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Original Research Article

Evaluation of central neuropathy in type 2 diabetes mellitus: a case control study

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ABSTRACT

Background: Diabetes mellitus (DM) is a global pandemic affecting almost every organ in the body. Peripheral nervous system involvement in diabetes is well known but there are not many studies on central nervous system involvement. Visual evoked potential (VEP) is a sensitive, non-invasive test to detect central demyelination of optic nerve. The objective was to compare the visual evoked potentials in type-2 DM patients with that of healthy controls and to find out if any correlation is there with the duration and glycaemic control of the disease and to compare incidence of peripheral and central neuropathy in DM patients.
Methods: Author included 50 DM patients and 50 age and sex matched controls. Patients with previous stroke, demyelination, diabetic retinopathy and other ophthalmological disorders were excluded. VEP was recorded using pattern reversal stimulation with EMG RMS MARK II machine and p100 latency was measured.
Results: P100 latencies (ms) was significantly prolonged in diabetics with mean±SD of (111.24±5.28 ms) as compared to controls (101.30±1.66 ms) with p value <0.003. Also, there was significant correlation between duration of DM and P100 latency prolongation, but no significant correlation was present when compared with glycaemic control.
Conclusions: Central neuropathy is very common in DM. It is related to duration of DM and not HbA1c unlike PNP which is related to both. Central neuropathy occurs even prior to development of retinopathy or PNP. Hence, VEP is a non-invasive and sensitive screening tool for early neurological involvement in DM.

Keywords: Central neuropathy, Diabetes mellitus, Glycaemic control, Peripheral neuropathy, Retinopathy, Visual evoked potentials

INTRODUCTION

Diabetes mellitus (DM) is a global pandemic affecting almost every organ in the body.[1] It is a disease of metabolic dysregulation affecting various organs. Nervous system is one of the important organs to be affected in diabetes mellitus. Excess polyol influx, advanced glycosylation end products, excessive oxidative stress and deficiency of neurotrophic factors cause neuropathy.[2] Any part of the nervous system can be affected but the peripheral nerve involvement is the commonest clinical manifestation. The incidence of peripheral neuropathy in type 2 DM as per a study done

in south India was 19.1%.[3] The prevalence increases as the duration of DM increase, only 10% have peripheral neuropathy at time of diagnosis of DM but nearly 50% have neuropathy after 25 years duration.[4] Thus, duration and glycemic control of diabetic patients also play integral role in the development of peripheral neuropathy.

The peripheral nervous system involvement in DM has been studied extensively in various studies.[5,6] But central nervous system involvement in DM has not been studied in detail. The term "central neuropathy" has been unknown until recently. Only after few western studies described subclinical optic nerve involvement in DM by electrophysiological studies the term central neuropathy was recognized. Only 0.6% of diabetic patients have optic nerve involvement resulting in optic atrophy.[7]

Visual evoked potential (VEP) is a noninvasive, sensitive tool to measures the P100 latency which reflects the functional abnormalities of optic pathway even in early stages.[8] Author decided to evaluate the central neuropathy in DM patients and compare with controls. Although there were few similar studies in past, most of them were reported in western literature. Hence, author aimed to compare the visual evoked potentials in type-2 diabetes mellitus patients with that of healthy controls and to find out if there is any correlation with duration of DM or glycemic control of diabetes patients with P100 latency.

METHODS

This prospective case control study was conducted in department of neurology in a tertiary Care Medical College Hospital in Tamil Nadu, India. 50 diabetic patients newly diagnosed as well as known case of DM who fulfilled the WHO criteria for diagnosing DM (random plasma glucose of >11.1 mmol/l or fasting plasma glucose >7.0 mmol/l or two hour plasma glucose concentration >11.1 mmol/l two hours after 75 g anhydrous glucose in an oral glucose tolerance test (OGTT) were considered as cases and 50 age and sex matched controls were chosen.[9] Patients with long standing history of hypertension and with the past history of cerebrovascular accident, evidence of optic atrophy, past history of optic neuritis, visual acuity less than 6/18, patients consuming >100 ml of alcohol daily, patients with peripheral nervous system disease unrelated to diabetes mellitus, patients with diabetic retinopathy, cataract, glaucoma and vitreous hemorrhage and patients with type 1 diabetes mellitus were excluded from the study.

