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Blink Reflex in Early Diagnosis of Trigemino-Facial Pathway Involvement in Type II Diabetes Mellitus Patients with Peripheral Neuropathy

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Abstract: Cranial neuropathy occurs at higher incidence in diabetic patients than general population. It often occurs, either clinically or subclinically, coexistent with diabetic peripheral neuropathy (DPN). Blink reflex may detect subclinical involvement of cranial nerves and their central pathway. The aim of the current work was to assess the usefulness of blink reflex in the early diagnosis of trigemino-facial pathway involvement in type II diabetic patients with peripheral neuropathy. The study included 20 diabetic patients (4 males and 16 females), mean age of 52.25 ± 8.91 years with clinical and electrophysiological evidences of peripheral neuropathy and 30 healthy subjects as control group. Patients were subjected to full neurological examination including cranial nerves. Assessment of peripheral neuropathy was done using the Total Neuropathy Score-Reduced (TNSr). Electrophysiological study was performed for both groups including motor conduction study of posterior tibial and deep peroneal nerves, sensory conduction study of sural nerves and blink reflex study. Results showed that none of the patients had clinical evidence of cranial neuropathy. Blink reflex abnormalities were detected in a total of 7 patients (35%). Right R1 latency, ipsilateral and contralateral R2 latencies of both sides were significantly prolonged in patients ($p< 0.001$) compared to control group. In addition, there was significant reduction in R1amplitude in diabetic patients compared to control group ($p<0.001$). Blink reflex latencies correlated positively with TNSr. It was concluded that blink reflex is a useful method in diagnosis of the subclinical involvement of trigemino-facial pathway in type II diabetic patients with peripheral neuropathy.

Key words: Blink Reflex · Trigemino-Facial Pathway · Diabetes Mellitus · Peripheral Neuropathy

INTRODUCTION

Diabetes mellitus (DM) is the most common cause of neuropathy among metabolic disorders [1], where diabetic neuropathy (DN) prevalence rate has been estimated to be between 10-66% [2, 3]. There are various forms of DN including distal sensorimotor polyneuropathy, small fiber sensory polyneuropathy, pure autonomic polyneuropathy, proximal nerve syndromes and isolated mononeuropathies of cranial nerves, intercostal nerves or peripheral nerves [4]. Mononeuropathy involves damage or destruction of an isolated nerve or nerve groups including cranial nerves. The oculomotor (III) and facial (VII) nerves are among the most commonly affected [5].

Existing electrophysiological tests are used in detecting subclinical abnormalities of the peripheral nerves [6, 7]. Subclinical DN has been defined as the presence of a nerve injury caused by DM in the absence of clinical findings [8, 9] . Blink reflex is considered to be a valid mean of revealing subclinical abnormalities of cranial nerves in DM [10]. Blink reflex is the electrical correlate of the clinically evoked corneal reflex, involving the stimulation of the supraorbital branch of the ophthalmic division of the trigeminal nerve unilaterally and recording from the inferior orbicularis oculi muscles bilaterally [11]. It produces two kinds of responses; an early response, or R1 and a delayed response, or R2. R1 is considered to be a pontine reflex. R2 is recorded bilaterally: ipsilateral (IR2) and contralateral (CR2) and

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relies on a more complex pathway that includes interneurons at the level of the pons and the lateral medulla [7, 11]. Accordingly, blink reflex is useful in detecting abnormalities anywhere along the reflex arc including peripheral (trigeminal and facial nerves) and central pathways (pons and lateral medulla) [11].

Abnormal blink reflex responses in diabetic patients were found in several previous studies [12-14]. Nazliel *el al*. [12] reported subclinical blink reflex abnormalities in 55% of diabetic patients. IR2 and CR2 latencies of diabetic patients were prolonged relative to controls and showed a positive correlation with the duration of disease. Trujillo-Hernandez *et al.* [13] found that only 14.8-31.9% of the patients had significant alterations in blink reflex latencies compared to control group, such alterations were present even in diabetic patients with a relatively short period of disease evolution.

