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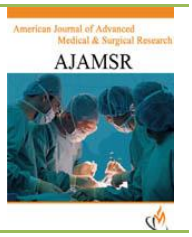

RISK FACTORS THAT ARE ASSOCIATED WITH DEVELOPMENT AND SEVERITY OF LARGE FIBER POLYNEUROPATHY IN TYPE 2 DIABETICS IN SAUDI POPULATION: A RETROSPECTIVE CASE CONTROL STUDY

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ABSTRACT
Diabetic large fiber polyneuropathy (DLPN) is a well known complication of type 2 diabetes. Other than glycemic control there is no definitive treatment available for effective treatment of DLPN. Thus identifying the risk factors for development and their association with severity of DLPN in diabetic patients helps to understand and treat the DLPN effectively. To study the effect of different variables, development and severity of DLPN as compared to controls. A retrospective case control study conducted in a university hospital in the western region of Saudi Arabia. The sample of cases was collected retrospectively from year 2005 – 2012. **A** total of 122 patients with established diagnosis of diabetes were subjected to Electromyography (EMG) and nerve conduction Studies (NCS) to identify the patients who had DLPN and to see whether statistical significance with the various possible risk factor in development and severity of DLPN In case and control groups. The study showed no statistical correlation between the potential predictors studied and the development and severity of DLPN in study group, diabetic patient with DLPN and controls. In Saudi type 2 diabetic population studied there was no correlation between the various predictors' development and severity of DLPN. Larger prospective studies may be needed to identify the potential risk factors for the development of DLPN.

INTRODUCTION

The prevalence of T2DM is rapidly increasing worldwide and predicted to rise by 42% between years 2003-2025 [1]. Recent data from Saudi Arabia shows prevalence of T2DM Is 29% in adult Saudi Population [2]

Diabetic polyneuropathy leads to high morbidity and mortality and adversely affects the quality of life. The pathogenesis of diabetic polyneuropathy is poorly understood. Other than hyperglycemia no other definitive predictors or precipitating factors were established for the development of diabetic polyneuropathy [3]. The research studies identifying the predictors and risk factors for developing large fiber diabetic polyneuropathy are scarce in Saudi Arabia. We design a case control retrospective study to study whether any commonly associated diseases or factors with diabetics contributed to development and severity of large fiber polyneuropathy (DLPN) as compared with control subjects. Identifying such factors contributing to DPLN may help to prevent and treat DLPN in diabetic population.

METHODS

A retrospective case control study was performed in a university hospital in western region of Saudi Arabia. The sample cases were randomly picked up from diabetic patients attended to neurology clinic with symptoms of neuropathy between 2005- 2012. Detailed review of

medical records was performed, demographic features and detailed medical history in relevant to planned risk factors was recorded. Details of investigations included planned risk factors complete blood counts, renal function, proteinuria, thyroid function, serum vitamin B12 level, Serum 25 Hydroxy cholicalciferol (ViataminD3) level were abtained.MRI brain, echocardiogram were recorded in appropriate patients who required these investigations. Electromyography (EMG) and Nerve conduction studies (NCS) results were recorded for total 122 patients. We defined the case group (DLPN) as any diabetic patient with clinical manifestation of peripheral neuropathy and recorded abnormalities in the nerve conduction studies indicating large fiber nerve involvement while the case group was defined as any diabetic patient with clinical presentation of peripheral neuropathy recorded normal nerve conduction study which mean no significant involvement of the large fibers, the patients with DLPN were 82 patients while 40 patients showed no evidence of DLPN ; control group. We focused in our study on the following variables ; the following variable: (duration of diabetes, thyroid status, anemia, renal impairment, vit D deficiency, history of stroke(hemorrhagic and ischemic stroke), The presence of hypertension, ,insulin use, Presence of HF(heart failure) and smoking.

The study was approved by the ethical committee of the institute. We classified severity of large fiber diabetic polyneuropathy was classified as mild, moderate, severe and very severe (end stage) by following criteria in table no: 1

Statistical analysis

Descriptive statistics such as frequencies, percentages, Chi-scare test were used to determine the predictors for the development of DLPN in both cohorts. P value < 0.05 was considered as significant association of variable with the development of DLPN.

In the present study, we measured the relative risk of development of large fibers in the diabetic patients in correlation with the following variable: (duration of diabetes, thyroid status, anemia, renal impairment, vit D deficiency, history of stroke (hemorrhagic and ischemic stroke), the presence of hypertension, insulin use, presence of HF(heart failure) and smoking.

RESULTS

Table 2 shows characteristics of study and control population. The majority of sample of the study group and control group ages falls between 51-70 years and statistical analysis reveals no significant difference in between two groups. The gender analysis was performed and again did not have any statistical significance in both groups studied. The duration of diabetes in study cohort was determined by taking history from the cases studied. The majority of cases in both cohorts the duration of diabetes were more than 10 years (53%), there was no significant stoical difference between two groups to predict the occurrence of DLNP apart from the presence of anemia and the use of high dose of insulin.

