



**Research Article**

JMR 2015; 1(3): 83-86  
May- June  
ISSN: 2395-7565  
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## Pattern Visual Evoked Potential in Non Diabetic offspring's of Type II Diabetes

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### ABSTRACT

Metabolic abnormalities in diabetes mellitus involves ganglionic and preganglionic elements in the entire retina and macular region causing visual disturbances. Subclinical central nervous system (CNS) dysfunctions have been reliably detected by visual evoked potentials in patients with uncomplicated diabetes and normal brain Computed tomography (CT) scan. The offspring of diabetic parents have a higher risk of diabetes and a possibility of diabetic retinopathy. The study aims at evaluating visual evoked potential in asymptomatic, non-diabetic offspring of diabetic parents. A total of 150 individuals in each group (case and controls) were enrolled after Written and informed consent. Institutional ethical Committee approval was obtained. Visual evoked potential (VEP) recordings were done using the standard procedure given in Recommended Standards for VEP, Guidelines 9B. The statistical analysis revealed significant difference in controls and offspring of diabetic parents in terms of P100 latency in both left and right eye ( $P < 0.05$ ). The offspring of diabetic parents may be screened with VEP, as, prolongation of P100 latency a direct sign of retinal damage and demyelination could add the risk to the fact that they may be in a pre-diabetic stage without clinical manifestation, but there may be subclinical optic pathway involvement which mandates active intervention to reduce the co-morbidity associated with diabetes.

**Keywords:** Diabetes mellitus, Visual evoked potentials, P 100 Latency, Offspring, Subclinical, Retinal damage.

### INTRODUCTION

The prevalence of diabetes mellitus (DM) in adult populations is 6.6% worldwide and its estimated that about 438 million people will be affected by DM in the year 2030. According to the Diabetes Atlas 2013 published by the international Diabetes Federation, the number of the people with diabetes in India is currently around 65 million and is expected to rise to 80 million by 2030<sup>[1]</sup>.

The injurious effects of hyperglycemia may be due to macro vascular complications such as coronary artery disease, peripheral artery disease and stroke or may be microvascular complications such as diabetic nephropathy, diabetic peripheral neuropathy and central neuropathy. The impairment of the central nervous system (CNS) is a frequent microvascular complication of diabetes, but the exact pathophysiology seems to be multifactorial, similar to the genesis of diabetic peripheral neuropathy<sup>[2]</sup>. Metabolic abnormalities in DM involves ganglionic and preganglionic elements in the entire retina and macular region. Visual disturbances may attribute to macular edema and delayed neural conduction<sup>[3]</sup>.

Retinopathy threatening Vision is rare in type 1 diabetic patients in the first 3 to 5 years of diabetes or before puberty. During the next two decades nearly all type 1 diabetic patients develop retinopathy<sup>[4]</sup>. Up to 21% of patients with type 2 diabetes have retinopathy at the time of first diagnosis of diabetes and had developed some degree of retinopathy overtime<sup>[5]</sup>.

Subclinical CNS dysfunctions are reliably detected by evoked potentials in patients with uncomplicated diabetes and patients with normal brain CT scan<sup>[6]</sup>. In the event of metabolic inflammation, it seems that these first-order neurons get attacked readily, which negatively impact neuronal regulatory cascades. With diffuse involvement of the retina, including the macula and the periphery, both the ERG and VEP have been documented to be absent. On measuring Visual evoked potential for Diabetic patients, abnormal changes in latencies of the visual evoked potentials, especially delay of P100 was noted<sup>[7,8]</sup>.

Abnormalities of CNS and related pathways can be measured by evoked potential studies in an efficient manner sub clinically and has been used as an important diagnostic method. Of all the evoked potentials visual, auditory and somatosensory are widely used for clinical purposes<sup>[9]</sup>. Diabetic retinopathy occurs both in type 1 and 2 and has been shown that nearly all type 1 and 75% of type 2 will develop retinopathy

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with 15 years duration<sup>[10]</sup>. Hence it is possible to detect asymptomatic diabetic retinopathy sub clinically before its clinical diagnosis by using visual evoked potential. Not many studies have been found to be done in the offspring of diabetic parents using VEP as the modality. Studies done by Brinciotti M, *et al* in 2007 and 2011<sup>[11,12]</sup> measured VEP in the offspring of diabetic mothers also showed prolongation of P100 latency in offspring. Hence, the offspring of diabetic parents may be prone to development of diabetes in future, which can be detected sub clinically by measuring VEP. Our study aims at evaluating visual evoked potential in the offspring of diabetic parents (maternal diabetes, paternal diabetes and both).