Accordingly, affection of cranial nerves and their proximal connections has been detected in diabetic patients using blink reflex. However, results in literature were contradictory regarding the percentage of blink reflex abnormalities and there was no clear detailed description of the patterns of these abnormalities. The aim of current study was to evaluate the role of blink reflex in early detection of trigemino-facial pathway involvement in type II diabetic patients with peripheral neuropathy (PN).

Objectives: The aim of this work was to study the usefulness of the blink reflex in early diagnosis of trigemino-facial pathway involvement in type II diabetic patients with peripheral neuropathy.

MATERIALS AND METHODS

Twenty patients with clinical diagnosis of DM were enrolled in the study. Patients were recruited from those attending the outpatient clinics of Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Alexandria University. Diabetic patients were included if they had confirmed diabetic sensorimotor polyneuropathy according to the definitions of minimal criteria for typical diabetic peripheral neuropathy (DPN) [15].

Patients with one or more of the following were excluded:

- Prior history of cranial nerve lesions.
- Cerebrovascular disease.
- Diseases, other than DM, associated with neuropathy e.g. liver disease, kidney disease, hypothyroidism, autoimmune diseases and tumors.
- Drugs recognized as potentially causing neuropathy (drug induced neuropathy) e.g. vincristine, phenytoin, isoniazid, statins and fluoroquinolones.

In addition, 30 healthy, age and sex, matched subjects were included as the control group. All participants were informed about the nature of the study and informed consents were taken from all studied participants. The study was approved by the ethics committee of Alexandria Faculty of Medicine.

Patients Were Subjected to:

Full neurological examination [16-18] including cranial nerves examination focusing on trigeminal and facial nerves.

Assessment of Peripheral Neuropathy Severity Using the Total Neuropathy Score-Reduced (TNSr) [19]: TNSr is an evaluation index for grading of peripheral neuropathy. It combines information obtained from grading of symptoms, signs and nerve conduction studies (sural and peroneal nerves response amplitude) and provides a single measure to quantify neuropathy. Its values range from 0-28 . Each neuropathy item is scored on a 0-4 scale. Higher total scores correlate with more severe neuropathy.

Glycated Hemoglobin(HbA1c) was measured to determine disease control.

Electrophysiological Assessment: Electrophysiological study was performed for both groups. Neuropack 2 electromyography apparatus (MEB-7102K) and (MEB-9400) from Nihon Kohden (Japan) were used to perform the electrophysiological studies. Temperature of the room was adjusted for standardized techniques.

The study included motor conduction study [20] of the posterior tibial and deep peroneal nerves, sensory nerve conduction study [20] of sural nerves and blink reflex study [11]. Regarding *motor conduction study*, compound muscle action potential (CMAP) peak to peak amplitude, distal latency (DL) and nerve conduction velocity (NCV) of the leg segment were determined. As for *sensory conduction study* of sural nerves, sensory nerve action potential (SNAP) peak to peak amplitude and leg segment sensory conduction velocity (SNCV) were determined [20].

As for blink reflex study [11], the patients were asked to be in a relaxed state, lying supine on the examining table, with eyes either open or gently closed. Recording was performed simultaneously from both sides of the face using a two-channel recording apparatus. *Stimulation site* was superior orbital fissure; stimulating the supraorbital nerve (branch of the ophthalmic division of the trigeminal nerve) ipsilaterally. *Recording sites* were orbicularis oculi muscles bilaterally. G1 were placed below the eye just lateral and inferior to the pupil at mid-position. G2 were placed just lateral to the lateral canthus bilaterally.

The stimulation was supramaximal; the current was turned up in small increments (usually 3-5 mA) from a baseline of 0 mA till supramaximal stimulation was reached. No more than 15 to 25 mA was needed to obtain supramaximal stimulation. Once supramaximal stimulation was achieved, four to six responses were obtained on a rastered tracing and superimposed to determine the shortest response latencies. The duration of the electrical pulse was set to 200 µs. For recording the CMAP from the inferior orbicularis oculi muscle, the initial sensitivity was set at 100 to 200 µV per division, the sweep speed was set at 5 to 10 ms per division and the filter motor settings were 10 Hz and 10 kHz. The ground electrode was placed on the chin. The following parameters were recorded; ipsilateral R1 (IR1), ipsilateral R2 (IR2) and contralateral R2 (CR2) latencies.