Informed consent was obtained from patients who were willing to take part in the study. Institutional Ethical committee clearance was obtained. Cases were subjected to detailed history to rule out stroke, history of optic neuritis and other ophthalmological conditions. Detailed clinical examination, peripheral nervous system examination and ophthalmological evaluation including visual acuity, fundus examination was performed in all subjects. Later all patients were subjected to visual evoked potential test.

VEPS were recorded using RMS EMG EP mark 2 machines with 2 channel and routine silver chloride disc electrodes. The PC based RMS machine was used, and pattern reversal method was followed to record P100 latency. The parameters usually recorded are P100, N70 and N155. Of these P100 is most important and it indicates latency of positive wave. They were measured in microvolts.

Statistical analysis

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 17 software package. An independent sample t-test was used to compare the means of two continuous variables. A correlation between two continuous, parametric variables was done using Pearson's correlation. Chi-square tests and Fisher's exact test were used where indicated and p value $p < 0.05$ was considered significant.

RESULTS

The mean age of the study population was 58.44. There were 29 males and 21 females. 7 cases were 40 to 50 years old, 24 between 50 to 60 years and 19 more than 60 years. In this study, P100 latencies (ms) was significantly prolonged in diabetics with mean±SD of (111.24±5.28 ms) as compared to controls (101.30±1.66 ms) with p value <0.003 (Table 1).

Table 1: Pearson correlation coefficient of P100 latency with HBA1c and duration of diabetes.

Variable	Pearson correlation coefficient (r)	P value
Duration of diabetes	0.693	<0.001
HbA1c	0.036	0.81

Among 50 cases 41 cases had prolonged P100 latency when compared to controls only one had P100 prolongation which was statistically very significant. Hence, 81% of diabetic patients in these cases had central neuropathy (Figure 1). Author also noted that mean prolongation of P100 in cases was much more than in controls.

Author further divided the cases into two groups. Those with uncontrolled DM with HbA1c >7 and those with well controlled DM with HbA1c <7. Among the 30 cases in uncontrolled DM group 26 had P100 prolongation and in 20 cases in well controlled group 15 had prolonged P100 latency. 86% of uncontrolled group and 75% of well controlled group had P100 prolongation (Figure 2).

But this was not statistically significant (p value was 0.293). Similarly, author looked into duration of DM and

classified the cases into 3 groups as <5 years, 5 to 10 years and >10 years. Among the 20 cases in <5 years group 12 had abnormal P100 and in 5 to 10-year group 9 out of 10 had abnormal P100. In >10-year group all 20 had prolongation of P100 which was statistically significant (p value <0.03). Hence, author noted 100% of cases with >10-year DM had abnormal VEP whereas only 60 % had prolonged P100 in <5-year group (Figure 3).

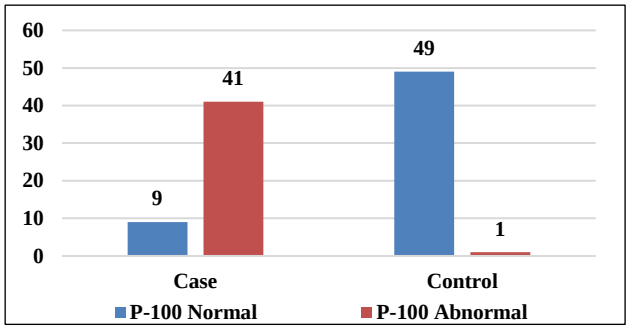

Figure 1: P100 in Case v/s control.

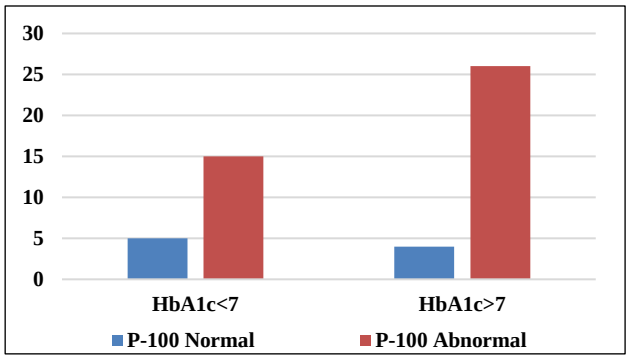

Figure 2: P100 v/s HbA1c.

