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ASSESSMENT OF NERVE CONDUCTION STUDY AND ELECTROENCEPHALOGRAM ABNORMALITIES IN TYPE 2 DIABETES MELLITUS

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Abstract

Background and aims: *This study aims to evaluate the electroencephalographic and nerve conduction changes in type 2 diabetes mellitus (T2DM) patients with and without peripheral neuropathy (DPN) and to investigate the relationship with other variables such as age, gender, duration of the diabetes and the degree of metabolic control.* ***Materials and methods:*** *This was a cross- sectional study, including 100 patients with T2DM and 100 control subjects, aged 34 to 77 years. All patients enrolled in the study were subjected to full assessment, including: history, biochemical and electrophysiological tests.* ***Results****: The study found that patients with diabetic peripheral neuropathy (DPN) in comparison to patients without DPN and control subjects were older, had longer duration of diabetes and poorer glycemic control reflected by fasting blood glucose and glycated hemoglobin. The electrophysiological findings showed that patients with DPN have significant differences in nerve conduction study (NCS) parameters when compared to patients without DPN and control subjects in the form of axonal degeneration and demyelination. They also had abnormalities of the electroencephalogram (EEG) which are correlated with nerve conduction study severity.* ***Conclusion:*** *Routine NCS is an important method for evaluating DPN. Investigating sensory nerves of lower limbs is helpful in discovering the early stages of DPN when other tested nerves are normal. The F-wave can be used as a sensitive indicator for the early diagnosis of DPN and it can help to detect the subclinical lesions. EEG examination in diabetic patients with severe DPN is important in showing the defect in the central nervous system.*

key words: *Electroencephalography, Diabetes mellitus, Nerve conduction study*

Introduction

Diabetes Mellitus (DM) is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [1]. Patients with long standing diabetes are at risk for developing various complications. There are two types of diabetic complications – microvascular and macrovascular. Microvascular complications include nephropathy, retinopathy, neuropathy and diabetic foot [2], while macrovascular

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complications include cerebrovascular, peripheral vascular and cardiovascular diseases [3].

Diabetic neuropathy is a descriptive term that encompasses a spectrum of clinical and subclinical syndromes with different anatomical distributions, clinical courses, and possibly, different underlying pathogenic mechanisms [4]. It is the most common microvascular complication of DM with a prevalence rate reaching 45–50% [5]. Diabetic peripheral neuropathy (DPN) is by far the most common type of diabetic neuropathy. In clinical practice, diabetic peripheral neuropathy is synonymous with diabetic neuropathy [6]. Hyperglycemia is clearly playing a key role in the development and progression of diabetic neuropathy as well as of the other microvascular complications of diabetes [7].

Clinically, DPN affects first the most distal extremities, resulting in a stock and glove pattern of sensory loss [8]. DPN affects both small fibers (myelinated and un-myelinated), as well as the large myelinated nerve fibers. However, the earliest manifestations might be due to the small-fiber involvement [9]. DPN can be diagnosed by a variety of methods with different sensitivity and specificity. The initial step in the diagnosis is a detailed history and careful clinical examination focusing on signs and symptoms in the distal parts of the limbs where disease usually begins [10].

Diabetes mellitus also leads to functional and structural changes in the brain which affect learning and hippocampal synaptic plasticity [11]. Specialized neurons within the hypothalamus have the ability to sense and respond to changes in ambient glucose concentrations. Sodium-coupled glucose co-transporters (SGLTs) have a novel role for glucose sensing by hypothalamic glucose-excited neurons [12]. Glucokinase, which is selectively expressed in brain regions containing glucose sensing neurons [13], acts as the glucose sensor in hypothalamic neurons, converting the glucose signal to changes in adenosin triphosphate (ATP) concentration and thereby setting the level of K_{ATP} channel activity [14]. DM impairs glucose homeostasis in the brain, hyperglycemia being considered the key factor responsible for the elevated oxidative damage leading to brain dysfunction in diabetes and causing neurological disorders due to perturbation in utilization of glucose [15].