Statistical Analysis: Data were analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range, arithmetic mean, standard deviation and median. The distribution of quantitative variables was tested for normality per group using Kolmogorov-Smirnov test. In all statistical tests, level of significance used was 0.05, below which the results were considered to be statistically significant. Qualitative variables were compared using chi-squared test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's exact test .For normally distributed quantitative variables, Student t-test was used to compare two different groups. For abnormally distributed quantitative variables, Mann Whitney test was used for comparing between two different groups. Pearson correlation was used to measure of strength of linear correlation between two quantitative variables.

RESULTS

The study included twenty patients with a mean age of 52.25 ± 8.91 years, ranged from 35 – 67 years and thirty healthy subjects as control group with a mean age of 50.03 ± 5.03 years, ranged from 39 – 58 years. Patients group consisted of sixteen females (80%) and four males (20%) while the control group consisted of 21 females (70%) and 9 males (30%). There was no statistically significant difference between both groups as regard the age ($p = 0.267$) or sex ($p = 0.430$). Patients had mean disease duration of 14.3 ± 4.81 years and ranged from 8 – 25 years. Five (25%) patients were on oral hypoglycemic drugs, 12 (60%) patients were on insulin therapy and only 3 (15%) patients were on both types of treatment. Total neuropathy score of patients ranged from 6 – 22 with a mean of 14.1 ± 3.77. HbA1c ranged from 6.9 – 13.2 with a mean of 9.95 ± 2.08.

Regarding peripheral electrophysiological study parameters, all the studied patients had electrophysiological evidence of peripheral neuropathy in the form of slowing of the conduction velocities, prolongation of distal latencies and/or low amplitude or absent response. Patients had significantly lower SNAP amplitude and slower conduction velocity of sural nerves in comparison to the controls ($p<0.001$). As regards deep peroneal and posterior tibial nerves, patients had significantly delayed distal latency ($p=0.003$, $p<0.001$ respectively), lower CMAP amplitude ($p<0.001$) and slower conduction velocities ($p<0.001$) in comparison with control group.

As for blink reflex study, Table (1) shows statistically significant prolongation of blink reflex latencies of patients compared to control group including prolonged right R1 ($p=0.001$), R2I and R2C ($p<0.001$) as well as prolonged left R2I and R2C ($P<0.001$). There was statistically significant increase in R1 and R2C side-to-side latency difference in patients compared to control group ($p<0.001$, $p=0.014$ respectively).

Individual Data Analysis: Latencies of right and left blink reflex of control group were gathered from which we calculated the cut off values of blink reflex latencies using mean ± 3SD in order to reduce the risk of false positive results. Table (2) shows the cut off values of blink reflex latencies and Table (3) shows the frequency of abnormalities in blink reflex latencies among the studied patients according to these cut off values.

Table 1: Comparison between patients and control groups according to blink reflex latency

Blink Reflex latency			Patients (n=20)	Control group (n=30)	Test of sig. (p)
Right Blink Reflex Latency (ms)	R1	Mean ± SD	11.77 ± 1.99	10.2 ± 0.56	Z=-3.271 (0.001*)
		Min - Max	10.0 - 18.5	9.0 - 11.2	
		Median	11.2	10.3	
	R2I	Mean ± SD	34.38 ± 4.33	29.63 ± 1.99	Z=-4.489 (<0.001*)
		Min - Max	30.0 - 47.7	26.3 - 33.3	
		Median	32.85	29.5	
	R2C	Mean ± SD	35.07 ± 5.77	30.09 ± 2.23	Z=-3.524 (<0.001*)
		Min - Max	29.0 - 52.0	24.8 - 34.2	
		Median	33.1	30.5	
Left Blink Reflex Latency (ms)	R1	Mean ± SD	10.93 ± 1.45	10.19 ± 0.58	Z=-1.090 (0.276)
		Min - Max	9.0 - 14.9	9.0 - 11.2	
		Median	10.8	10.3	
	R2I	Mean ± SD	34.17 ± 3.78	29.75 ± 2.22	t=4.885 (<0.001*)
		Min - Max	26.8 - 41.7	24.7 - 33.1	
		Median	34.0	29.5	
	R2C	Mean ± SD	35.67 ± 3.91	30.34 ± 2.11	Z=-4.516 (<0.001*)
		Min - Max	29.8 - 44.1	26.3 - 35.8	
		Median	36.3	30.5	
Side-to-Side Latency Difference (ms)	R1	Mean ± SD	1.34 ± 1.55	0.12 ± 0.25	Z=-4.667 (<0.001*)
		Min - Max	0.0 - 6.8	0.0 - 0.9	
		Median	0.9	0.0	
	R2I	Mean ± SD	2.88 ± 2.13	1.76 ± 1.64	t=1.975 (0.055)
		Min - Max	0.4 - 9.2	0.0 - 6.3	
		Median	2.3	1.7	
	R2C	Mean ± SD	4.12 ± 3.73	1.87 ± 1.81	Z=-2.462 (0.014*)
		Min - Max	0.3 - 14.2	0.0 - 4.8	
		Median	3.1	1.5	

