STUDY OF EFFECT OF TYPE 2 DIABETES MELLITUS ON COGNITIVE FUNCTIONS BY EVENT RELATED POTENTIAL P300

Manjeet Singh1, Naresh Kumar2, Sushma Sood3, Renu Garg4, Uma Garg5 and Jeewandeep Kaur1

1Department of Physiology, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, Haryana, India
2Department of Physiology, SHKM Government Medical College, Nalhar, Mewat, Haryana, India
3Department of Physiology, Pt. BDS, PGIMS, Rohtak, Haryana, India
4Department of Biochemistry, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, Haryana, India
5Department of ENT, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, Haryana, India

*Author for Correspondence

ABSTRACT

The study was conducted to investigate the influence of type 2 diabetes mellitus on cognitive functions by measuring event related potential P300 (ERP P300) in 30 patients of type 2 diabetes mellitus aged 46-75 years with disease duration more than 5 years and compared them with control group. Diabetics had significantly longer P300 latency which was neither correlated with plasma glucose level nor with duration of disease. P300 amplitude was significantly reduced in diabetics. Thus ERP P300 can be very useful in detecting cognitive decline early in course of diabetes.

Key Words: Diabetes Mellitus Type 2, Cognition, ERP P300

INTRODUCTION

Type 2 diabetes is due to defect in insulin production and its action which can result in cognitive dysfunction (Alvarenga et al., 2005). Cognition is the process of obtaining, organizing and using intellectual knowledge. It is a sequence of mental operations involving input and storage of information along with calling up and processing relevant information from stored memory (Kaplan & Sadock’s Synopsis of psychiatry, behavioral sciences / clinical psychiatry, 2007). Few studies used conventional cognitive tests like Mini Mental State Examination, Digit Symbol Test and Trail B Test and demonstrated that diabetes is associated with lower levels of cognitive functions (Gregg et al., 2000; Kalmijn et al., 1995). But when a relatively new electrophysiological cognitive test Event Related Potential (ERP) P300 was used, conflicting results were obtained. Few studies observed that there was no significant association between type 2 diabetes and altered cognitive functions tested by P300 (Kurita et al., 1995; Tandon et al., 1999; Dey et al., 1997) while Cosway et al (2001) found no significant change in P300 in type 2 diabetes. Therefore the present study was undertaken to investigate the influence of diabetes mellitus on cognitive functions assessed by ERP P300.

ERP is the external recording of the endogenous electrical activity of the underlying brain structure resulting from a stimulus bound activity. P300 is recorded by using oddball paradigm, in which subject is attentive and consciously distinguish an acoustic stimulus (target/rare) from a group of other acoustic (nontarget/frequent) stimuli (Alvarenga et al., 2005). ERPs consist of a series of positive and negative waves that are generated above the brainstem. With frequent tone, a negative N1 – positive P2 complex is seen. With rare stimulus, a negative N1- positive apparent P2 – negative N2 – positive P3 complex is seen. The P3 (P300) component of this response has latency of nearly 300 – 350 ms following the onset of rare stimuli and is of positive polarity (Goodin et al., 1994). P300 latency is an index of processing time required before response generation; so it is a sensitive temporal measure of neural activity underlying the process of attention allocation and immediate memory (cognitive functions). P300 latency is negatively correlated with mental function in normal subjects, with shorter latencies associated with
superior cognitive performance. P300 amplitude varies from 5-20 microvolt (µV) but may reach up to 40 µV. P300 amplitude is proportional to attention given to a task and high amplitude has been associated with superior memory performance. P300 amplitude can be viewed as measure of CNS activity that reflects the processing of incoming information when it is incorporated into memory representation of stimulus and the context in which the stimulus occurs (Polich, 1998).

MATERIAL AND METHODS

Institutional ethical committee cleared the protocol. Subjects were divided into two groups. Group I (test group) was comprised of 30 patients (M:20, F:10) of type 2 diabetes in age group more than 40 years (range 46-75 years) with disease duration more than 5 years and on drug treatment attending Medicine OPD of a North Indian Medical College. Patients of hypertension, severe anemia, deafness, any psychiatric & neurological disorder or subjects taking any drug other than drugs for diabetes were excluded. Group II (control group) was comprised of age and sex matched 30 control subjects (healthy volunteers).