Materials and method

The study was conducted in the Neurophysiology and Diabetes Unit of Merjan Medical City in Al-Hilla Governorate during the period from October 2014 till June 2015. One hundred type 2 diabetes (T2DM) patients (34 males and 66 females) selected randomly were included as the patients` group. They were selected according to the presence of complaints such as pain, paresthesia and/or a sense of weakness at their extremities, especially lower limbs. Their age ranged from 34 to 77 years. Additionally we included as control group 100 normal healthy adults 34 to 70 years old**.** All the patients with T2DM had negative past medical history, and at least a symptom of DPN. All that accepted to participate in the study undergone the same clinical, biochemical and electrophysiological assessments in Marjan Teaching Hospital during the time of study.

Data collection tools

A specially designed data sheet was used in this study, that contained: a) questionnaires, b) anthropometric measurements (weight, height, Body Mass Index (BMI), c) biochemical investigations (HbA1c and fasting blood glucose - FBG), and d) electrophysiological assessments.

a-Questionnaires:.A complete medical history was taken for each patient and control

subject, including name, age, gender, occupation, address, duration of DM, type of treatment of DM, smoking history, hypertension, symptoms (pain, paresthesia and/or a sense of weakness at their extremities, especially lower limbs).

b-Measurements: Height (in centimeters) was measured using a listed stripe and weight (in kilograms) was measured using a digital balance. BMI was calculated using the formula weight (kg) /height^2(m)^2 [16].

c-Biochemical investigations: Blood samples were collected from healthy controls and diabetic patients in the morning between 08:00 and 10:00 am to minimize the effect of diurnal variation [17], after a period of 8 – 10 hours fasting by vein puncture using 5 ml disposable syringes. Fasting blood glucose (FBG) and HbA1c were measured and diabetes diagnosed according to the American Diabetes Association criteria [1].

Electrophysiological assessment

Nicolet® nerve conduction study (NCS) machine was used for electrophysiological testing. Nerve conduction studies included the distal sensory latency (DSL), sensory conduction velocity (SCV) and sensory amplitude (Amp), measured for the median, ulnar and sural nerves, as well as distal motor latency (DML), motor conduction velocity (MCV), motor amplitude (Amp) measured for median, ulnar and tibial nerves. All measurements were performed both in T2DM patients and the control group.

F-wave study

The only difference of F-wave from the NCS is that of placing the stimulating electrodes, instead of the anode. Square pulses of 0.1 msec duration, at a frequency of 1 stimulus/sec, and negative polarity are used. The stimulus intensity is increased gradually to arrive at the supra-maximal level, that is 50% higher than the current producing the maximal direct muscle response.

EEG machine

The Nicolet One® EEG was used in this study given its functional sophistication and flexibility in a 21 channel clinical EEG system. The Nicolet One amplifier is attached with a thin, durable, fiber-optic interface impervious to electrical, radio and magnetic interference.

EEG montage

a-Monopolar Technique: the use of one active recording electrode placed on the area of interest, a reference electrode in an inactive area, and a ground

b- Bipolar Technique: the use of two active electrodes on areas of interest.

Results

There was no significant association between DPN and patients` medical history as shown in Table 1.

The distribution of patients by diabetes mellitus- related factors shows that 58.0% of patients are on insulin and 66.0% have DM for less than ten years, respectively. The overall mean HbA1c was 8.83±2.51%, with 85.0% of patients having HbA1c > 6.4%. The overall mean FBG was 10.44±3.74 mmol/l, with 83.0% of patients having FBG > 7.0 mmol/l, as shown in Table 2.

There was a significant association between DPN and the type of treatment, duration of DM, HbA1c, and FBG as shown in Table 3.

There were significant differences regarding the mean median nerve motor latency, amplitude, and conduction velocity, median sensory latency, amplitude, and conduction velocity between DM patients and controls, as shown in Table 4.

Table 1. The association of peripheral neuropathy with patients` medical history.