n= number, Sig=significance, SD= standard deviation, Min= minimum, Max= maximum, R1=ipsilateral R1, R2I= ipsilateral R2, R2C= contralateral R2, t: Calculated value for Student t-test, Z: Z-score of Mann-Whitney test, *: Statistically significant at $p \leq 0.05$, ms=millisecond.

Table 2: Cut off values of blink reflex latencies

Blink Reflex studies		Mean	SD	Cut off
Right and Left Blink Reflex Latency (ms)	R1	10.20	0.56	11.88
	R2I	29.69	2.09	35.96
	R2C	30.20	2.16	36.68
Side-to-Side Latency Difference (ms)	R1	0.12	0.25	0.87
	R2I	1.76	1.64	6.68
	R2C	1.87	1.81	7.30

SD= standard deviation, R1= ipsilateral R1, R2I= ipsilateral R2, R2C= contralateral R2, ms= millisecond.

Table 3: Frequency of abnormalities of blink reflex latency in the studied patients

		Normal		Abnormal	
Blink Reflex latency		n	%	n	%
Right Blink Reflex Latency (ms)	R1	14	70	6	30
	R2I	16	80	4	20
	R2C	17	85	3	15
Left Blink Reflex Latency (ms)	R1	18	90	2	10
	R2I	18	90	2	10
	R2C	17	85	3	15
Side-to-Side Latency Difference (ms)	R1	15	75	5	25
	R2I	19	95	1	5
	R2C	16	80	4	20

n= number of studied patients, R1= ipsilateral R1, R2I= ipsilateral R2, R2C=contralateral R2, ms= millisecond

