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Prevalence of and risk factors for cranial neuropathy in diabetic and non-diabetic patients

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Abstract. – OBJECTIVE: Diabetes mellitus (DM) is a major global health concern and is associated with high morbidity and mortality as well as poor quality of life. This health burden is mostly due to complications associated with DM. Cranial nerve neuropathy is not a well-studied complication of DM. In this study, we aimed to study the prevalence and risk factors for the development of cranial neuropathy in diabetic patients.

PATIENTS AND METHODS: This is a cross-sectional study among diabetics who are attending Almanhal Primary Healthcare Center, Abha, Aseer Province, Saudi Arabia. A total of 714 subjects were included, 238 of them were in the study group and 476 were controls chosen randomly from the same community. SPSS program was used to calculate demographic, clinical, and biochemical parameters as well as to measure the statistically significant differences. Analysis was conducted using the SPSS statistical package and *p*-value lower than or equal to 0.05 was considered statistically significant.

RESULTS: The diabetic patients were significantly older than the control group; the mean standard deviation (SD) age was 59.78 (8.26), and 34.04 (9.45) for both study and control groups, respectively. The prevalence of cranial neuropathy was higher in diabetic patients. Among diabetic patients, hyperlipidemia, gestational DM, compliance with DM treatment, and the presence of microvascular complications of DM are significant risk factors for the development of cranial neuropathy.

CONCLUSIONS: Our results indicate that the prevalence of cranial neuropathy is higher in the diabetic population than in the non-diabetic population. The oculomotor and trigeminal nerves were the most commonly affected nerves in diabetic patients compared to the abducent and facial nerves in non-diabetic patients.

Key Words:
Diabetes mellitus, Prevalence, Saudi Arabia, Cranial neuropathy.

Introduction

Diabetes mellitus (DM) is a common disease that affects millions of patients globally. The incidence of DM varies from one country to the other based on population genetics, exposure to the risk factors, and healthcare to the affected patients[1]. In Saudi Arabia, DM prevalence has been estimated to be the second highest among other Middle Eastern countries. Estimates[2] also indicate a rising incidence of DM in Saudi Arabia and other global communities. Complications related to DM have been extensively reported in the literature. These complications include micro-and macrovascular events that can significantly impact the affected patient's health and quality of life[3]. Peripheral neuropathy is a microvascular complication of DM that is common among diabetic patients, with a prevalence of up to 60% and is well studied[4,5]. Cranial neuropathy, though is another microvascular event, is rare in diabetics and is not well explored. Despite extensive studies[6,7] on the epidemiology of diabetic neuropathy in general, there is a relative scarcity of knowledge regarding factors associated with cranial neuropathy in diabetic patients. Cranial neuropathy in diabetic patients is more frequently seen in older individuals with a long duration of diabetes[5]. A previous study[9] among Saudi diabetic patients found VI and III cranial nerves to be the

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most frequently affected cranial nerves[8]. Other risk factors are chronic diabetes micro and macroangiopathies namely: retinopathy, nephropathy, neuropathy, and major vessel diseases.

We aim to estimate the prevalence of and risk factors for cranial neuropathy among diabetics and compare these to a non-diabetic control group in Saudi Arabia.

Patients and Methods

This is a cross-sectional study on the prevalence of and risk factors for cranial neuropathy in diabetic patients in comparison to a non-diabetic control group. The study subjects were chosen randomly from diabetic patients who are attending Almanhal Primary Healthcare Center, Abha, Aseer Province, Saudi Arabia. The control non-diabetic group was randomly selected from the same community. The data was collected by a purposely constructed questionnaire. The collected data included demographic items, physical and smoking habits, medical comorbidities, medication use, detailed information on DM, detailed information on cranial neuropathy incidents and patterns, and stroke incidents. The questionnaire was filled out *via* telephone interviews from diabetic patients and *via* social media applications from the non-diabetic control group through an electronic version of the questionnaire. A total of 714 participants were included, 238 of them were in the study group and 476 were controls.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS version 22, IBM. Corp., Armonk, NY, USA) program was used to calculate demographic, clinical, and biochemical parameters as well as to measure the statistically significant differences.

The two study groups were compared for the presence of cranial neuropathy and its risk factors. We applied Student's *t*-test and Chi-square test to measure the significance of differences between groups and regression analysis to measure the significance of risk factors associated with the development of cranial neuropathy. The level of significance was set at *p*-value lower than 0.05.