#### AIM

To evaluate the Pattern VEP in non diabetic offspring of Diabetic parent(s)

#### METHODOLOGY

150 individuals in each group (case and controls) were considered.

Written and informed consent was obtained from the subject in regional language if they are more than age of 16, or from their parents if they are younger than 16 years. Institutional ethical Committee approval was obtained.

#### Inclusion Criteria

- Offspring of diabetic parent(s) on the WHO criteria with
  - normal blood pressure
  - normal glucose level
  - without refractive error (refractive error is corrected by spectacles)
  - Normal BMI.
- Age: 15 to 24 years.
- Both male and female.

#### Exclusion Criteria

- Offspring of non-diabetic parent(s).
- Offspring of diabetic parents, whose parents also have associated illness such as
  - Hypertension
  - Obesity
  - Hyper/hypothyroidism.
- Offspring of diabetic parents with
  - Altered blood pressure
  - Altered glucose level
  - Obesity
- Age: >24 and < 15 years

Age, BMI and gender matched healthy subjects attending Master Health Check-Up in our Hospital was taken as controls.

By using the MEDICAID POLYRITE instrument, VEP readings were taken by adopting the standard procedure given in Recommended Standards for Visual Evoked Potential, Guidelines 9B: Guidelines on Visual Evoked Potential published by American Neurophysiology society in 2008.

#### Equipment Setup

##### Montage:

- Channel 1-FPz-Reference electrode.

- Vertex-Cz-ground electrode
- C-Oz-active electrode.

#### Stimulation

- Black and white checkerboard was used. Distance between subject and screen was maintained as 100cm.
- Contrast- 80%.
- Size of pattern- 14 X 16 minutes.
- Rate of stimulation- 4-8Hz.
- Mean luminance of the central field-50cd/m<sup>2</sup>
- Background Luminance- 20 -40cd/m<sup>2</sup>.

#### Vep Parameters

The following parameters were considered during the study:

- Latency of N75 msec
- Latency of P100 msec
- Latency of N145 msec
- Amplitude of P100 – N 75  $\mu$ V

#### Statistical analysis

The statistical analysis was done using SPSS software 20.0 versions. The parameters were analysed using Student independent unpaired 't' test.  $P < 0.05^*$  is considered as significant;  $P < 0.01^{**}$  is considered as highly significant.

#### RESULTS

Overall 150 offspring of diabetic parents (figure 2) was compared with 150 ages, BMI and sex matched normal controls (Figure 1). Mean age was 19.34 in cases and 19.48 in controls (P-value = 0.655).

Type 2 Diabetes is a multifactorial disorder in which variants of mitochondrial DNA plays an important role. Mitochondrial DNA is maternally inherited and highly polymorphic. The central role played by the mitochondria in insulin secretion and signal transduction emphasizes that mutations in mt-DNA predisposes greater risk of type 2 diabetes in the offspring of affected women when compared to the unaffected. The study population also highlights the Maternal Diabetic Preponderance (Figure 1)

One-way ANOVA was used to test the differences between the three groups. (Table 1)

- GROUP 1: History of Paternal diabetes only
- GROUP 2: History of maternal diabetes only
- GROUP3: History of either parents diabetic (both maternal and paternal).

Comparative analysis of the P 100 Latency between the study and Control Group, evidently showed statistical difference in P-100 Latency ( $p < 0.05$ ) (Figure -2). Increase in P-100 Latency could predict asymptomatic diabetic retino-optic conduction delay in the offspring of Diabetic Parents, sub clinically before overt clinical diagnosis.

The lifetime risk of developing diabetes is ~40% in the offspring of one parent with type 2 diabetes, and approaching 70% if both parents have diabetes. Hence the offspring of both parents diabetic (group 3) have a higher risk of Domain accordance, when we did comparative analysis (Table 2) within the case population, there was a significant ( $p=0.025$ ) increase in the P100 latency of the left eye of offspring of both the parents (group 3) when compared with the offspring of maternal and paternal diabetes (group 1 and 2).

There was no significant difference in latencies of offspring only with maternal diabetes (group 2) and offspring only with paternal diabetes (group 1). But, there is significant delay in the latency P100 of left eye in the offspring of both the parents (group 3) than group1 and group2 (Figure 3). Further, there was no correlation between the age of onset of diabetes in the parents to the VEP of the offspring.

## DISCUSSION

In type 2 Diabetes, the odds ratio for offspring of a single affected parent is 3.5 compared to those with no parental diabetes history and it increases to 6.1 if both the parents are affected<sup>[13]</sup>. Type 2 Diabetes as mentioned is a multifactorial disorder in which variants of mitochondrial DNA would play an important role. Mitochondrial DNA is maternally inherited and highly polymorphic. The central role played by the mitochondria in insulin secretion and signal transduction is evident by the fact that mutations in mt-DNA predisposes greater risk of Type 2 diabetes developed in the offspring of affected women when compared to affected Men<sup>[14]</sup>.