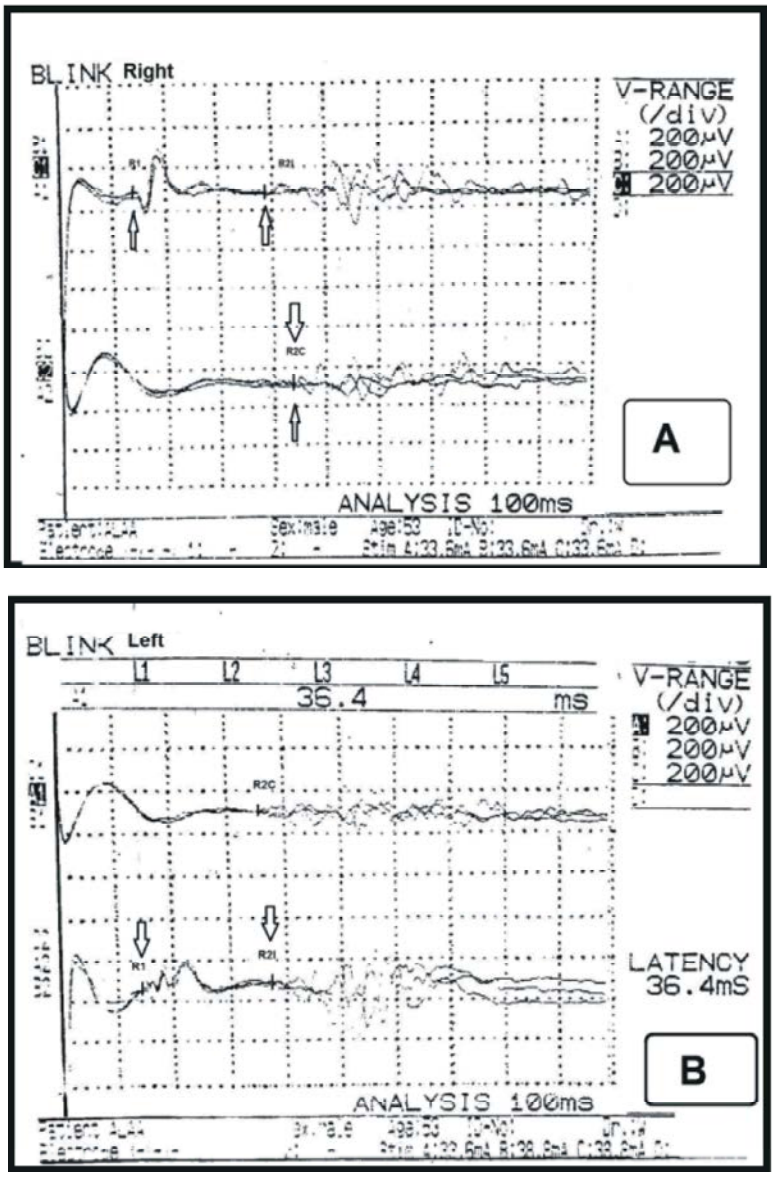

Fig. 1 (A&B): 53 years old male patient showed right trigeminal neuropathy and left facial neuropathy pattern. *Right trigeminal neuropathy* is marked in *fig. A* by arrows pointing up, prolonged right R1 *14* ms (cut off 11.88 ms), Right R2I *39.6* ms (cut off 35.96 ms) and right R2C *44.2* ms. (cut off 36.69 ms) latencies. *Left facial neuropathy* is marked in Fig. (B and A) by arrows pointing down, prolonged Left R1 13.6 ms (cut off 11.88ms), left R2I 38.2 ms (cut off 35.96 ms) and right R2C 44.2 ms. (cut off 36.69 ms) latencies.

Abnormalities were detected in a total of 7 patients (35%). Four patterns of abnormalities were detected including *2 patients with trigeminal neuropathy*, *2 patients with facial neuropathy*, *two patients had combined trigeminal neuropathy with facial neuropathy and one patient with subclinical central lesion.* Fig. 1(A and B) shows combined trigeminal and facial neuropathy pattern of blink reflex recorded in one of the studied patients.

Regarding blink reflex amplitude, right R1 mean amplitude was 0.35 ± 0.36 μV and ranged from 40 to 1800 μV, left R1 amplitude mean was 0.41 ± 0.42 μV and ranged from 80 to 2000 μV, while control mean R1 amplitude was 0.77±0.29 μV. There was statistically significant reduction in amplitude of R1 on both sides in diabetic patients in comparison to control group (p=0.001). The cut off value of R1 amplitude was calculated using mean ± 2SD of the matched control group. Abnormal R1 amplitude was

