BLINK REFLEX ALTERATIONS IN RECENTLY DIAGNOSED DIABETIC PATIENTS

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KEY WORDS:

ABSTRACT

Objective: To determine the frequency of blink reflex alterations and to examine the influence of hyperglycemia in inducing the alterations in recently diagnosed Type 2 diabetes mellitus patients.

Methodology: A cross-sectional study was carried out on patients having asymptomatic diabetes with a period of evolution under 10 years. In all 47 patients (26 women and 21 men), serum glycemia levels were determined and the latency onset of the blink reflex components were measured.

Results: The average patient age was 44.5 ± 11.0 (mean ± SD) years with a diabetes evolution period of 4.3 ± 2.9 (mean ± SD) years. After a fasting serum glucose test, the diabetic patients were catalogued as normoglycemic (≤126mg/dl) or as hyperglycemic (>126mg/dl) and subjected to a blink reflex test. The results obtained from the diabetic patients were compared with those from a non-diabetic control group. 14.8-31.9% of the diabetic patients showed alterations in blink reflex component latencies. The differences compared with the control group were significant (p<0.05).

Conclusions: Diabetes, as is well-known, can affect the central and peripheral nervous system and there does not appear to be a link between glycemic levels and blink reflex components. However, blink reflex alterations were present even in diabetic patients with a relatively short period of disease evolution.
INTRODUCTION

Diabetic neuropathy (DN) is an early and common complication in patients with the metabolic disease of diabetes mellitus (DM). In US alone, there are close to 16 million patients with diabetes mellitus and it has been estimated that one-third of them have DN.1-2 Studies on the prevalence of DN are difficult to evaluate because of a lack of consistency in the definition of neuropathy and the methods used for its detection. However, depending on the diagnostic criteria employed, a 10-66% prevalence of DN in diabetics 3-6 has been shown.

The so-called subclinical or asymptomatic DN has been defined as the presence of a nerve injury caused by DM in the absence of clinical findings7-8.

Electrophysiological methods are useful in DN diagnosis and they are also used in detecting subclinical abnormalities, the nerve conduction test being one of the most common methods used. Although classical nerve conduction studies have concentrated exclusively on the peripheral nerves, the experience of some authors working with diabetic patients suggests that neurological alterations occur at a variety of anatomical levels, including the central nervous system (CNS). Consequently, since the 1970s, electrophysiological tests such as the blink reflex test (BR) have been used to evaluate CNS status in diabetic patients.9,10 Thus, the diagnostic value of BR has been well-established in patients with peripheral and brainstem lesions,11,12 although the central pathway is still a debatable issue 13.

As was previously shown by Kimura and Dumitru, 9,10 blink reflex is analogous to the corneal reflex, involving the stimulation of the trigeminal nerve through its ophthalmic branch (supraorbital), from where afferents travel to the pons, mesencephalon, and cerebral cortex to make final connections with several cranial nerves (mainly the facial nerve). In response to stimulation, these afferents trigger the response, a blink reflex that can be recorded as ipsilateral or contralateral to the site of stimulation. Stimulation of the ophthalmic nerve branch produces two kinds of responses in the eyelid orbicular muscle: an early response, or R1 and a delayed response, or R2. Of these, R1 is evoked only on the stimulated side and is considered to be a pontine reflex. In contrast, R2 is recorded bilaterally following unilateral stimulation, and relies on a more complex pathway that includes interneurons at the level of the pons and the lateral medulla 9,10.
In his work carried out on diabetics, Kimura reports that 10% of symptomatic diabetics exhibited an altered R1 component. This statement was recently confirmed by Urban et al.\textsuperscript{14}.

On the other hand, it has been demonstrated that diabetic patients with metabolic non-control possess a diminished velocity of conduction, which is recovered when hyperglycemia is corrected\textsuperscript{15,16}. Neau et al.\textsuperscript{17} studied 21 uncontrolled diabetics and found an elongation of the R1 and R2 components of BR. In addition, Stambolius et al.\textsuperscript{18} have shown that in hyperglycemia the BR components have prolonged latencies. These studies have been carried out on open populations with clinical manifestations of DM or with provoked hyperglycemia. With the aim of extending the previous studies, we have set out to determine the frequency of BR alterations in diabetic patients with a short period of disease evolution in order to detect possible injuries to the CNS and to examine the influence of hyperglycemia in inducing the alterations.