Procedure for P300

Subjects were informed about nature of procedure and informed consent was taken. The subject was made to lie down comfortably and relaxed on a couch in a soundproof room with closed eyes. Rare tone (2 KHz) and frequent tone (1 KHz) of 85dB were applied on both ears together in 20% and 80 % in frequency in random through headphones. Total 300 stimuli were applied at rate of 1 stimuli/sec (Alvarenga et al., 2005; Kurita et al., 1995; Mavioglu et al., 1999). Band pass filter was 0.2 -100 Hz (Goodin et al., 1994). The volume conducted evoked responses (bioelectrical signals) were picked up from the scalp by using Ag/AgCl electrodes placed as per 10–20 International system of placement (Tandon et al.,1999; Cosway et al., 2001 ). The recording sites on scalp were cleaned with alcohol or spirit. After applying electrolyte paste on recording surface of Ag/AgCl electrodes, one active electrode was attached on vertex (Cz), one as ground electrode to forehead (Fz) and two reference electrodes to right and left mastoid designated as A1 and A2 respectively. All the electrodes were plugged to a junction box keeping skin to electrode impedance below 5 K ohms. Subjects were asked to avoid sleep and identify the rare stimulus, counting in loud voice. Responses with artifacts were automatically rejected (Alvarenga et al., 2005; Kurita et al., 1995; DeGiorgio et al., 1993). The signals were picked by electrodes and were filtered, amplified, averaged, displayed on the screen of EMG EP MK II equipment (Electromyography, Evoked potential machine, MK II model, Recorders and Medicare System Private Ltd. Chandigarh, India) and recorded. Two reproducible recordings were taken for a subject and averaged together to obtain the final measurement (Goodin et al., 1994 and Polich, 1998). Latencies of P2, N2, P3 and amplitude of P300 waves were measured.

Glycemic Levels

Fasting plasma glucose (FPG) and postprandial plasma glucose (PPPG) were measured in all subjects before the test.

Statistics

All the data so obtained was analyzed statistically by using ‘Student’s t-test’ and ‘Pearson’s correlation of coefficient’ were calculated between various parameters by using SPSS version 10.

RESULTS

Both groups (control and test) were age and sex matched. The differences in height, blood pressure and hemoglobin of test and control groups were not significant. Weight and body mass index; fasting blood sugar and postprandial blood sugar levels were significantly higher in test group (table 1). Test group had significantly higher P300 latency than control group (p < 0.001). There was significant increase in P300 latency in males & females of test group in comparison with males & females of control group (table 2). Test group had significantly decreased P300 amplitude than control group (p < 0.001) as well as there was significant decrease in P300 amplitude in males & females of test group in comparison with males &
An Online International Journal Available at http://www.cibtech.org/jms.htm

Research Article

females of control group (table 3). There was no significant correlation between P300 latency and age of control, FPG, PPPG and duration of diabetes (table 4).

Table 1: Comparison of sociodermographic and biochemical parameters of control and test groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 30)</th>
<th>Test (n = 30)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.23 ± 5.59</td>
<td>57.86 ± 7.82</td>
<td>&gt; 0.05*</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>62.83 ± 6.87</td>
<td>68.66 ± 11.19</td>
<td>&lt; 0.05**</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.77 ± 2.55</td>
<td>26.31 ± 4.16</td>
<td>&lt; 0.05**</td>
</tr>
<tr>
<td>FPG (mg %)</td>
<td>84.76 ± 7.43</td>
<td>139.6 ± 37.86</td>
<td>&lt; 0.001**</td>
</tr>
<tr>
<td>PPPG (mg %)</td>
<td>108.26 ± 8.4</td>
<td>200.76 ± 55.66</td>
<td>&lt; 0.001**</td>
</tr>
</tbody>
</table>

*No significant **Significant

Table 2: Comparison of mean P300 latency between control and test groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control --P300 latency (ms)</th>
<th>Test -- P300 latency (ms)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>282.75 ± 9.29</td>
<td>319.19 ± 19.13</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Female</td>
<td>285.61 ±10.7</td>
<td>323.02 ± 27.29</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Total</td>
<td>283.7 ± 9.69</td>
<td>320.94 ± 21.75</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