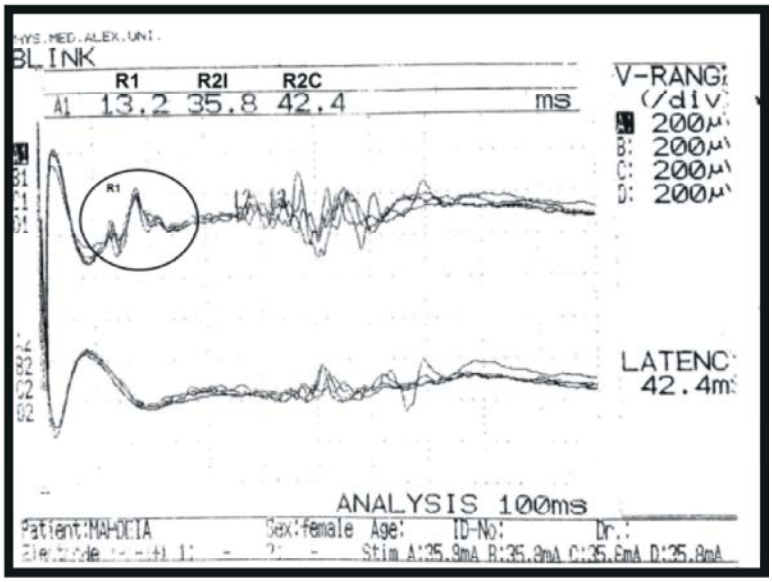

Fig. 2: 52 years old female patient showed right polyphasic R1.

Table 4: Correlation of blink reflex latencies with age, disease duration, HbA1c, TNSr and sural nerve conduction study parameters in investigated patients

			Right Blink Reflex Latency n=20			Left Blink Reflex Latency n=20			Side-to-Side Latency Difference	
Studied variables			R1	R2I	R2C	R1	R2I	R2C	R1	R2C
Age		r	0.196	0.091	0.101	0.250	0.098	0.267	0.022	0.270
		p	0.421	0.702	0.671	0.302	0.683	0.255	0.928	0.250
Disease duration		r	-0.049	0.178	0.223	-0.020	-0.050	-0.099	0.099	0.264
		p	0.844	0.452	0.344	0.934	0.834	0.678	0.679	0.261
HbA1c		r	0.019	0.035	-0.063	-0.205	-0.188	-0.079	0.054	-0.185
		p	0.939	0.882	0.792	0.401	0.428	0.740	0.820	0.436
TNSr		r	0.169	0.447*	0.570*	0.479*	0.619*	0.377	0.226	0.421
		p	0.490	0.048*	0.009*	0.038*	0.004*	0.101	0.339	0.065
Rt sural nerve	SNAP									
		r	0.034	-0.108	-0.117	0.006	-0.521*	-0.390	-0.107	-0.524*
		p	0.889	0.649	0.622	0.981	0.019*	0.089	0.653	0.018*
	SNCV	r	0.167	-0.001	-0.038	0.609*	-0.017	0.409	-0.030	0.146
		p	0.623	0.997	0.912	0.047*	0.960	0.212	0.930	0.669
Lt sural nerve	SNAP	r	0.290	-0.043	-0.106	0.053	-0.469*	-0.312	0.137	-0.507*
		p	0.244	0.862	0.665	0.833	0.043*	0.194	0.575	0.027
	SNCV	r	0.196	-0.089	-0.029	0.570	-0.291	0.162	0.065	0.074
		p	0.563	0.794	0.932	0.067	0.386	0.635	0.850	0.830

n= number of patients, R1= ipsilateral R1, R2I= ipsilateral R2, R2C= contralateral R2, HbA1c= Glycated haemoglobin, TNSr= Total Neuropathy Score-Reduced SNAP= sensory nerve action potential, SNCV= sensory nerve conduction velocity, Rt=right, Lt=left, r: Pearson's correlation coefficient, p: p-value, *: Statistically significant at $p \leq 0.05$

considered if it is less than 280 µV. Reduced amplitude of R1 was recorded in 11 patients. Reduction of R1 amplitude was noticed in patients with normal as well as prolonged R1 latencies. On the other hand, one of the studied patients had facilitated R1 recorded bilaterally (right R1 amplitude = 1800 µV and left R1 amplitude = 2000 µV).

Shape of R1 (Polyphasic R1): Though R1 response is usually a simple biphasic or triphasic waveform, polyphasic R1 was observed in two patients. Fig. (2) shows polyphasic R1 in one of the studied patients. The number of phases can be calculated by counting the number of baseline crossings and adding one.

Table (4) shows the correlation of blink reflex latencies with age, disease duration, HbA1c, TNSr and sural nerves conduction study parameters. There was a moderate positive correlation between TNSr and right R2I latency ($p = 0.048$), right R2C latency ($p = 0.009$), left R1 latency ($p = 0.038$) and left R2I latency ($p = 0.004$). There was a moderate negative correlation between sural nerves amplitude on both sides and left R2I latency ($p = 0.019$, $p = 0.043$) as well as R2C side-to-side latency difference ($p = 0.018$, $p = 0.027$).