**METHODS**

A cross-sectional study was carried out on 47 subjects (26 women, 21 men) with DM, selected from a group of out-patients attended at internal medicine clinic of Menofiya Hospital University. After a thorough interview, a neurological examination was per-formed on each patient. None of the patients presented objective or subjective manifestations of DN (absence of reflex or sensitive-motor alterations). Due to possible BR interference, patients with an increased level of serum creatinine (>2mg/dl), who were chronic users of alcohol, with antecedents of cervical trauma, with diabetic retinopathy degree III-IV, with amaurosis or clinical manifestations of metabolic decompensation (polyphagia, polyuria, polydipsia or Kussmaul respiration), with cerebrovascular disease, with cardiovascular disease, or with trigeminal neuralgia or facial paralysis, were all excluded from the study. In addition, patients with cardiac pacemakers or sensitivity to electrical currents were also excluded from the study. The mean age for the patients with diabetes was 44.5 ± 11 years (mean ± SD; range 26-59 years), and the mean height was 1.63 ± 0.09m range (1.45-1.1.80). The disease duration was 4.3 ± 2.9 years (range 1-9 years). All 47 patients had non-insulin-dependent DM and were treated with oral hypoglycemic agents. A fasting serum glucose test was carried out on all patients. On the basis of the serum glucose test results the patients were classified as hyperglycemic (when the glycemia value was higher than 126mg/dl) or normoglycemic (when the value was lower than or equal to 126mg/dl).
The control group consisted of 20 healthy volunteers (11 women, 9 men). None of these subjects had any evidence or history of diabetes, hypertension or cardiac or cerebral vascular disease. The mean age of the control subjects was 41 ± 10.2 years (range 27-60 years) and the mean height was 1.69 ± 0.07m (range 1.59-1. 88m). The electrophysiological study was carried out in the Clinical Electrophysiology that of physical medicine department of Menofiya Hospitals.

**BLINK REFLEX TEST**

Neurapack electromyograph was used and the patient was laid supine on a bed in a quiet, temperature regulated (25-32 °C) and electrically shielded room. A ground electrode was placed on the patient's chin, and stimulation was performed via a cathode placed on the ophthalmic arch. The active recording electrode was placed between the lower and middle part of the inferior lid, and the reference electrode was placed on lateral just to lateral canthus at 4 cm from the external edge of the active electrode. The intensity of the stimulus was 15-25 mA and 0.1 ms duration. The signal was filtered with a range of 10 kHz for high and 10 Hz for low signals. Sweep Speed was 5ms and gain was established in 200 μV. The frequency of pulses was 1-2Hz. Four stimuli were applied to each side every 10s. The results obtained were averaged and the parameter used for the analysis was latency to onset (measured from the stimulus artifact to the initial deflection for each response) superimposed and take the shortest latency.

**Statistical Analysis:**

Means and standard deviation were used; and the latency to onset of left $R1$, right $R1$, left ipsilateral $R2$, right ipsilateral $S2$, left contralateral $R2$ and right contralateral $R2$, was considered to be altered when it was more than 3 standard deviations from the normal mean value (healthy volunteers). The results of the previous analysis are presented as percentages between the two groups of diabetics (normo and hyperglycemic). To determine the differences between them, we used the statistical test $\chi^2$ with a Yates correction or the exact Fisher test with two tails. Results were considered significant when $p<0.05$. The unpaired Student's $t$ test was used to compare weight differences between normo and hyperglycemic diabetic patients. ANOVA (similar variances) or Kruskall-Wallis (heterogeneous variances) tests were used to compare latencies to onset of $R1$, $R2$ ipsilateral and $R2$ contralateral of blink reflex from normo and hyperglycemic diabetic patients. We used a confidence interval of 95% and the probe was
considered significant when \( p<0.05 \). The product-moment correlation coefficient \((r)\) was used to find the correlation between hyperglycemia and latency to onset of \( R1, R2 \) ipsilateral and \( R2 \) contralateral components in diabetic patients. For this test, we used a confidence interval of 95% and an F statistic.

**RESULTS**

In the present study, 47 diabetic patients were analyzed; 22 were normoglycemic (NG) and 25 were hyperglycemic (HG). They were distributed by sex in the following way: 11 women and 11 men NG, 14 women and 11 men HG. The glycemia value for the NG patients was 102.9 ± 12.5 mg/dl, while it was 248.5 ± 75.3 mg/dl for the HG patients. The average length of diabetes evolution was 3.5 ± 3.0 (mean ± SD) years for NG and 4.2 ± 2.9 for HG. Body weights for NG and HG were 72.2 ± 16.6 (mean ± SD) kg and 74.8 ± 13.8 kg, respectively, \( p = 0.7 \).