Results

Sociodemographic Characteristics

A total of 714 respondents were included in the analysis; 238 were in the diabetic group and 476 were in the non-diabetic group. Among diabetic patients, 97.5% were type II, while 2.5% were type I. Macrovascular complications of DM were present in 8%, while microvascular complications of DM were present in 30% of the diabetic cohort. Among diabetic women, 13% had gestational DM, and 30.8% of the cohort had HBA1C results of >8.0.

The diabetic cohort was significantly (p<0.0001) older with a mean (SD) age of 59.78 (8.26), compared to 34.04 (9.45) in the non-diabetic reference group. In addition, the diabetic group had significantly more males and was substantially physically active (more than 4 hours of exercise per week) in comparison to the reference group (p<0.0001 for each) (Table I). Furthermore, the diabetic group significantly had more non-

Table I. Demographic differences between diabetic and non-diabetic groups.

Variable		Diabetic (N = 238)		Non-diabetic (N = 476)		
		N	%	N	%	p
Age	MEAN (SD)	59.78 (8.26)		34.04 (9.45)		< 0.0001
Gender	Male	139	58.8	169	35.5	< 0.0001
	Female	99	41.2	307	64.5	
Physically active	Yes	41	17.2	30	6.3	< 0.0001
	No	197	82.8	446	93.7	
Smoking	Yes	18	7.6	81	17.0	< 0.005
	No	220	92.4	395	83.0	
Other comorbidities	Yes	184	77.3	43	9.03	< 0.0001
	No	54	22.7	433	90.97	
Hyperlipidemia	Yes	143	60.1	11	2.3	< 0.0001
	No	41	39.9	465	97.7	
Hypertension	Yes	135	56.7	15	3.2	< 0.0001
	No	50	43.3	461	96.8	

SD: standard deviation.

DM medical comorbidities, hyperlipidemia, and hypertension than the reference group ($p<0.0001$ for each) (Table I). Smoking, on the other hand, was significantly less common among diabetic patients compared to non-diabetics ($p=0.005$) (Table I).

Prevalence and Risk Factors of Cranial Neuropathy

Cranial neuropathy was significantly ($p=0.0091$) more prevalent in diabetic patients compared to non-diabetic control subjects (2.1% *vs.* 0.21%, respectively) (Table II).

Regression analysis was performed to find out the risk factors for cranial neuropathy (Table III). None of the demographic factors, body max index (BMI), physical activity level, or smoking was associated with the risk of cranial neuropathy development in either group. In the control group presence of non-DM medical comorbidities ($p=0.001$), hyperlipidemia ($p=0.0001$), and hypertension (p-value=0.0001) appeared as risk factors for the development of cranial neuropathy. Among diabetic patients, hyperlipidemia, gestational DM, compliance with DM treatment, and the presence of microvascular complications of DM were found to be significant risk factors for the development of cranial neuropathy ($p=0.01$, 0.002, 0.034, 0.001, respectively) (Table III).

Patterns of Cranial Neuropathy

Table IV shows the patterns of cranial neuropathy among diabetics. The oculomotor and trigeminal nerves were the sole and equally involved. One patient had a bilateral oculomotor nerve, and another had both oculomotor and trigeminal nerve involvement. The left side was involved in all patients for each cranial neuropathy incident.

The cranial neuropathy occurred within 5 years of DM diagnosis in 50% of patients and appeared to present earlier for the oculomotor nerve compared to the trigeminal nerve. None of the patients experienced multiple attacks of cranial neuropathy involving the same nerve with recovery in between attacks. All cases of oculomotor nerve palsy failed to recover, while two-thirds of the trigeminal nerve neuropathy recovered within six months of the first attack.

The pattern of cranial neuropathy in the only one affected non-diabetic subject was starkly different from that in diabetic patients (Table V). The affected patient had abducens and facial nerve palsy on the right side with multiple attacks. None of these features were present in any diabetic patients. Interestingly, no patient in either group developed stroke after the onset of cranial neuropathy (Figure 1).

Discussion

In the present study, we aimed to estimate the prevalence of cranial neuropathy and its risk factors in a homogeneous cohort of diabetic patients and compare these to non-diabetic control from the same community. Our results indicate that the prevalence of cranial neuropathy is 10 times higher in the diabetic than the non-diabetic group, (2.1% *vs.* 0.21%, respectively). Furthermore, the pattern of cranial neuropathy was different between the groups. The oculomotor (III) and trigeminal nerves (V) were the only cranial nerves affected in the diabetic group, the abducent (VI) and facial nerves (VII) were the only ones affected in the non-diabetic group. Recurrence of cranial neuropathy was only reported in the non-diabetic group as comparted to the diabetic group. Spontaneous recovery was observed in the diabetic group with cranial nerve V palsy as compared to no recovery in the diabetic group with cranial nerve III palsy. A previous investigation in Saudi Arabia by Saleh and Bosley[8] reported that cranial nerves III, IV, and VI were the only ones affected in their diabetic population over a follow-up period of 8 months. Another similar investigation that was al-

Table II. Comparison of diabetic to non-diabetic group regarding the prevalence of cranial neuropathy.