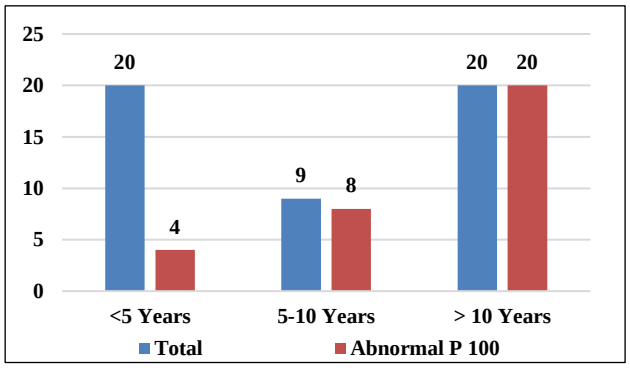

Figure 3: P100 v/s duration of DM.

Author also evaluated peripheral neuropathy (PNP) with central neuropathy and classified the cases into those with PNP and without PNP. Among 24 cases without PNP 18 had prolonged P100 and 23 out of 26 had abnormal P100 in PNP group. 75% and 88% of cases had prolonged P100 in the above groups. There was no statistical significance, but author found central neuropathy occurring in almost equal percentage in patients with or without PNP (Figure 4).

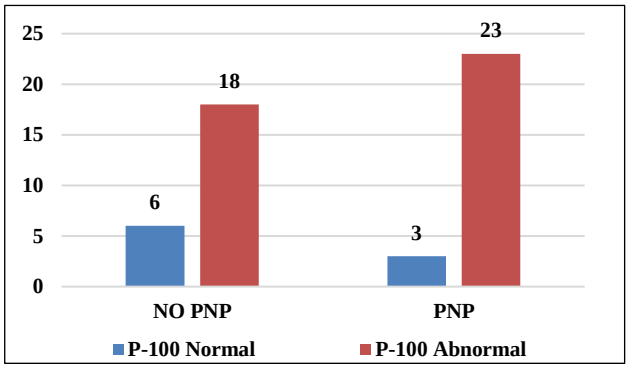

Figure 4: P100 v/s peripheral neuropathy (PNP).

DISCUSSION

In this study, P100 latencies (ms) was significantly prolonged in diabetics as compared to controls. Similar to this study Dolu H et al, Szabela D et al, Li P et al, Algan M et al, and Comi G et al, also concluded prolongation of P100 in diabetic population in their studies.[10-14] It may be due to functional disturbance in visual conduction pathway rather than demyelination or axonal loss. It is also possible that early diabetic preretinopathy due to retinal ganglion cell loss may also contribute to P100 prolongation.[15]

Author observed significant correlation exist between duration of DM and P100 latency prolongation and no significant correlation with glycemic control. Ziegler et al, and Li P et al, have also summarized that P100 prolongation correlated well with glycemic control of DM and even improved with short term glycemic control.[13,17] But Szabela D et al, and Algan et al, concluded there was no correlation between duration of DM and P100 prolongation.[10,14] This may be due to reduced velocity of nerve conduction in optic nerve whereas in shorter disease duration inner retinal layers suffer neuro sensory deficits but photo receptors remain unaffected.[17] Dolu H et al, concluded that central neuropathy in DM correlates well with duration of DM and not glycemic control.[11]

Author believed that since the sample size was small in most studies and they also included both type 1 and type 2 DM it produced varying results.[18] Moreover, in this study 81% of cases had prolonged P100 whereas only 50%-30% of cases had P100 latency abnormality in other studies.[10-14]

Author also found there was no correlation between central and peripheral neuropathy (PNP) and central neuropathy occurs much earlier to PNP. Exact pathophysiology for central neuropathy is not known. Author suggested it may be multifactorial like PNP both metabolic and vascular factors playing a role.

Accumulation of neuropoietic cytokines like TNF-alpha, TGF-beta in visual conduction pathway probably causes delay in P100 latency. As duration of DM increases further accumulation of mediators cause further P100 prolongation.[19]

Main limitation of this study was the sample size. Although the sample size is largest when compared to other similar studies author suggest still larger samples are required to validate the findings in this study. Many of type 2 DM patients who were above 60 years may have age related changes unrelated to DM causing prolonged P100. Future research is warranted among diabetes patients with below 60 years of age.

CONCLUSION

Author concluded central neuropathy occurs even prior to development of retinopathy or PNP. VEP is a non-invasive and sensitive screening tool to detect early neurological involvement in DM. Since, there is a very high incidence of P100 prolongation in DM patients its usefulness in evaluation of multiple sclerosis in a diabetic patient may be limited.

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Ethical approval: The study was approved by the IHEC

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