Table (1):

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26-59 Years</td>
<td>44.5 ± 11 years</td>
</tr>
<tr>
<td>Length</td>
<td>1.45 – 1.80 m</td>
<td>1.63 ± 0.09 m</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>1-9 Years</td>
<td>4.3 ± 2.9 years</td>
</tr>
<tr>
<td>Control group</td>
<td>Age (27-60 Years)</td>
<td>41 ± 10.2 year</td>
</tr>
<tr>
<td></td>
<td>Height</td>
<td>1.59 – 1.88 m</td>
</tr>
</tbody>
</table>

Table (2): Summary of the mean values ± SD and statistical significance for \( R1 \) and \( R2 \) latencies of BR in control patients, normoglycemic diabetics (NG) and hyperglycemic diabetics (HG).

<table>
<thead>
<tr>
<th>Patients</th>
<th>rR1</th>
<th>rR1</th>
<th>rR21</th>
<th>IR21</th>
<th>rR2c</th>
<th>IR2c</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG (n = 25)</td>
<td>12.5 ±</td>
<td>12.2 ±</td>
<td>34.9 ±</td>
<td>33.5 ±</td>
<td>33.9 ±</td>
<td>35.6 ±</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>3.2</td>
<td>3.9</td>
<td>8.1</td>
<td>8.3</td>
<td>3.3</td>
</tr>
<tr>
<td>HG (n = 22)</td>
<td>12.5 ±</td>
<td>12.3 ±</td>
<td>37.1 ±</td>
<td>35.3 ±</td>
<td>37.0 ±</td>
<td>36.6 ±</td>
</tr>
<tr>
<td></td>
<td>1.13</td>
<td>0.9</td>
<td>6.1</td>
<td>6.8</td>
<td>6.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Controls (n = 20)</td>
<td>11.1 ±</td>
<td>11.0 ±</td>
<td>31.5 ±</td>
<td>31.3 ±</td>
<td>30.6 ±</td>
<td>30.9 ±</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>0.9</td>
<td>2.1</td>
<td>2.3</td>
<td>2.4</td>
<td>2.5</td>
</tr>
<tr>
<td>p</td>
<td>0.0009</td>
<td>0.0001</td>
<td>0.002</td>
<td>0.02</td>
<td>0.0004</td>
<td>0.00008</td>
</tr>
</tbody>
</table>

\( r, \) Right; \( I, \) Left; \( l, \) ipsilateral; \( c, \) contralateral; \( p, \) statistical significance. Latencies of \( R1 \) and \( R2 \) Components of BR are expressed in milliseconds.
Our results showed that the right R1 component was altered in 21.2% of the 47 diabetic patients (5 NG, 5 HG, $X^2 = 0$, $p = 0.9$) while the left SI component was altered in 14.8% of the patients (2 NG, 5 HG, $X^2 = 0.4$, $p = 0.5$). The right ipsilateral R2 was altered in 27.6% of the patients (8 NG, 5 HG, $X^2 = 0.2$, $p = 0.4$) while the left ipsilateral R2 was altered in 21.2% of the patients (5 NG, 5 HG, $X^2 = 0$, $p = 0.9$). The right contralateral R2 was
altered in 27.6% of the patients (9 NG, 4 HG, $\chi^2 = 2.4, p = 0.1$) and the left contralateral $R2$ was altered in 31.9% of the patients (7 NG, 6 HG, $\chi^2 = 0.3, p = 0.5$). As can be seen, the percentage of altered patients was very similar between NG and HG.

The comparison between groups is shown in Table 2 which summarizes the mean values for the latency of the $R1$ and $R2$ components (right and left sides) of the blink reflex recorded in NG and HG patients. A significant difference from the control was found in $R1$ ($p<0.05$) and a significant difference from the control was found for both the right ipsilateral $R2$ and left ipsilateral $R2$ components ($p<0.05$) in the diabetic patients. The latency values obtained for contralateral right $R2$ and the contra-lateral left $R2$ were each significantly different ($p<0.05$) from the control as well.

Finally, a correlation analysis was carried out to determine if hyperglycemia was a determinant factor contributing to the alteration seen in the electrophysiological test. Thus we correlated the glycemia levels with the latencies of all BR components: for right $R1$ $r = 0.02$ (1C - 0.28 ± 0.28, $F = 0.1$), for left $R1$ $r = 0.06$ (1C - 0.28 ± 0.29, $F = 0.1$), for right ipsilateral $R2$ $r = 0.17$ (1C - 0.26 ± 0.31, $F = 1.3$), for left ipsilateral $R2$ $r = 0.1$ (1C - 0.27 ± 0.29, $F = 0.4$), for right contralateral $R2$ $r = 0.3$ (1C - 0.16 ± 0.4, $F = 6.9$) and for left contralateral $R2$ $r = 0.25$ (1C - 0.22 ± 0.34, $F = 3.1$). As shown, the right contralateral $R2$ was the BR component most associated with hyperglycemia, although it was not statistically significant.