Group	No. of subjects	Cranial neuropathy incident			
		Frequency	%	95% CI	*p*-value
Diabetic	238	5	2.10%	0.34-4.61	0.0091
Non-diabetic	476	1	0.21%		

Table III. Risk factors for cranial neuropathy in diabetic and non-diabetic groups.

	Diabetic group				Non-diabetic group			
	Unstandardized Coefficients	Standardized Coefficients			Unstandardized Coefficients	Standardized Coefficients		
Variable	ß	ß	*t*	*p*-value	ß	ß	*t*	*p*-value
Age	4.48	0.078	1.2	0.231	-13.9	-9.4	1.4	0.14
Gender	0.192	0.056	0.862	0.39	0.356	0.34	0.742	0.459
BMI	0.555	0.064	0.99	0.232	1.78	1.39	1.287	0.199
Physical activity	0.408	0.059	0.905	0.366	0.001	0.004	0.088	0.930
Smoking	0.077	0.042	0.644	0.52	-.171	0.021	0.452	0.651
Non-DM medical comorbidity	0.177	0.061	0.932	0.352	0.912	0.285	3.2	0.001*
Hyperlipidemia	0.049	0.168	0.261	0.010*	0.091	0.298	6.8	0.0001*
Statin use	0.007	0.012	0.146	0.884	0.21	0.181	1.18	0.219
Hypertension	0.00001	0.00	0.004	0.907	0.067	0.254	5.72	0.0001*
DM type	0.26	0.14	0.362	0.718	-	-	-	-
DM duration	0.009	0.001	0.021	0.983	-	-	-	-
Female gestational DM	0.48	0.204	3.209	0.002*	-	-	-	-
DM Rx compliance	0.839	0.137	2.128	0.034*	-	-	-	-
Last HBA1C	0.25	0.38	0.585	0.559	-	-	-	-
Presence of macrovascular complication of DM	0.123	0.065	1	0.318	-	-	-	-
Presence of microvascular complication of DM	0.708	0.220	3.41	0.001*	-	-	-	-

DM: Diabetes mellitus, HBA1C: Glycated hemoglobin A1c. *Shows a statistically significant *p*-value.

Table IV. Patterns of cranial neuropathy in diabetic group.

Case	Affected cranial nerve	Symptoms	Duration between DM and CN diagnoses	Number of attacks	CN recovery	Time to recovery
1	III left	Binocular double vision.	Within 1-5 years of DM diagnosis	1	No	
2	III left V left	III: Binocular double vision. V: Bouts of shearing, severe, and shooting pain in the unilateral face	III: Within 1-5 years of DM diagnosis. V: Within 1-5 years of diagnosis	1 1	No No	
3	III Bilateral	Drooping of eyelids, Binocular double vision	Within 5-10 years of DM diagnosis.	1	No	
4	V left	Pain that feels like an electric shock, triggered by chewing, touching, brushing teeth, talking, drinking, shaving.	More than 10 years of DM diagnosis.	1	Yes	Within 6 months of CN diagnosis
5	V left	Pain that feels like an electric shock, triggered by chewing, touching, brushing teeth, talking, drinking, shaving.	Within 5-10 years of DM diagnosis.	1	Yes	Within 6 months of CN diagnosis

DM: diabetes mellitus, CN: cranial neuropathy, III: oculomotor nerve, V: trigeminal nerve

Table V. Patterns of cranial neuropathy in non-diabetic group.

Case	Affected cranial nerve	Symptoms	Number of attacks	CN recovery after last attack
1	VI Right	VI: Binocular double vision.	2	No
	VII Right	VII: Drooping of the eyelid Inability to elevate the eyebrow on the affected side	2	No

CN: cranial neuropathy, VI: abducens nerve, VII: facial nerve.

so conducted in Saudi Arabia by Al Kahtani et al[9] reported that the relative incidence of each cranial nerve palsies was estimated to be 2.8%, 36.36%, and 53.11% for cranial nerves IV, III, and VI, respectively. These rates were also comparable with the findings of previous investigations[10,11] from other countries. In our study we did not notice a case of cranial nerve VI affection in our diabetic population, and the only affected case was from the non-diabetic group. Other worldwide investigations demonstrated that the abducent nerve (VI) was the most commonly reported cranial nerve palsy in their diabetic populations[10-12]. Previous investigations[8,10,11] have also demonstrated that cranial nerve IV was affected, and none of our patients developed any similar clinical observations. The differences between the findings of our study compared to abovementioned might be attributable to the differences in the sample size and the significance of the baseline demographics which might be risk factors for the development of cranial palsies in some populations over others. Further, the presence of a large control group in this study compared to its lack in the literature enhances its findings.