Variable	DPN		χ^2	*P* values
	Present	Absent		
Smoking habit Smokers - N (%) Non-Smokers - N (%)	 8 (11.3) 63 (88.7)	 2 (6.9) 27 (93.1)	0.437	0.509
Hypertension Yes - N (%) No - N (%)	 33 (46.5) 38 (53.5)	 10 (34.5) 19 (65.5)	1.209	0.273
BMI Normal weight (18.5-24.9 kg/m^2) - N (%) Overweight (25-29.9 kg/m^2) - N (%) Obese (≥ 30 kg/m^2) - N (%)	 16 (22.5) 23 (32.4) 32 (45.1)	 9 (31.0) 12 (41.4) 8 (27.6)	2.643	0.267

Table 2. The distribution of patients by diabetes mellitus- related factors.

Variables	Frequency (%)
Type of treatment Insulin OHD Total	 58 (58.0%) 42 (42.0%) 100 (100.0%)
Duration of DM < 10 years ≥ 10 years Total	 66 (66.0%) 34 (34.0%) 100 (100.0%)
Hemoglobin A1c Normal (< 5.7%) Pre-DM (5.7-6.4%) DM (> 6.4%) Total	 12 (12.0%) 3 (3.0%) 85 (85.0%) 100 (100.0%)
Fasting Blood Glucose Normal (< 5.5 mmol/l) Pre-DM (5.5-7 mmol/l) DM (> 7 mmol/l) Total	 9 (9.0%) 8 (8.0%) 83 (83.0%) 100 (100.0%)

OHD=Oral Hypoglycemic Drug DM= Diabetes Mellitus

Table 3. The association of peripheral neuropathy with diabetes mellitus- related factors.

Variables	DPN		χ^2	*P* values
	Present (%)	Absent (%)		
Type of treatment Insulin OHA	 47 (66.2) 24 (33.8)	 11 (37.9) 18 (62.1)	6.753	0.009*
Duration of DM < 10 years ≥ 10 years	 42 (59.2) 29 (40.8)	 24 (82.8) 5 (17.2)	5.112	0.024*
Hemoglobin A1c Normal (< 5.7%) Pre-DM (5.7-6.4%) DM (> 6.4%)	 1 (1.4) 2 (2.8) 68 (95.8)	 11 (37.9) 1 (3.4) 17 (58.6)	26.259	<0.001**
Fasting Blood Glucose Normal (< 5.5 mmol/l) Pre-DM (5.5-7 mmol/l) DM (> 7 mmol/l)	 2 (2.8) 3 (4.2) 66 (93.0)	 7 (24.2) 5 (17.2) 17 (58.6)	17.685	<0.001**

OHD=oral hypoglycemic drug; DM-Diabetes Mellitus; * significant; ** highly significant

Table 4. Mean differences of median nerve parameters by study groups.

Median nerve parameters	Mean ±SD		t-test	p value
	Patients	Control		
Motor Lat (ms)	2.70±1.16	2.05±0.90	4.444	<0.001**
Motor amp (mv)	8.01±6.38	7.38±1.35	0.975	0.331
Motor CV (m/sec)	51.42±7.60	60.81±4.38	10.693	<0.001**
Sensory Lat (ms)	2.50±0.60	2.08±2.52	1.639	0.103
Sensory amp (µv)	21.51±17.34	41.38±7.64	10.481	<0.001**
Sensory CV (m/sec)	50.18±8.82	56.52±5.45	6.105	<0.001**

La t= latency; amp = amplitude; CV = conduction velocity; **highly significant

Table 5. Mean differences of ulnar nerve parameters by study groups.

Ulnar nerve parameters	Mean ±SD		t-test	p value
	Patients	Control		
Motor Lat (ms)	2.70±1.16	2.05±0.90	4.444	<0.001**
Motor amp (mv)	8.01±6.38	7.38±1.35	0.975	0.331
Motor CV (m/sec)	51.42±7.60	60.81±4.38	10.693	<0.001**
Sensory Lat (ms)	2.50±0.60	2.08±2.52	1.639	0.103
Sensory amp (µv)	21.51±17.34	41.38±7.64	10.481	<0.001**
Sensory CV (m/sec)	50.18±8.82	56.52±5.45	6.105	<0.001**

Lat=latency; Amp=Amplitude; CV=Conduction Velocity; ** highly significant

Table 6. Mean differences of tibial, peroneal and sural nerve parameters by study groups.