** Significant

Table 3: Comparison of mean P300 amplitude between control and test groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group P300 amplitude (µV)</th>
<th>Test group P300 amplitude (µV)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6.12 ± 3.33</td>
<td>3.95 ± 1.92</td>
<td>&lt;0.05**</td>
</tr>
<tr>
<td>Female</td>
<td>5 ± 3.17</td>
<td>1.53 ± 1.55</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Total</td>
<td>5.75 ± 3.27</td>
<td>3.148 ± 2.12</td>
<td>&lt; 0.01**</td>
</tr>
</tbody>
</table>

**Significant

Table 4: Pearson’s coefficient of correlation between P300 latency and various parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FPG</th>
<th>PPPG</th>
<th>Duration of diabetes</th>
<th>Age of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>P300 latency</td>
<td>-0.024*</td>
<td>- 0.00033*</td>
<td>0.157*</td>
<td>0.032*</td>
</tr>
</tbody>
</table>

*non-significant

DISCUSSION

We aimed to find out cognitive dysfunction in type 2 diabetes by ERP P300. Inspite of taking treatment, patients had poor glycemic control established by their higher glycaemic levels. Central nervous system complications in these patients can lead to diabetic encephalopathy characterized by apoptotic neuronal loss and cognitive decline (Sima et al., 2004). Structural and functional brain changes are observed with both recurrent severe hypoglycemia and hyperglycemia. Alterations in cerebral blood supply, altered neurotransmitter metabolism and metabolic derangements play significant role in pathogenesis of diabetic neuropathy (Kurita et al., 1995; Das et al., 2001; Biessels et al., 1994). Hippocampus, temporo-parietal junction and cerebral cortex are main generators of P300 (Polich, 1998; Tarkka et al., 1996). Type 2 diabetic patients had more cortical and subcortical atrophy with more deep white mater lesions and infarcts. These patients were associated with poor glycemic control and cognitive deficits (Manschot SM et al., 2006). Whatever be the etiology, the abnormalities of diabetic metabolism interact with generators of P300 in cerebral cortex to cause delay in cognitive process (Tandon et al., 1999). In our study, we also observed significantly higher P300 latency was in test group than controls (table 2) suggesting cognitive decline. Our observations are similar to many other studies (Alvarenga et al., 2005; Kurita et al., 1995; Tandon et al., 1999; Dey et al., 1997; Cosway et al 2001, Kurita et al., 1996). Whereas Cosway et al., (2001) and Mavioglu et al., (1999) observed non significant increase in P300 latency in diabetics in
comparison with controls. P300 amplitude was significantly reduced in test group, again suggesting impaired cognition (table 3). Whereas many other studies observed reduction of amplitude but it was not significant (Alvarenga et al., 2005; Cosway et al 2001; Mavioglu et al., 1999). As there was insignificant correlation between P300 latency and age of control (table 4) similar to study by Dey et al., (1997) suggesting thereby no relation between them whereas Kurita et al., (1995) and Kurita et al., (1996) found significant correlation. This difference in opinion may be due to difference in sample (number of control) and their age. A larger sample can give more specific result. There was no significant correlation between P300 latency and duration of diabetes as shown in the table 4. Many studies observed similar results (Kurita et al., 1995; Tandon et al., 1999; Dey et al., 1997; Kurita et al., 1996). This can be explained on the basis that cognitive dysfunction occurs during earlier course of disease due to uncontrolled metabolism and this dysfunction does not depend on recent metabolic derangement (Kurita et al., 1995).

As all diabetic patients included in present study did not show any CNS symptoms as well as they had a minimum of 5 years of diabetes, so we can say that electrophysiological changes depicting cognitive dysfunction starts few years before appearance of any CNS symptom and this observation was in concordance with study conducted by Pozzessere et al (1988). Thus ERP P300 can be very useful in detecting subclinical cognitive decline early in course of diabetes.

**Conclusion**

Cognitive dysfunction should be recognized as a definite complication of type 2 diabetes. ERP P300 can easily detect cognitive decline before appearance of any neurological symptoms and signs so it should be included in routine diagnostic armamentarium to find out any subclinical cognitive decline early in course of diabetes.

**REFERENCES**


Research Article


