Blink Reflex in Type 2 Diabetes Mellitus

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Purpose: An evaluation of the extent of damage of the central nervous system in diabetes mellitus is of high value in current research. Electrophysiological abnormalities are frequently present in asymptomatic patients with diabetes mellitus. Diabetic cranial neuropathy is one of the complications of the disease. Blink reflex is used to diagnose subclinical cranial neuropathy. The objective is to test the utility of blink reflex in detecting subclinical cranial nerve involvement in patients with type 2 diabetes mellitus.

Methods: Forty patients with type 2 diabetes mellitus, aged from 30 to 60 years examined clinically and neurologically. Blink reflex and nerve conduction studies for the upper and lower limbs were performed and compared with 20 matched normal controls.

Results: Diabetic patients with peripheral neuropathy showed significant prolonged distal latency and reduced amplitudes of the R2C response compared with the control, patients without peripheral neuropathy showed insignificant changes. Alteration of R2 correlated with the type of treatment and the duration of the disease. In patients without peripheral neuropathy, ulnar sensory distal latencies showed significant positive correlation with R2I latency, whereas its Conduction Velocity (CV) showed significant positive correlation with R2C amplitudes and negative correlation with R2C latency.

Conclusions: R2C is the most sensitive parameter in the blink reflex, which can help in the diagnosis of subclinical diabetic cranial neuropathy.

Key Words: Diabetic neuropathy, Cranial neuropathy, Blink reflex, Peripheral neuropathy.

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Diabetic neuropathy is an early and common complication in diabetic patients (Harris et al., 1993). Damage to the peripheral nervous system is particularly frequent in these patients (Meral et al., 2007), isolated cranial nerve palsies are less frequent, whereas simultaneous multiple cranial neuropathy are relatively rare (Harris et al., 1995; Meral et al., 2007). The oculomotor and facial nerves are among the most commonly affected, whereas the fifth, ninth, and tenth nerves are less often affected (Adler et al., 1997). Electrophysiological methods specially nerve conduction studies are used in detecting subclinical diabetic peripheral neuropathy (PN) (Uzun et al., 2006), whereas it is more difficult in case of subclinical cranial neuropathy (Bagai et al., 2008; Guney et al., 2006). Although nerve conduction studies have concentrated exclusively on the peripheral nerves (Jurado et al., 2009), many others experienced neurologic alteration at a variety of anatomic levels, including the central nervous system (Singh et al., 2006). Electrophysiological studies of the blink reflex with particular emphasis on the late responses shown to be an effective method for revealing subclinical involvement of cranial nerves (Nazliel et al., 2001).

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PURPOSE OF THE STUDY

The aim of this study was to test the utility of the blink reflex in detecting subclinical cranial neuropathy in type 2 diabetic patients.

SUBJECTS AND METHODS

A cross-sectional study was conducted on 60 subjects; 40 patients aged from 30 to 60 years, with type 2 diabetes mellitus recruited from Endocrinology/Internal Medicine outpatient clinic, Beni Suef University Hospital, with duration of diabetes mellitus >12 months. Diabetes was diagnosed when repeated fasting blood glucose level was ≥ 110 mg/dL according to World Health Organization (1999) before receiving anti-diabetic measures. These were compared with 20-age and sex matched normal volunteers.

Division of Subjects

Group I was formed of 20 diabetic patients (8 men and 12 women) with PN diagnosed either clinically or through nerve conduction studies. Group II was formed of 20 diabetic patients (7 men and 13 women) without clinical and/or neurophysiologic evidence of PN, and Group III was formed of 20 healthy controls (6 men and 14 women).

We excluded; patients with previous or current cranial nerves involvement, clinical evidence suggesting brainstem lesions, cerebrovascular disease or any other central disorder, general diseases associated with neuropathy (as nutritional deficiencies, malignancy, other endocrinal disorders, hepatitis C virus, renal impairment, toxic exposures, etc), or treated with drugs recognized as potentially causing neuropathy.

Informed written consent was obtained from patients. The study was approved by the Medical Research Ethical Committee, Cairo University (Appendix 1).