Nerve parameters	Mean ±SD		t-test	p value
	Patients	Control		
Tibial Lat(ms)	4.96±1.44	3.33±0.36	10.884	<0.001**
Tibial amp (mv)	5.80±4.34	12.23±2.98	12.196	<0.001**
Tibial CV(m/sec)	36.28±10.24	51.67±5.56	12.699	<0.001**
Peroneal Lat (ms)	4.67±1.55	2.63±0.42	13.199	<0.001**
Peroneal amp (mv)	3.79±4.98	4.51±1.42	12.699	<0.001**
Peroneal CV (m/sec)	36.46±11.09	48.34±3.63	10.176	<0.001**
Sural Lat (ms)	3.09±0.76	1.69±0.25	17.163	<0.001**
Sural amp (µv)	7.58±8.08	18.81±6.32	10.934	<0.001**
Sural CV (m/sec)	29.88±17.00	52.57±6.57	12.445	<0.001**

Lat = latency, Amp=Amplitude, CV = Conduction Velocity; ** highly significant

There were significant differences regarding ulnar motor latency, amplitude and conduction velocity, ulnar sensory latency amplitude and conduction velocity between DM patients and controls, as shown in Table 5.

There were significant differences in the means of tibial latency, amplitude and conduction velocity, peroneal latency, amplitude and conduction velocity and sural latency, amplitude and conduction velocity between DM patients and controls as shown in Table 6.

There were significant differences regarding the mean of median motor conduction velocity, sensory latency, sensory amplitude and sensory conduction velocity according to the presence of DPN as shown in Table 7.

Table 7. Mean differences of median nerve parameters according to DPN.

Median nerve parameters	Mean ±SD		t-test	p value
	(+) DPN	(-) DPN		
Motor Lat (ms)	3.98±1.17	3.47±1.49	1.813	0.073
Motor amp (mv)	7.98±3.09	8.33±2.04	0.561	0.576
Motor CV (m/sec)	46.34±5.76	52.94±4.59	5.489	<0.001**
Sensory Lat (ms)	3.27±0.95	2.53±0.62	3.845	<0.001**
Sensory amp (µv)	15.10±14.38	27.65±12.56	4.103	<0.001**
Sensory CV (m/sec)	40.54±10.64	49.52±7.14	4.165	<0.001**

DPN = Diabetic Peripheral Neuropathy, Lat = latency, amp = Amplitude, CV = Conduction Velocity; ***** significant

Table 8. Mean differences of ulnar nerves parameters according to DPN.

Ulnar nerve parameters	Mean ±SD		t-test	p value
	(+) DPN	(-) DPN		
Motor lat(ms)	2.93±1.31	2.07±0.80	5.731	0.001**
Motor amp(mv)	7.61±6.70	7.74±2.91	-0.19	0.849
Motor CV(m/sec)	49.46±7.70	59.77±4.83	-11.60	0.001**
Sensory lat(ms)	2.66±0.63	2.08±2.22	2.14	0.033
Sensory amp(µv)	19.40±17.30	38.06±11.99	-8.95	0.001**
Sensory CV(m/sec)	48.49±8.60	56.05±6.09	-7.23	0.001**

DPN = Diabetic Peripheral Neuropathy, Lat = latency, amp = Amplitude, CV = Conduction Velocity; ****** highly significant

Table 9. Mean differences of tibial, peroneal and sural nerves by peripheral neuropathy.

