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Research Article

Evaluation of Brain Stem Function in Diabetics with and Without Distal Symmetrical Polyneuropathy Using the Blink Reflex

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Abstracts:

Background: Diabetic peripheral neuropathy (DPN) is the most common complication of T2DM. Neuropathy is a descriptor for a spectrum of clinical and subclinical symptoms with varying anatomical distributions, clinical histories, and perhaps underlying pathogenetic mechanisms. The distal Symmetrical sensory polyneuropathy is chronic, symmetrical, length-dependent sensorimotor. Studies of the blink reflex have shown potential as a method of assessing brainstem activity.

Objective: The primary purpose of this research was to assess the function of the blink reflex in the early detection of cranial nerves and brain stem dysfunction in diabetes patients with and without polyneuropathy. We also aimed to see whether there were differences in blink reflex abnormalities between individuals with and without polyneuropathy.

Methods: The study included a group of sixty diabetic patients. Clinician and electrophysiologist evaluations were used to determine the severity of neuropathy. Patients with diabetes were separated into two groups: those with and without neuropathy.

Results: A statistically significant difference between the two groups was found for C.R.2 latency and I.R.2 latency with a P-value <0.001. Except for the blink reflex's R1 latency, all other blink reflex parameters were statistically different between patients who experienced diabetic neuropathy and those who didn't. Regarding HbA1c, a significant positive association with IR2 latency and C.R.2 latency was noted, and a statistically significant negative association was found with I.R.2 duration and C.R.2 duration. Amplitudes of sural, tibial, and peroneal nerves were negatively associated with blink reflex latencies and positively associated with blink reflex duration.

Conclusion: Blink-reflex parameters (including ipsilateral R.2 latency and contralateral R.2 latency) are significantly associated with HBA1C level and degree of peripheral diabetic neuropathy.

Keywords: Blink reflex; Diabetic; Distal Symmetrical Polyneuropathy.

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Introduction:

Similar to the Central nervous system (C.N.S), the peripheral nervous system (P.N.S) is made up of both neurons and supporting glia, more especially Schwann cells. There are 12 cranial nerves and 31 pairs of spinal nerves. Afferent sensory neurons transmit information from peripheral sensory receptors to the C.N.S, whereas efferent motor neurons transmit information from the C.N.S to glands and muscles (1).

Diabetes mellitus is a collection of metabolic diseases defined by hyperglycemia brought on by inadequate or resistant insulin (2). The most frequent consequence of T2DM is diabetic peripheral neuropathy (D.P.N) (3). A range of clinical and subclinical symptoms with different anatomical distributions, clinical histories, and perhaps underlying pathogenetic processes are described by the term "neuropathy." [4] The most prevalent kindof DPN is assumed to be distal symmetrical sensory polyneuropathy, which is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy (5). Electro diagnostic studies are important for the estimation of peripheral neuropathy, and nerves are compared bilaterally to determine if a significantasymmetry exists (6). Few electrophysiological researchers have previously focused on cranial nerves and the C.N.S., instead mostly focusing on limb nerve conduction velocity and F.wave (7).

Electrophysiological investigations, such as those of the blink reflex, have proven to be a useful tool for identifying cranial nerve subclinical involvement in generalized neuropathies. Clinical investigations have historically been the only means of evaluating brainstem function. However, a recent technological improvement has enabled the use of electro-physiologic methods to examine different brainstem pathways. Studies on the blink reflex have helped assess brainstem function (8).

Generalized polyneuropathy may generate bilateral blink-reflex abnormalities. Despite a considerable number of research documenting blink-reflex abnormalities in diabetes patients with polyneuropathy have appeared in the scientific literature, very few studies have explored the blink reflex alterations in diabetics without polyneuropathy (8).

In diabetes patients, the blink reflex has been utilized to assess the C.N.S. Surface or needle electrodes may be used to record reflex responses from the inferior parts of both orbicularis oculi muscles at the same time. The ophthalmic division of the trigeminal nerve mediates the reflex's afferent limb. The efferent limb is served by the facial nerve (9).

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Patients and Methods

This cross- sectional study is conducted at the neurophysiology unit in Ghazi Al-Hariri Hospital in Baghdad during the period from the first of November, 2021 to February, 2022, which included a total of 60 patients who attended the neurophysiology unit after a referral from the Neurology Department.

The study included on a group of sixty 60 type 2 diabetic patients: 12 females and 48 males. Both clinical and electrophysiological criteria were used to determine the severity of the neuropathy (5). Patients with diabetes were separated into two groups: those with and without diabetic neuropathy. Following standard protocol, we checked for muscle atrophy and weakening as well as deep tendon reflexes, sensitivity to touch, pinprick, and position, and tested vision and hearing. A tuning fork tuned to 128 hertz was used to assess how strong a vibration felt (10).