DISCUSSION

It is clear that nerve conduction is one of the most frequently used tests for early detection of damage resulting from diabetes complications. A prolonged lack of metabolic control can produce any type of nervous system injury: peripheral, autonomic, or central. Peripheral neuropathy is the most common and frequent manifestation of nervous system injury in diabetic patients. It is the first clinical manifestation of a lack of metabolic control. However, autonomic diabetic neuropathy, due to its visceral implications (of a sexual, digestive, urinary, or cardiac nature), has generated great research interest. Although central nervous neuropathies have been the least studied of those related with diabetes, the majority of them have a vascular etiology (as transitory cerebral ischemia, embolism, or thrombosis), so less consideration has been given to non-vascular nervous injuries.
As is well-known, some variables in diabetes (such as age, the period of diabetes evolution, and the degree of metabolic control) are all important determinants of the appearance of neuropathy. BR alterations have been shown in some injuries as cerebral ischemia or cerebral trunk infarcts. Our results show that there is an alteration in the latency of BR components in normoglycemic and hyperglycemic diabetes patients with a short period of disease evolution and to our knowledge, there are no previous studies reporting changes in BR in patients with such evolution. The range of prevalence is from 14.8% for the left R1 component to 31.9% for the left contralateral R2 component of BR. These results are in agreement with those obtained by others, such as Kimura and Dumitru. However, our values are higher than those obtained by Urban et al.

Since the final circuits of BR remain unknown, its utility as a diagnostic probe has increased over the last few years. Some BR components are altered in diabetes, such as the contralateral R2 component, which was the most marked alteration found in the patients in the present study. It is an alteration that could be related to damage in the central nervous system, mainly at the interneuron level. In a recent study where cerebral trunk injuries were evaluated through magnetic resonance imaging (MRI) and BR recording, ipsilateral and contralateral R2 alterations were shown to be indicative of great cerebral injury. More recently Koehler et al. have argued that BR possesses a high rate of exactitude in detecting cerebral trunk injuries and it is also known that the blink reflex pathway includes cerebellar connections relating it to a vestibulo-ocular reflex. Thus, these results indicate that central nervous system damage induced by diabetes may produce future alterations in cerebellar functions and in the vestibulo-ocular reflex.

Although there was no significant correlation between alterations in BR and glycemia observed in the present report we cannot discard the possibility that chronic hyperglycemia could play an important role in producing that kind of damage. Hyperosmolality may be the factor that actually causes the alteration in BR, since the brain is the organ most susceptible to receiving changes in osmolality and to being affected by them. On the other hand, there are several influences that can modulate BR: the noradrenergic system, pain fibers, and the dopaminergic system. In the dopaminergic system, blink reflex is affected mainly in the amplitude of the early component (R1). In contrast, the R2 component can be elicited by innocuous and noxious stimuli. Recently, Kaube et al. reported a new method to increase nociception specificity of the human blink reflex. We cannot totally discard the influence of pain fibers as a modifying factor in
changes in R2, however, nociceptive fibers abolish it, whereas we observed changes in R2 latencies. Finally, it is important to note that when analyzing results we used up to 3 standard deviations as the normal limit in order to reduce the risk of false positive results. Even so, the proportion of diabetic patients with alterations in BR was high. About 30% of normoglycemic and hyperglycemic diabetic patients showed evidence of subclinical damage, suggestive of damage at the level of crossing interneurons (brainstem), re-emphasizing that diabetes affects not only the peripheral nervous system, but the central nervous system as well. Most importantly, these alterations were detected in asymptomatic diabetic patients with a short period of disease evolution. BR could be used as a diagnostic non-invasive tool to detect early alterations in this type of patient.

REFERENCES


Tear Film Alterations in Recently Diagnosed DM

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Purpose:
The purpose of this study was to examine the tear film alterations in diabetic patients with recent diagnosis.

Methods:
A total of 47 diabetic patients (26 females, 21 males) were enrolled in this study. All patients were examined for tear film alterations using the Schirmer test.

Results:
The mean age of the patients was 44.5 ± 11 years. The mean duration of diabetes was 4.3 ± 2.9 years. The majority of patients (65%) had type 2 diabetes.

Conclusions:
Diabetic patients exhibit tear film alterations, which may indicate the onset of diabetic eye disease.

The results of this study suggest that tear film alterations can be used as an indicator of early diabetic eye disease.