All subjects were inquired about and examined for clinical evidence suggesting peripheral, cranial, or autonomic neuropathy, and full history about disease duration and medications received were taken. Fasting and 2 hours' postprandial blood glucose levels were measured. Complications of diabetes were assessed namely diabetic retinopathy and nephropathy.

Nerve conduction studies of the ulnar nerve (sensory and motor) in one limb, posterior tibial, and common peroneal (motor nerves in one limb) and the other sural (sensory) nerve, were done using surface electrodes. Supramaximal electrical stimulation was applied (by increasing stimulus intensity by 25% after reaching maximal amplitude), then distal and proximal segments stimulation were recorded for the motor nerves (wrist and elbow segments for the ulnar; medial ankle and popliteal fossa for PTN; anterior ankle and neck of fibula for the common peroneal nerve) and only distal stimulation for the sensory nerves. Then parameters including distal latency, amplitude (peak to peak), and conduction velocity were measured.

Conditions

Monitor time was set at 200 milliseconds, stimulus duration at 0.2 milliseconds, stimulus rate at 1 Hz, low frequency filter at 20 Hz, and high frequency filter at 3 KHz. Analysis time was similar in motor nerve conductions, 50 milliseconds, but 30 milliseconds for sensory nerve conductions. Also initial sensitivity was 200 μV for motor nerve conductions, but 20 μV for sensory nerve conductions.

Blink Reflex Assessment

Surface recording electrodes were placed over the inferior orbicularis–oculi muscles bilaterally for simultaneous recording of the compound motor action potentials. Supraorbital nerve was stimulated in the superior orbital fissure with supramaximal stimulation, with interstimulus interval of 10 seconds and random manual stimulation to avoid habituation.

Conditions

The sweep speed should be 5 to 10 milliseconds per division. Initial sensitivity should be set at 100 or 200 microvolts per division.

Responses

Early R1 and late R2 responses were obtained. R1 is ipsilateral to the side of stimulation, whereas R2 is bilateral; R2I ipsilateral and R2C contralateral (Kimura, 2001). The average reading of both R responses was calculated.

Statistical Analysis

Data were statistically described in terms of range, mean ± SD, frequencies (No. of cases) and percentages when appropriate. Parametric tests as *t*-test and non parametric tests (analysis of variance) for ordinal data and χ^2 for nominal data were used. A probability value (P) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, New York, NY) and SPSS (Statistical Package for the Social Science; SPSS Inc, Chicago, IL) version 15 for Microsoft Windows. Abnormal parameters were calculated as ≥ mean + 2SD from control.

RESULTS

The clinical and laboratory data of the patients are summarized in Table 1. Clinical findings of PN were paresthesias, stock hypoesthesia, lost ankle reflex, and/or distal weakness. The patient considered as having autonomic neuropathy if had postural hypotension, palpitation, and/or impotence in males.

In Group I, there were 12 patients with no clinical evidence of PN but showed electrophysiological evidence of PN (slowing of the conduction velocities, distal latencies prolongation, and/or small amplitude response). None of the patient in group II had clinical or neurophysiologic evidence of PN.

Blink Reflex

Abnormal responses in the form of prolonged mean latency of R2C were reported in 7 patients with PN (35%), 1 patient only without PN (5%) and in 8 patients (20%) with diabetes as a whole.

Comparison of Blink Reflex Parameters Between Study's Groups

The R2C in group I showed a statistically significant prolonged mean latency and a lower mean amplitude compared with group III ($P = 0.04$ and $P = 0.035$, respectively), whereas all other parameters were not statistically significant. There was no statistically significant difference between different parameters of blink reflex on comparing group I and group II as well as group II and group III (Table 2).

TABLE 1. Clinical and Laboratory Data of the Patients

Clinical and Laboratory Data	Group I (n = 20)	Group II (n = 20)
Age, years	49.25 ± 6.69	50.45 ± 8.51
Duration of DM, years	6.75 ± 4.30	5.65 ± 4.22
Type of treatment		
Oral hypoglycemic	13 (65%)	12 (60%)
Insulin	7 (35%)	8 (40%)
Clinical evidence of PN	8 (40)	0
Neurophysiological evidence of PN	20 (100)	0
Clinical evidence of AN	13 (65%)	12 (60%)
Fundus examination		
Normal	15 (75%)	17 (85%)
Proliferative diabetic retinopathy	3 (15%)	2 (10%)
Non proliferative diabetic retinopathy	2 (10%)	1 (5%)
Urine analysis*	$N = 13$	$N = 10$
Normal	6 (46.2%)	6 (60%)
Proteinuria	7 (53.8%)	4 (40%)
Fasting blood sugar	220.20 ± 83.1	160.9 ± 52.4
PP blood sugar	335.35 ± 98.6	262.0 ± 78.6

*Some patients refused to give urine sample for urine analysis.
PN, peripheral neuropathy; AN, autonomic neuropathy; PP, postprandial.