Diabetic neuropathy was seen in 35 patients; the other 25 patients did not have diabetic neuropathy.

Electrophysiological tests

Nerve conduction studies were done using a Dantec Natus electromyography device (KEYPOINT.NET Software v. 2.40). surface electrodes were used.

Blink reflex analysis was performed for them including latencies of (R.1, ipsilateral R.2, and contralateral R.2) and durations of (ipsilateral R.2 and contralateral R.2).

Nerve conduction studies of the limbs will be done for both upper and lower limbs including (Distal motor latency, Motor, and sensory conduction velocity, latency, and amplitude.

Statistical analysis

Shapiro-test and histogram were used to verify data distribution was normal. Depending on whether the distribution was normal or skewed, continuous variables were shown as means SD or medians with IQRs. Rates were used to describe categorical variables. Means were compared using the Welch two-sample t-test. The two-sample-t-test (2) or Fisher's exact test (F test) was used to analyze the significance of the gap between categorical variables. The correlation was calculated using Pearson's method. Statistical analysis and data management were carried out with the help of R and its accompanying statistical tools (R version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria).

Results:

The study included on a group of sixty 60 type 2 diabetic patients: 12 females and 48 males in the age range of 30–75 years (mean: 50 ± 10.2 years). The average duration of DM was 1–20 years (mean: 6.8 ± 4.2years)

The mean glycosylated hemoglobin value was 9.4 ± 2.3% (normal: 4.2–6.4).

Table 1 shows the clinical parameters of patients with and without diabetic neuropathy and the statistical significance between them. 34 out of 35 patients having neuropathy were males with a p-value of <0.001 difference with females.43% of cases with DN were smokers compared to 20% without DN. No difference was noticed regarding HbA1c between the two groups.

Table (1): Comparison of clinical data in those with and those without diabetic neuropathy (DN)

Characteristic	Without DN N = 25[1]	With DN N = 35[1]	*p*-value[2]
Age, years	50.0 ± 11.4	49.9 ± 9.5	>0.9
Gender			
Male	14 (56%)	34 (97%)	<0.001
Female	11 (44%)	1 (3%)	
Smoking	5 (20%)	15 (43%)	0.06
BMI, kg/m^2	26.8 ± 4.3	24.5 ± 3.6	0.03
T2DM duration, year	5.6 ± 4	7.6 ± 4.3	0.07
HbA1c	9.2 ± 1.9	9.5 ± 2.6	0.6

[1]Mean ± SD; n (%)
[2]Welch Two Sample t-test; Pearson's Chi-squared test; Fisher's exact test

Except for the blink reflex's R1 latency (*p*-value >0.2), all other Blink reflex parameters were statistically different between patients who experienced diabetic neuropathy and those who didn't (Table 2).

Table (2): Comparison of blink reflex parameters in those with and those without diabetic neuropathy (DN)

Characteristic	Without DN N = 25[1]	With DN N = 35[1]	p-value[2]
R1latencyRT, ms	11.7 ± 1.5	12.1 ± 1.7	0.3
IR2latencyRT, ms	37.9 ± 4.6	43.0 ± 4.4	<0.001
CR2latencyRT, ms	37.7 ± 5.0	42.9 ± 4.6	<0.001
IR2durationRT, ms	30.4 ± 9.4	22.6 ± 8.3	0.002
CR2durationRT, ms	31.6 ± 8.6	22.1 ± 7.8	<0.001
R1latencyLT, ms	11.7 ± 1.7	12.4 ± 2.0	0.2
IR2latencyLT, ms	39.4 ± 2.9	45.1 ± 6.0	<0.001
CR2latencyLT, ms	38.5 ± 4.4	44.4 ± 6.2	<0.001
IR2durationLT, ms	29.8 ± 6.6	21.2 ± 8.1	<0.001
CR2durationLT, ms	30.8 ± 6.5	21.6 ± 8.1	<0.001

[1] Mean ± SD; n (%)
[2] Welch Two Sample t-test
Abbreviations: IR2: Ipsilateral R2; CR2: Contralateral R2; BMI: Body Mass Index; HbA1c: Haemoglobin A1c

Correlations were analyzed between Sural, tibial and peroneal nerves amplitudes, duration of DM, and HbA1c levels and blink reflex parameters (Table 3). No statically significant correlation was found between the duration of diabetes mellitus and the blink reflex parameters. Regarding HbA1c, a significant positive association with IR2 latency and CR2 latency was noted (r = 0.3, P-value <0.001) and also, and a statistically significant negative association was found between IR2 duration and CR2 duration (*p*-value <0.001). Sural, tibial, and peroneal nerve amplitudes were negatively associated with Blink reflex Latencies and positively associated with

blink reflex duration. Except for R1 latency, all other blink reflex parameters were significantly correlated with lower limb nerve amplitudes.