Many risk factors have been reported in correlation with developing cranial neuropathies in diabetic and non-diabetic patients. In the present study, hyperlipidemia, gestational DM, compliance with DM treatment, and the presence of microvascular complications of DM are significant risk factors for the development of cranial neuropathy in the diabetic population. This is logical because all of these factors correlate with the potential to induce angiopathic changes with subsequent damage to the cranial nerves.

Hyperlipidemia was reported to be significantly associated with the development of microvascular complications in patients with DM, and therefore, it has been suggested that lipid-lowering medications should be prescribed to these patients[13-15]. However, a previous investigation by Al Kahtani et al[9] reported that hyperlipidemia was a significant protective factor against the development of nerve palsies and attributed this to the fact that these patients usually receive lipid-lowering modalities. This contradicts the finding from our study that showed hyperlipidemia as a risk factor for the development of cranial neuropathy and yet showed no protective effect of the lipid-lowering agents use against its development.

Therefore, urging patients to stick to their medical DM treatment and conducting routine check-ups for patients at high risk of developing DM-related complications in view of the aforementioned risk factors is critical. Neither age nor gender appeared as a significant risk factor for cranial neuropathy in this study. However, previous investigations have demonstrated that gender, age, and BMI were all significant factors for developing cranial nerve affection[7-9,11,16-17].

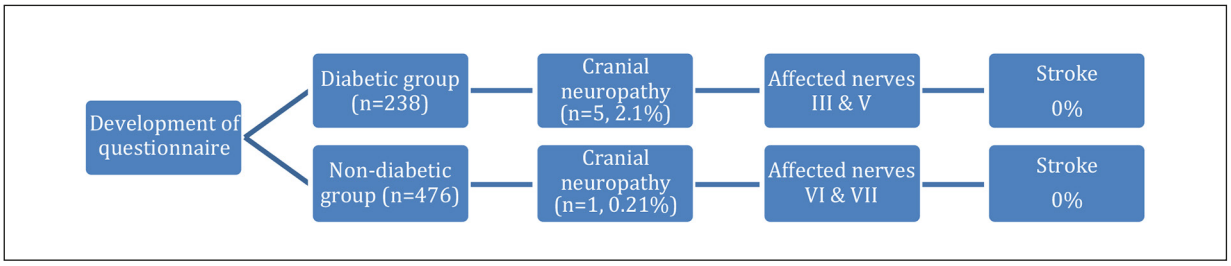

Figure 1. Research flow diagram.

In another context, hyperlipidemia, hypertension, and the presence of non-DM co-morbidity were the only significant factors for the development of cranial neuropathies in the non-diabetic control. Hypertension has been previously linked with the development of many micro-and macrovascular complications in both the diabetic and non-diabetic population[18-21], and it was previously demonstrated that if hypertension was associated with DM, the risk of developing cranial nerve palsies would increase to up to eight folds[21]. However, hypertension was not a significant factor in our diabetic group, which is similar to other previous investigations[9] and might be attributed to the fact that these patients are usually urged to stick to strict anti-hypertensive medications as part of their diabetic care[22-23].

Study Limitations

Our study might be limited by its cross-sectional design. Also, it is possible that the differences in the assessed baseline characteristics and demographics between the diabetic and non-diabetic groups might have influenced the findings of this study. Nonetheless, this study provides much-needed information on the prevalence of and the risk factors for the development of cranial neuropathy among diabetics.

Conclusions

Our results indicate that diabetics have ten times fold risk of cranial neuropathy than non-diabetic ones. The pattern of cranial neuropathy was also different between diabetics and non-diabetics. Moreover, hyperlipidemia, gestational DM, compliance with DM treatment, and the presence of microvascular complications of DM are significant risk factors for the development of cranial neuropathy among diabetics. Therefore, adequate attention should be given to these parameters to achieve better prevention.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

King Khalid University Research Ethics Committee approved the study (ECM#2021-5626).

Informed Consent

All participants gave their informed consent for the study publication.

Availability of Data and Materials

The data and materials that support the findings of this study are available on request from the corresponding author.

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