Blink Reflex Correlation to the Clinical and Nerve Conduction Parameters

A significant negative correlation between R2C amplitude and the disease duration was detected in group I ($r = -0.545$, $P = 0.013$). No significant correlation was found between the blink reflex and the fasting and/or postprandial blood sugar level.

There was no statistically significant difference in the parameters of blink reflex between patients with or without proteinuria or those with or without retinopathy as well as those with or without autonomic neuropathy ($P > 0.05$).

In group I, ulnar motor distal latencies showed significant positive correlation with R1 latencies ($r = 0.787$, $P = 0.001$) and negative correlations with R1 amplitudes ($r = -0.655$, $P = 0.003$). While its CV showed significant negative correlation with R1 latency ($r = -0.509$, $P = 0.031$) and positive correlation with R1 amplitude ($r = 0.509$, $P = 0.031$). The ulnar sensory distal latencies showed significant positive correlation with R1 latencies ($r = 0.587$, $P = 0.010$). Also, its CV showed significant negative correlation with R1 latencies ($r = -0.053$, $P = 0.023$).

In group II, ulnar motor distal latencies showed significant negative correlation with R1 amplitude ($r = -0.551$, $P = 0.012$). But its CV showed significant positive correlation with R1 amplitude ($r = 0.522$, $P = 0.018$). The ulnar sensory distal latencies showed significant positive correlation with R2I latency ($r = 0.621$, $P = 0.003$). While its CV showed significant negative correlations with R2C latencies ($r = -0.475$, $P = 0.034$) and positive correlation with R2C amplitude ($r = 0.511$, $P = 0.021$).

Blink Reflex in Relation to the Type of Treatment

Patients received insulin in groups I and II showed a statistically significant lower mean amplitude of the R2I and R2C

TABLE 2. Blink Reflex Parameters in the Study Groups

Blink Reflex		Group I (Mean ± SD)	Group II (Mean ± SD)	Group III (Mean ± SD)	*P*
R1	Latency (milliseconds)	11.83 ± 1.41	11.68 ± 1.06	11.76 ± 1.65	>0.05
	Amplitude (μV)	175.48 ± 134.86	107.08 ± 86.67	187.61 ± 152.03	>0.05
R2I	Latency (milliseconds)	37.03 ± 5.56	34.45 ± 2.95	34.18 ± 2.90	>0.05
	Amplitude (μV)	109.26 ± 106.50	103.03 ± 107.98	139.99 ± 128.35	>0.05
R2C	Latency (milliseconds)	38.33 ± 5.58*	34.99 ± 4.08	32.89 ± 5.60*	0.040*
	Amplitude (μV)	78.20 ± 48.71*	80.51 ± 69.12	108.58 ± 70.66*	0.035*

*Statistically significant $P < 0.05$ between marked groups.

compared with those received oral hypoglycemic treatment ($P = 0.025$ and $P = 0.010$, respectively).

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 (Adler et al., 1997). Peripheral neuropathy is the most common and frequent manifestation of nervous system injury in diabetic patients. Although central nervous neuropathies have been the least studied of those related with diabetes, the majority of them have a vascular etiology, less consideration has been given to nonvascular nervous injuries. It is well known that, many 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.

In this study, we found abnormal blink reflex in 35% of patients with PN and in 20% of patients with diabetes as a whole. This agree with the study done by Trujillo-Hernández et al. (2003) who found abnormality in 14.8% to 31.9% of the different elements of the blink reflex arc of their diabetic patients. However, our results were less than obtained by Nazliel et al. (2001) and Shakouri and Davoudi (2006) who reported abnormality in 55% and 54.4%, respectively in their diabetic patients with evident PN. Also, Urban et al. (2006) recorded prolonged latency of the facial nerve (the 2nd limb of the blink reflex) in 77.5% of diabetic patients.