Table (3): Correlation analysis of blink reflex with age, BMI, duration of DM, and HbA1C, and sural, Tibial, and peroneal nerve amplitudes.

		Age	Duration	HbA1c	Sural amp	Tibial amp	Peroneal amp
R1 latency	r[1]	0.2	0.01	0.1	- 0.2	-0.1	-0.04
	P-val[2]	0.02	0.9	0.3	0.1	0.2	0.7
IR2 latency	r[1]	0.3	0.5	0.3	- 0.3	-0.4	-0.4
	P-val[2]	<0.001	0.6	<0.001	0.02	<0.001	0.001
CR2 latency	r[1]	0.3	0.4	0.3	- 0.23	-0.4	-0.32
	P-val[2]	<0.001	0.7	<0.001	0.07	<0.001	0.01
IR2 duration	r[1]	0.03	-0.1	-0.3	0.3	0.27	0.4
	P-val[2]	0.6	0.2	<0.001	0.01	0.03	<0.001
CR2 duration	r[1]	- 0.01	- 0.2	-0.4	0.3	0.32	0.46
	P-val[2]	0.8	0.1	<0.001	0.009	0.01	<0.001

[1]Pearson's correlation coefficient
[2]Pearson's product-moment correlation

Discussion:

The purpose of this research was to examine the usefulness of the blink reflex in the early detection of cranial neuropathy in diabetes individuals with and without polyneuropathy, and its correlation with baseline characteristics of the patients. Blink reflex: The blink reflex waveform has two distinct parts, (R.1) and (R.2) (including I.R.2 and C.R.2). This study compared blink reflex parameters between diabetic patients who found they have neuropathy and those without neuropathy. The results showed that (R.1) latency did not show a significant difference between the diabetic patients with D.S.P.N and diabetic patients without D.S.P.N. These findings point to the possibility that exteroceptive, medium-thick myelinated A-beta fibers are responsible for the majority of (R.1) transmission, whereas nociceptive fibers are responsible for the majority of (R.2) (11).

Another observation of note there is a significant difference in (I.R.2), and (C.R.2) latencies between diabetics with and those without neuropathy this was agreed with Elkholy, et al. (2014) (12), it may be indicative of a more advanced stage of illness and widespread involvement of the peripheral and central nervous system. Individuals with generalized neuropathy have a greater risk of developing cranial nerve anomalies than diabetic patients without clinical PN, and this risk increases with the severity of the neuropathy (11). Pearson's correlation was used to explore the affecting factors of the blink reflex (including age, duration of diabetes, HbA1c, and DSPN) in patients with DM, and found that R2 latency and R2 duration was predictive factors for blink reflex abnormalities. The present study found that age is positively correlated with IR2 latency, and CR2 latency, in other words, increased age, the more abnormal the blink reflex this may be attributed to increasing age; in particular, complex reflexes tend to have longer delays (13).

Another observation of note is that the duration of DM is not related to blink reflex latency. These findings were inconsistent with those reported by Elkholy et al, (12), and those reported by Kazem and Behzad, (2006) (14), who found that the correlation was higher for R1 latency. Diabetes-related neuropathy slows neural transmission and reduces the size of nerve and complex muscle action potentials (11), so this study compared blink reflex parameters with the amplitudes of lower limb nerves and found that sural, peroneal, and tibial nerve amplitudes were negatively associated with the blink reflex latencies (including ipsilateral R.2 latency, and contralateral R.2 latency), and positively with (I.R.2 duration, and C.R.2 duration), in other words, When the amplitude of the blink reflex is low, it is abnormal. To detect polyneuropathy in its earliest stages, doctors go to the dorsal sural nerve. Symptoms of early or subclinical peripheral neuropathy may first be felt in the dorsal sural nerve, the most distant sensory nerve of the foot (15). It, therefore, is believed diabetes patients with widespread neuropathy are more likely to acquire cranial nerve problems than diabetic patients without nerve conduction abnormalities, and that severe global sensory and motor peripheral nerve involvement may be a sign for early cranial nerve involvement. Moreover, R.2 durations (including ipsilateral R.2 and contralateral R.2 durations) of patients with DSPN were shorter than those without D.S.P.N and this agreed with Xiao et al, (7). Who discovered that patients with D.S.P.N. had shorter R2 durations than normal subjects or diabetic patients without D.S.P.N. This discrepancy may be due to the fact that the reflex arc of R.2 is connected to intermediate neurons of the reticular structure via a multi-synaptic-connections that is susceptible to factors like thalamic and brain lesions and

psychological state (16). There was also a reduction in the number of interneurons connected to multisynaptic reflex activity and excitability, as seen by the shorter durations of ipsilateral R.2 and contralateral R.2. This means that in T.2.D.M. patients, not only does the latency of the blink reflex but also the length of R.2 reflect the degree of lesions in the brainstem, thalamus, and brain (7).