There was no correlation between blink reflex latencies and motor conduction parameters of deep peroneal and posterior tibial nerves. Furthermore, no relationship existed between blink reflex latencies and type of diabetes mellitus therapy in the current study.

DISCUSSION

Diabetes mellitus has a severe influence on the nervous system and it commonly affects the upper and lower extremity nerves more than cranial nerves [21]. Several clinical scales and additional tests have been proposed along decades to early detect distal symmetrical polyneuropathy and follow its progression [22]. Few routine electrophysiological tests are available to evaluate the cranial nerves and their proximal segments. The main objective of this study was to evaluate the efficacy of blink reflex for early diagnosis of trigemino-facial pathway involvement in DPN patients.

In the current study, 35% of studied patients had abnormal blink reflex which indicates that subclinical blink reflex abnormalities are not uncommon in DPN patients. There was statistically significant prolongation of blink reflex latencies (right R1, R2I and R2C of both sides) in patients compared to control group. This indicates a lesion anywhere along the trigemino-facial pathway including sensory pathway involvement [12-14], efferent arc involvement [14, 23], interneuron subclinical dysfunction [24, 25] or diffuse lesion in pontomedullary pathways [14, 26]. These results are in agreement with several previous studies [13, 14, 27-30]. Kazem and Behzad [14] studied blink reflex in type II diabetic patients with different grades of PN with disease duration ranging from 5 to 30 years. They found abnormalities in 54.4% of the studied patients. R1, R2I and R2C latencies were significantly prolonged relative to the control group ($p = 0.001$). Trujillo Hernandez *et al*. [13] studied blink reflex in asymptomatic type II diabetic patients with relatively short duration of disease evolution ranging from 1 to 9 years, however they observed abnormalities ranging from 14.8% for the left R1 latency to 31.9% for the left R2C latency.

Jalal *et al.* [27] and Pawar *et al.* [28] also studied blink reflex in type II DM patients with and without polyneuropathy. Jalal *et al*. [27] found abnormalities in 44.6% of the studied patients, while Pawar *et al.* [28] found abnormal blink reflex response in 67% of diabetic patients. The findings of both studies denoted that facial and trigeminal nerves are affected in diabetic patients though the disease remains clinically silent. Jalal *et al.* [27] also reported that diabetic patients with PN, which is either overt or subclinical, had five times more risk developing cranial neuropathy than diabetic patients without PN.

Blink reflex abnormalities that were restricted to either R1 or R2 were also detected in several studies [24, 25, 31] that assessed blink reflex in patients with DM with or without PN. They explained alteration in the blink reflex arc as being related to subclinical CNS damage particularly interneuron subclinical dysfunction in the low brainstem reticular formation.

In the current study, there was statistically significant reduction in amplitude of R1 in diabetic patients. In normal populations, R2 response amplitude occasionally shows marked variability and accordingly wasn't used for analysis. Decreased amplitude of blink reflex is suggestive of decrease in the number of facial motoneurons [32]. None of the previous studies relied on blink reflex amplitude in the comparison between patients and control except Elkholy *et al*. [25] who reported no statistically significant reduction in R1 amplitude of the studied patients compared to control group. Large R1 recorded on stimulation of both sides in one of the patients suggests the presence of subclinical central damage and might be explained by removal of corticobulbar inhibitory influences on facial motoneurons [33].

Four patterns of blink reflex abnormalities were detected in this study including trigeminal neuropathy, facial neuropathy and combined trigeminal & facial neuropathy as well as subclinical central lesion patterns. In agreement with the present study, Cruccu *et al*. [23] detected one patient with facial neuropathy in the severe diabetic polyneuropathy group and 12 patients with combined trigeminal and facial abnormalities in patients with mild polyneuropathy. Urban *et al*. [31] recorded prolonged latency of facial nerve in 77.5% of diabetic subjects. In addition, Xu *et al*. [34] as well as Guney [35] stressed upon the importance of blink reflex in locating extra-axial lesions (lesion of trigeminal or facial nerve) or clinically silent intra-axial lesions (brainstem functional

abnormalities) in patients with early polyneuropathy. Contrary to the present study, Kazem and Behzad [14] noticed no special pattern of involvement associated with the blink reflex abnormality in most of the studied patients. In addition, Contocostas *et al*. [26] found that 26% of the studied diabetic patients had abnormal blink reflex which did not follow a distinct localization but were due to diffuse pontomedullary dysfunction.