VEP is a simple, sensitive and objective technique for assessing the impulse conduction along the Visual pathways. Diabetes Mellitus is a common cause for VEP abnormalities, which could be explained by the presence of retinopathy or optic nerve involvement. Delay in the latency of the main positive wave P100 is very sensitive in detecting retinopathy<sup>[15]</sup>. Visual impairment in retinopathy may be due to macular edema and retinal thickening which may even lead to visual loss<sup>[16]</sup>. VEP is also a valuable method to detect diabetic preretinopathy in type 1 DM and hence helps in subclinical detection of retinopathy<sup>[17]</sup>. Optic nerve involvement due to Type II DM occurs prior to the onset of symptoms which also can be detected by VEP by prolongation of 100 latency.

In our study, there is significant delay in the P100 latencies in both eyes of cases when compared with controls. This result is in accordance with the study of Brinicoitti<sup>[11,12]</sup>, who recorded the VEP in the offspring of mothers having gestational diabetes and concluded the presence of delay in P100 latency.

In the overall population, including case and control, the number of offspring of both parent diabetic (group 3-5%) was considerably lesser than the either parent diabetic (group 2 and 3-45%). This result coincides with the genetic study done by Poulton J, *et al*<sup>[18]</sup> in which the overall population including case and control, only 3.6% had both parent diabetic while either parent incidence was about 32.8%. The lifetime risk of developing diabetes is ~40% in offspring<sup>[19]</sup> of one parent with type 2 diabetes, and approaching 70% if both parents have diabetes<sup>[20]</sup>. Hence the offspring of both parents diabetic (group 3) have a higher risk of DM.

In accordance, when we did comparative analysis within the case population, there was a significant ( $p=0.025$ ) increase in the P100 latency of the left eye of offspring of both the parents (group 3) when compared with the offspring of maternal and paternal diabetes (group 1 and 2). This monocular prolongation of latency may be due to asymmetrical involvement of retina<sup>[21]</sup>. The unilateral VEP abnormality, obtained by full field monocular stimulation is likely to be due to prechiasmatal involvement of the visual pathway.

## To summarize

- Optic nerve involvement due to Type II DM occurs prior to the onset of symptoms which also can be detected by VEP by prolongation of 100 latency.

The central role played by the mitochondria in insulin secretion and signal transduction is evident by the fact that, mutations in mt-DNA

predisposes greater risk of type 2 diabetes developed in the offspring of affected women when compared to affected Men.

But the lifetime risk of developing diabetes is ~40% in the offspring of one parent with type 2 diabetes, and approaching 70% if both parents have diabetes. Hence offspring of both parents diabetic (group 3) have a higher risk of DM and so a higher risk of Retino –Optic Conduction Delay.

The monocular prolongation of latency may be due to asymmetrical involvement of the retina. The unilateral VEP abnormality, obtained by full field monocular stimulation is likely to be due to prechiasmatal involvement of the visual pathway.

## CONCLUSION

Type 2 diabetes parents' offspring showed significant delay in the P100 latencies of VEP of both right and left eye when compared with the controls. Comparison within the case group, offspring of both parents diabetic showed prolongation of P100 latency of the left eye than the offspring of either parents having diabetes. Keeping these findings in mind, we may conclude that the offspring with both parents diabetic, have a higher risk of diabetes in the future and higher chance of retinal involvement. There was no significant difference between the latencies of maternal and paternal diabetes. The prolongation of P100 latency is a direct sign of retinal damage and demyelination. Hence, the offspring of diabetic parents may be screened with VEP, as, prolongation of P100 latency could add the risk to the fact that they may be in a pre-diabetic stage without clinical manifestation with their blood sugar levels normal, but there may be subclinical optic pathway involvement which causes the delay in the latency. Critically, even in patients without clinical retinopathy, PVEP can detect preclinical micro vascular and/or neurodegenerative changes within or upstream the retina. Active Intervention module, scheduled on this target population reduces the morbidity and mortality.

## ACKNOWLEDGEMENT

The authors of this study gratefully acknowledge the receipt of Funding by ICMR, support and help provided by all the staff of the Department of Physiology and the Department of Ophthalmology.

## AUTHORS CONTRIBUTIONS

AA\* – Title, Study design, Participated in data collection of the VEP recording, coordination, reference collection, compilation and Drafted the manuscript. JR – Participated in data collection of the VEP recording, helped to draft the manuscript and assisted in collecting references.

## CONFLICTS OF INTEREST

None declared.

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