Nerve parameters	Mean ±SD		t-test	p value
	(+) DPN	(-) DPN		
Tibial Lat (ms)	5.14±1.57	3.60±0.75	9.26	0.001**
Tibial Amp (mv)	4.23±3.14	11.64±3.53	-14.73	0.001**
Tibial CV (m/sec)	32.87±9.57	50.08±6.43	-15.14	0.001**
Peroneal Lat (ms)	4.80±1.32	3.02±1.23	-9.32	0.001**
Peroneal Amp (mv)	2.93±3.71	4.83±3.49	-3.59	0.001**
Peroneal CV (m/sec)	33.03±11.09	47.55±4.22	-13.24	0.001**
Sural Lat (ms)	3.42±0.77	1.87±0.42	17.23	0.001**
Sural Amp (µv)	4.42±4.52	18.02±7.30	-14.24	0.001**
Sural CV (m/sec)	23.19±15.69	51.15±6.60	-17.61	0.001**

DPN = Diabetic Peripheral Neuropathy, Lat = latency, Amp = Amplitude, CV = Conduction Velocity; ****** highly significant

For ulnar nerve, there were significant mean differences of ulnar motor latency, conduction velocity, ulnar sensory amplitude, conduction velocity according to the presence of DPN as shown in Table 8.

The mean differences of tibial, peroneal and sural nerves NCS according to the presence of DPN are shown in Table 9.

There were significant mean differences of F- waves for median, ulnar, tibial and peroneal nerves between DM patients and controls as shown in Table 10.

Table 10. Mean differences of F waves nerves by study groups.

F wave latency	Mean ±SD		t-test	p value
	Patients	Control		
Median nerve (ms)	28.80±4.59	22.63±0.99	13.149	<0.001**
Ulnar nerve (ms)	28.30±5.43	23.57±1.24	8.478	<0.001**
Peroneal nerve (ms)	54.11±8.41	43.43±2.61	12.127	<0.001**
Tibial nerve (ms)	57.64±9.17	45.75±1.63	12.764	<0.001**

DPN = Diabetic Peripheral Neuropathy; ****** highly significant

Table 11. Mean differences of F waves according to DPN presence.

F wave latency	Mean ±SD		t-test	p value
	(+) DPN	(-) DPN		
Median nerve(ms)	28.80±4.59	22.63±0.99	12.56	0.001**
Ulnar nerve(ms)	22.30±5.43	23.57±1.24	11.50	0.001**
Peroneal nerve(ms)	54.11±8.41	43.34±2.61	17.47	0.001**
Tibial nerve(ms)	57.64±9.17	45.75±1.63	22.85	0.001**

DPN=Diabetic Peripheral Neuropathy; ******highly significant

Table 12. The association between EEG results and patients' age and gender.

Variable	EEG Finding		χ^2	*P* values
	normal (%)	abnormal (%)		
Age group < 50 years ≥ 50 years	 32 (38.1) 52 (61.9)	 1 (6.4) 15 (93.6)	6.165	0.013*
Gender Male Female	 24 (28.6) 60 (71.4)	 10 (62.5) 6 (37.5)	6.895	0.009*

***** significant

Table 13. The association of EEG findings with diabetes mellitus - related factors.

Variables	EEG Findings		χ^2	*P* values
	normal (%)	abnormal (%)		
Type of treatment Insulin OHD	 42 (50.0) 42 (50.0)	 16 (100.0) 0 (0.0)	13.793	<0.001**
Duration of DM < 10 years ≥ 10 years	 62 (73.8) 22 (26.2)	 4 (25.0) 12 (75.0)	14.369	<0.001**
Hemoglobin A1c Normal (< 5.7%) Pre-DM (5.7-6.4%) DM (> 6.4%)	 12 (14.3) 3 (3.6) 69 (82.1)	 0 (0.0) 0 (0.0) 16 (100.0)	2.596	0.258
Fasting Blood Glucose Normal (< 5.5 mmol/l) Pre-DM (5.5-7 mmol/l) DM (> 7 mmol/l)	 9 (10.7) 8 (9.5) 67 (79.8)	 0 (0.0) 0 (0.0) 16 (100.0)	2.766	0.246

EEG = Electroencephalogram, OHD = Oral Hypoglycemic Drug, DM = Diabetes Mellitus; ******highly significant

There were significant mean differences of F- waves according to DPN presence as shown in Table 11.

The association of EEG findings with patients' age and gender are shown in Table 12.

The association of EEG findings with diabetes mellitus - related factors are shown in Table 13.