In the present study, polyphasic R1 was recorded in 2 patients. Normally, R1 response is disynaptic reflex and it is usually stable and reproducible, with biphasic or triphasic morphology [11]. The underlying pathology of DM is mixed axonal degeneration and demyelination [4]. Demyelination leads to temporal dispersion which occurs as the individual nerve fibers fire at different times [36]. In diabetic patients, there is a greater lag time in conduction of different fibers, leading to increased temporal dispersion of the waveform, which may explain this finding.

These findings show that blink reflex abnormalities are not always constant and don't follow a certain pattern, but differ among studies in type of abnormality, pattern of abnormality and correlations with different clinical and electrophysiological parameters. These differences in the incidence of blink reflex abnormalities in previous studies and the present one may be related to patient selection, disease duration and recording techniques.

Blink reflex abnormalities in diabetic patients can be explained in view of the pathophysiology of DN. First, the prolonged lack of metabolic control which can produce any type of nervous system injury [2]. In addition, the majority of central nervous system neuropathies in DM have a vascular etiology (as transitory cerebral ischemia, embolism, or thrombosis). Blink reflex alterations have been shown in patients with cerebral ischemia or cerebral trunk infarcts [37, 38]. Furthermore, chronic hyperglycemia initiates and amplifies processes that produce reactive oxygen species which is one of the major causes for diabetic complications. Hyperglycemia leads to aggravation of oxidative damage leading to vascular complications [39]. Persistent hyperglycemia also induces activation of inflammatory cascade [40, 41] and proinflammatory cytokine upregulation pathways [42] leading to neuroinflammation which play a vital role in structural and functional damage of the peripheral nerves leading to DPN. It's worth mentioning that mitochondrial abnormalities and mitochondria associated oxidative stress stand at a central position in the pathogenesis of DN [43].

In the current study, there was no correlation between blink reflex latencies and patients' age or HbA1c which is in agreement with Nalziel *et al*. [12]. A possible explanation is better disease control prior to blink reflex testing. In addition, we observed a moderate positive correlation between TNSr and blink reflex latencies which is expected and comes in agreement with several previous studies [23-25, 27, 28, 44, 45]. Cruccu *et al*. [23] detected abnormal R1 and R2 latencies in patients with severe PN, while in patients with mild PN they detected only prolonged R1 latency. Kohara *et al.* [45] and similarly Nazliel *et al.* [12] stated that patients with generalized neuropathy have a higher chance of developing cranial nerve abnormalities than diabetic patients without clinical PN.

In the present study, there was no correlation between blink reflex and type of treatment which can be explained by the patients' noncompliance to therapy. This was contrary to other investigators [28, 45] who found that blink reflex alteration correlated with the type of treatment. We did not observe any correlation between blink reflex abnormalities and the duration of diabetes which was contrary to other investigators [12, 28]. On the other hand, Trujillo Hernandez *et al.* [13] reported that blink reflex abnormalities were present even in diabetic patients with short disease duration which comes in agreement with the current study. This indicates that these abnormalities can occur at any point in the course of the disease in coexistence with PN.

CONCLUSIONS

It was concluded that blink reflex abnormalities can be detected in absence of clinical features reflecting the usefulness of the blink reflex in early diagnosis of subclinical affection of trigemino-facial pathway in diabetic patients. Accordingly, patients can be identified and treated early through strict glycemic control which seems to be critical for prevention, stabilization and even improvement of DN.

It is recommended to include blink reflex in the electrophysiological workup for the evaluation of neurological complications in diabetic patients. Future large studies of blink reflex in these patients are needed to determine the prevalence of trigemino-facial pathway involvement in diabetes mellitus.

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