.006*
Green / Black	Right	109.97±2.06[a]	106.39±2.16[b]	0.001*
	Left	110.40±2.37[a]	106.95±2.56[b]	0.005*

Superscripts - Comparison with in each group - Right vs Left
Non-Identical Superscripts (a vs b) are Significant at 5% level of significance
Identical Superscripts (a vs a / b vs b) are non-significant
***** p value < 0.05

Table 3: Pearson Correlation of HbA1c with the VEP parameters of diabetics and non diabetics

Parameters	Diabetics		Non Diabetics	
Stimulation	**R**	**p value**	**R**	**p value**
White / Black - Right	0.637	0.048*	- 0.122	0.738
White / Black – Left	-0.064	0.861	- 0.276	0.440
Red / Black - Right	0.407	0.243	0.195	0.589
Red / Black – Left	0.495	0.146	- 0.351	0.321
Blue / Black - Right	0.136	0.708	0.064	0.860
Blue / Black – Left	0.221	0.539	- 0.287	0.422
Green / Black - Right	0.273	0.445	- 0.093	0.799
Green / Black – Left	0.464	0.177	0.080	0.827

***** p value < 0.05

DISCUSSION

In this cross sectional case control study of color pattern visual evoked potentials done with 15 diabetics and 15 controls, the basic characteristics with respect to age did not show any significant difference between the diabetics as compared to non diabetics. This implies that the two groups in the study were comparable with respect to the age and the results further obtained were not influenced by age.

The HbA1c of diabetics was significantly increased as compared to non diabetics. This observation is substantially evident since the inclusion criteria were to have newly diagnosed T2DM. The authors by applying such an inclusion criteria wanted to observe the effect of hyperglycemia in a newly detected T2DM on the VEP parameters. Further it washy pothesized that the color vision as assessed by the color PRVEP was probably deranged as a result of the hyperglycemia. The P100 latency after White / Black PRVEP was significantly delayed (increased) in diabetics as compared to non diabetics. The P100 latency after Red / Black PRVEP was significantly delayed (increased) in diabetics as compared to non diabetics. The P100 latency after Blue / Black PRVEP was significantly delayed (increased) in diabetics as compared to non diabetics. The P100 latency after Green / Black PRVEP was significantly delayed (increased) in diabetics as compared to non diabetics. These findings in the diabetic patients of the study support our hypothesis of an altered / changed visual processing for different primary colours.

These changes were observed inspite of no referable complaints to the eye as evidenced by the history and ophthalmological examination at the commencement of the study. These results are very similar to those observed in earlier studies.[9] There was no significant difference in P100 latency between right and left eye within the same group - diabetics / non diabetics after PRVEP and color PRVEP. We observed that the P100 latencies were bilaterally delayed contrary to earlier studies, some of which have reported unilateral delay.[10, 11] Though affection of diabetic neuropathy to the peripheral nerves is a well-known fact, the involvement of the CNS in diabetic neuropathy is gaining momentum.[12] The bilateral delay in P100 latency suggests the diffuse affection of diabetic neuropathy for the optic nerve and the visual pathway.

The delay in P100 latency suggests the incidence of demyelination in the optic nerve inspite of the absence in symptoms of optic neuritis or atrophy in diabetics. This signifies that the demyelination causing central optic neuropathy is similar to that observed in other demyelinating diseases like multiple sclerosis.[10,11]

Pearson Correlation of HbA1c with P100 latencies in diabetics was statistically significant for Black / White PRVEP. Pearson Correlation of HbA1c with P100 latencies indiabetics was not significant for Red / Black, Blue / Black, Green / Black PRVEP. Diabeticcentral neuropathy as observed in T2DM has not shown any clinical evidence of optic neuritis and visual acuity abnormalities; hence T2DM may not be significant cause of optic neuritisun like T1DM or juvenile diabetes. Such diabetic central neuropathy could be present in T2DM with or without symptoms.[13,14,15]

Subclinical sensory neuropathy is seen in early T2DM.[16,17] This early neuropathy changes is due to the segmental demyelination which is a hallmark finding of diabetic neuropathy[17,18] which occurs in a significant number of subjects. The demyelination can lead to changes ranging from slowing of nerve conduction to complete block based on the extent of damage caused. Such demyelinated nerves cannot conduct the impulses at aphysiological frequency resulting in either slowing or complete block.[19] These changes could probably explain the

delay observed in P100 latency of the VEP parameters studied. The other possibilities of delay in P100 latency could also be based on slowing of salutatory conduction, an increased synaptic delay at retinal, geniculate and cortical levels of the visual pathway.[19,20] Reports also suggest that a slow continuous conduction in the demyelinated optic nerve could be the basis for the delay in P100 latencies observed.[21]

This study clearly establishes an abnormal PRVEP and color PRVEP in T2DMas evidenced by the delay in P100 latency as discussed. The lack of correlation between HbA1c and the VEP parameters does not raise the possibility that the mechanisms explained for the abnormal VEP may be different from the factors leading to DR and diabetic neuropathy. In addition to this discussion it is important to mention that hyperglycemia of T2DM has tobe considered as a possible causation of the abnormal VEP observed. This in turn inducts the implication of insulin in electrolyte transport in the brain and widens the scope for further study.[22,23]

CONCLUSION

There is a delayed P100 latency observed in T2DM as compared to non diabetics. This delay could be of various possibilities and importantly due to demyelination which is the main frame of the abnormal PRVEP. HbA1c does not correlate well with the PRVEP parameters in these newly detected diabetics. This warrants the possibilities of worsening scenario in long standing, chronic diabetes.

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