Conclusions: Blink reflex components (including ipsilateral R.2, contralateral R.2 latencies and durations) are significantly associated with HBA1C level and degree of peripheral diabetic neuropathy.

Authors Declarations:
We hereby confirm that all the figures and tables in the manuscript are ours. Those which are not, have been permitted for re-publication (attached with the manuscript). The authors have signed an ethical consideration approval-Ethical Clearance: The local ethical committee had approved the projecting of the Autism Center, Ghazi Al-Hariri Surgical Specialties Hospital Teaching, Baghdad. According to the code number (44360) on 10.10.2021.
Conflicts of Interest: None.

Author Contributions:
Study conception & design: (Sulaf E. Izzat & Ghassan Th. Saeed). Literature search: (Sulaf E. Izzat) name). Data acquisition: (Sulaf E. Izzat). Data analysis & interpretation: (Sulaf E. Izzat & Ghassan Th. Saeed)). Manuscript preparation: (Sulaf E. Izzat). Manuscript editing & review: (Sulaf E. Izzat & Ghassan Th. Saeed)).

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أهمية منعكس الطرفة كعلامة فسيولوجية عصبية لاعتلال الاعصاب المحيطية السكري

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الخلاصة:
خلفية البحث: اعتلال الأعصاب المحيطية السكري (DPN) هو أكثر المضاعفات انتشارًا لـ T2DM. الاعتلال العصبي هو واصف لمجموعة من الأعراض السريرية ودون السريرية مع توزيعات تشريحية مختلفة ، وتاريخ سريري ، وربما آليات مسببة للأمراض الكامنة. اعتلال الأعصاب الحسي المتماثل البعيدة هو حسي مزمن متماثل يعتمد على الطول. أثبتت دراسات انعكاس الطرفة أنها مفيدة لتقييم وظيفة جذع الدماغ.
الاهداف : الهدف الأول من هذه الدراسة هو تقييم دور منعكس الوميض للتشخيص المبكر لاعتلال الأعصاب القحفية لدى مرضى السكري المصابين أو غير المصابين باعتلال الأعصاب المتعدد. كان من اهتمامنا أيضًا التحقيق في مقارنة التغيرات الانعكاسية الطرفة في مرضى السكري الذين يعانون من اعتلال الأعصاب المتعدد والذين لا يعانون منه.
المرضى وطرق العمل/ المواد وطرق العمل: اشتملت الدراسة على مجموعة من 60 مريضًا بالسكري تم تقييم الاعتلال العصبي من خلال مجموعة من المعايير السريرية والكهربية. تم تقسيم مرضى السكري إلى مجموعتين حسب الإصابة باعتلال الأعصاب السكري من عدمه.
الاستنتاجات: كان هناك فرق ذو دلالة إحصائية بين الحالات والمجموعة الضابطة من أجل زمن انتقال C.R.2 ، ووقت استجابة I.R.2 بقيمة P <0.001. باستثناء زمن استجابة R1 الخاص ببرنامج blink reflex (قيمة P> 0.2) ، كانت جميع معلمات انعكاس Blink الأخرى مختلفة إحصائيًا بين المرضى الذين يعانون من اعتلال الأعصاب السكري وأولئك الذين لم يعانوا من ذلك. فيما يتعلق بـ HbA1c ، لوحظ وجود ارتباط إيجابي مهم مع زمن انتقال IR2 وزمن استجابة C.R.2 (قيمة P <0.001) وأيضًا ، تم العثور على ارتباط سلبي ذي دلالة إحصائية مع مدة I.R.2 ومدة C.R.2 (قيمة P <0.001). ارتبطت اتساع الأعصاب السمعية والظنبوبية والشظوية سلبًا مع اختفاء انعكاس الطرفة وارتبطت بشكل إيجابي بمدة انعكاس الوميض.
مفتاح الكلمات: منعكس وميض ,مريض بداء السكري، اعتلال الاعصاب المحيطيه