Discussion

In our study hypertension did not have any association with the presence of diabetic neuropathy. This is consistent with data of another study [18] that found there is no association between DPN and blood pressure. In this study, smoking was also not related to the prevalence of DPN ($P > 0.05$), although data from some studies suggest a positive relationship between cigarette smoking and DPN [19]. This lack of association may reflect a pattern of survival. Those who smoked may have died of a smoking-related illness, including cardiovascular disease, neoplasia and other causes of death before having had the opportunity to develop DPN. Smoking narrows and hardens the arteries, reducing blood flow to the legs and feet. This makes it more difficult for wounds to heal and damages the integrity of the peripheral nerves [20].

We observed that the prevalence of DPN is higher in obese diabetics than in those with a normal BMI, but not statistically significant. This is corroborated with the finding of Akbar et al. [18]. The association could be explained by abdominal obesity, thick subcutaneous adipose tissue, low muscle mass, insulin resistance, and hyperinsulinemia.

This study showed there is a significant association between PNP and the duration of diabetes which is in agreement with the data of Ghosal et al. [21], explaining why patients with advanced DPN have longer duration of diabetes compared to those with milder forms, and that those patients that develop diabetic foot who has severe neuropathy and vascular disease have longer duration of diabetes compared to those that do not.

We demonstrated that there is a significant association between DPN and the type of treatment: DPN is more frequent in patients treated with insulin than in non-insulin treated patients, as in previous studies [18]. A higher prevalence of DPN among insulin-treated patients could be attributable to their longer duration of diabetes, delay in insulin treatment and possible insulin neuritis at the time of neurologic examination.

As expected, patients with DPN had significantly higher HbA1c which is in agreement with previously published data [22,23]. Similarly, there was a significant difference between FBG levels between patients with and without DPN, as previously demonstrated [24]. It's assumed that chronic hyperglycemia represents the main causative factor involved in the pathogenesis of diabetic neuropathy. Nerve damage may be directly induced by the accumulation of intracellular glucose with its consequences like the generation of advanced glycation end-products (AGEs), enhanced oxidative damage or protein kinase C activation [25].

Sensory nerve conduction studies indicated significant differences between DM patients and controls and between patients with and without DPN. The explanation of this finding is that sensory nerves have a smaller diameter than motor nerves and travel for longer distances in the body than motor nerves, being exposed more to the injurious effects of diabetes [26]. This mechanism was described also in other studies [22,27].

Motor nerve conduction study that we performed in patients with and without DPN and

control subjects showed significant differences between these groups regarding the median motor conduction velocity, tibial latency, amplitude, conduction velocity, peroneal latency, amplitude, and conduction velocity. Motor nerves are large myelinated fast conducting fibers that are affected by hyperglycemia and subsequent metabolic and neurovascular derangement in diabetes. This study is in consistence with other ones [22,27,28] in which motor nerve involvement is one of the important electrophysiological manifestation of DPN.

In this study, the results of F waves were significantly different for the median, ulnar, tibial and peroneal nerves in patients with DPN in comparison with those without DPN. This is in agreement with the results of Wang et al. [29].

Elderly patients with insulin treated T2DM (10 male and 6 female) and severe DPN have been reported to have a slowing of the EEG activity over the central cortex and a reduction in alpha activity over the parietal area, compared with the control group, and also a reduced activity in the beta band has been reported in this group with diabetes. Elderly patients with T2DM demonstrate decreased beta activity over posterior regions of the brain as shown also by Coorey et al [30]. In our study, a total of 22.5% of DM patients with DPN had abnormal EEG. The impairment of glucose homeostasis in the brain is the key factor responsible for the elevated oxidative damage leading to brain dysfunction in diabetes and causing neurological disorders due to perturbation in utilization of glucose [30].

Conclusion

This study shows that investigating sensory nerves of lower limbs is helpful in discovering early stages of DPN before the appearance of the first symptoms. F-wave can be used as a sensitive indicator for the early diagnosis of DPN and it could be used to detect subclinical lesions. EEG changes in diabetic patients consist of diffuse slowing of the background activity and highlights the defect in the central nervous system.

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