The abnormalities in this study were restricted to R2C, as prolonged mean latencies and smaller amplitudes in diabetic patients with PN compared with the control. Trujillo-Hernández et al. (2003) also reported that R2C was the most frequent abnormality found in their patients. The central way of the reflex arc of R2 is multisynaptic. Holstege et al. (1986) postulated that blink premotor area located at the pontine and medullary tegmental fields projecting into the blink motoneuronal pool would probably be involved in R2 blink reflex component. Prolongation to Gasser ganglion, throughout the tractus spinalis trigeminalis reached the second-order neurons located on the nucleus spinalis trigeminalis. From here, a long interneuronal ascending system connected to the ipsilateral and contralateral facial nuclei. This multisynaptic pathway included the lateral propriobulbar system of the reticular formation, lying medial to the trigeminal spinal nucleus. So this alteration in the blink reflex arc could be related to damage in the central nervous system at the interneuron levels in the low brainstem reticular formation.

Our results showed that R1 parameters did not show significant difference between the patients and the control groups. These results agree with the study done by Guney et al. (2008) who found no difference between the diabetic patients and controls and that done by Trujillo-Hernández et al. (2003) who reported that R1 was the least recorded abnormality in their diabetic patients. These results suggest that R1 is mainly conducted by exteroceptive, medium thick myelinated A-beta fibers, whereas R2 is predominantly conveyed by the nociceptive, thin myelinated A-delta fibers.

In this study, 7 patients (35%) with PN showed abnormal absolute latency values of the blink reflex compared with 1 patient (5%) without PN, which could be attributed to a more severe disease process and signifying a more diffuse involvement of both peripheral as well as central nervous system. Severe generalized sensory motor PN involvement may be a marker of cranial nerve involvement; patients with generalized neuropathy have a higher chance of developing cranial nerve abnormalities than diabetic patients without clinical PN (Kohara et al., 2000). In agreement with us, abnormal blink reflex was correlated with the severity of PN in Shakouri and Davoudi (2004) and Guney et al. (2008) and to the type of treatment in Kohara et al. (2000). However, blink reflex could not be correlated to the presence of medical complications or autonomic neuropathy.

The R2C amplitude negatively correlated with the disease duration, which was not the case with latency. Shakouri and Davoudi (2004) and Guney et al. (2008) found that abnormal blink reflex was correlated with the duration of diabetes mellitus. However, Trujillo-Hernández et al. (2003) found that blink reflex alterations can be present even in diabetic patients with a relatively short period of disease.

CONCLUSIONS

The contralateral R2 is the most sensitive parameter of the blink reflex arc, which could elicit subclinical cranial neuropathy in type 2 diabetes mellitus patients. Alteration of blink reflex is correlated with the type of treatment and the duration of the disease.

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APPENDIX 1

N-54-2011

Cairo University
Faculty of Medicine
Research Ethics Committee

جامعة القاهرة
كلية الطب
صادر ٢٤ ديسمبر ٢٠١١
التاريخ
لجنة أخلاقيات البحث العلمي

NOTICE OF APPROVAL

Date:**24-12-2011**

Protocol title: **Blink reflex in diabetes mellitus**
Principal investigator: **Dr.Saly Hassan El kholy &Dr. Hanan Hosny abd elalim**

Institution or organization: **Cairo University**
Decision: APPROVAL

Dear Dr : **Saly & Dr. Hanan**

The Research Ethics Committee **(REC),** has reviewed and **approved** the above mentioned **protocol** on " 24-12-2011". **You may begin your investigation.** Approval is granted for one year from the date of initial approval. At the end of this period as the principal investigator you will be asked to submit required documents for continuing review.

As principal investigator you will need to:

- Notify the REC Chair immediately after any **serious adverse events** experienced by participants of the investigational study or as reported to you by the sponsor/manufacturer/co- investigators.
- You may not initiate **changes** in approved research protocol without REC review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.
- يحظر سفر أى عينات بشريه من المبحوثين خارج جمهوريه مصر العربية الا بعد موافقة الجهات الامنية .