Table 3 illustrates the severity of large fiber involvement among the cases of study, the majority of cases 67(81.7%) had moderate severity.

The results in table 4 show the affection of different nerve components in cases of the study. It's clear that majority of the cases of the study have axonal nerve involvement (54.9%). Table 5 showing the association of development of DLPN and various risk factors studied.

Table 1. Classification of large fiber diabetic polyneuropathy

Mild	Abnormal SNAP in lower limbs
Moderate	Abnormal SNAP and CMAP in lower limbs
Severe	Absent lower limb response +/- any upper limb abnormality or abnormality in both lower and upper limbs.
Very Severe (End stage)	Absent of upper and lower limb responses.

SNAP : Sensory nerve action potential , CMAP : Compouned motor action potential

Table 2. Predictors for the occurrence of DLNP

Characteristics	**Cases (large fiber peripheral neuropathy) N (%)**	**Control (non large fiber PN) N (%)**	***p*-value[b]**	**OR**	**95% CI**
Age in years (Mean ± SD)	60.4±12.94	54.55±8.0			
Less than 50 N=26	14 (11.5)	12 (9.8)	0.10	0.48	Lower=0.20
>50 years N=96	68 (55.7)	28 (23.0)		χ^2 =2.68	Upper =1.17
Gender					
Male n=68	59 (48.3)	9 (7.4)	0.00	0.42	Lower =3.65

Female n=54	23 (18.9)	31 (25.4)		χ^2 =26.65	Upper =21.41
Duration of disease (Mean ± SD) =<10 y n=39 =>10 years n=76	17 (14.8) 61 (53.0)	22 (19.2) 15 (13.0)	0.00	0.19 χ^2 =15.89	Lower=0.081 Upper =0.44
Thyroid function n=117 Normal =96 Hypothyroidism=21	69 (59.0) 10 (8.5)	27 (23.1) 11 (9.4)	0.032	2.81 χ^2 =4.62*	Lower=1.07 Upper =7.38
CBC N =116 Normal =71 Leukopenia=3 Anemia =42	52 (44.8) 0 (0.0) 25 (21.6)	19 (16.4) 3 (2.6) 17 (14.7)	**0.016**	χ^2 **=8.31***	
Renal function N=113 Normal =99 Impaired =14	68 (60.2) 12 (10.6)	31 (27.4) 2 (1.8)	**0.19**	0.37 χ^2 =1.720	Lower =0.08 Upper =1.73
Smoking N=140 n=19 Yes =19 No =102	15 (12.4) 67 (55.4)	4 (3.3) 35 (28.9)	0.26	1.96 1.29	Lower =0.60 Upper=6.35
hemorrhagic stroke N=120 Yes =1 No=119	0 (0.0) 81 (67.5)	1 (0.8) 38 (31.7)	**0.15**	3.13 χ^2 =2.09	Lower =2.41 Upper =4.07
Ischemic stroke=120 Yes =9 No =111	7 (5.8) 74 (61.7)	2 (1.7) 37 (30.8)	0.49	1.75 χ^2 =0.47	Lower=0.35 Upper =8.85
Heart failure N=120 Yes =6 No=114	5 (4.2) 76 (63.3)	1 (0.8) 38 (31.7)	0.40	2.50 χ^2 =0.722	Lower=0.28 Upper=22.16
INSULIN USE N=113 High dose= 28 Low dose =7 Nothing =78	24 (21.2) 1 (0.9) 51 (45.1)	4 (3.5) 6 (5.3) 27 (23.9)	0.001	χ^2 =13.38**	Lower =2.28 Upper =2.60
Vit D N=107 Normal =69 Low = 19 Very low = 19	65 (60.7) 6 (5.6) 8 (7.5)	4 (3.7) 13 (12.1) 11 (10.3)	0.00	χ^2 =**42.28	Lower =1.24 Upper =1.54

* Significant association $P<0.05$ ** significant association $P < 0.01$

Table 3. The severity of large fiber involvement among the participants

	Frequency	Percentage%
Mild	3	3.7
Moderate	67	81.7
Severe	9	11.0
Very Severe(End stage)	3	3.7
Total	82	100

Table 4. The affection of different nerve components among participants

	Frequency	Percentage%
Axonal	45	54.9
Demyelinating	4	4.9

Mixed	33	40.2
Total	82	100

Table 5. Risk factors for the development of DLPN

Characteristics	**Mild**	**moderate**	***Moderate severe***	***Severe***	**End stage**	***p*-value[b]**	**OR**	**95% CI**
Thyroid function n=79 Normal =69 Hypothyroidism=10	3=3.8% 0=0.0%	29=36.7% 2=2.5%	28=35.4% 5=6.3%	6=7.6% 3=3.8%	3=3.8% 0=0.0%	0.23	χ^2 =5.62	Not significant
CBC =116 Normal = 52 Low hemoglobin level =25	1=1.3% 2=2.6%	23=29.9% 7=9.1%	22=28.6% 11=14.3%	4=5.2% 4=5.2%	2=2.6% 1=1.3%	0.42	χ^2 =3.88	Not significant
Nephropathy =80 Normal =68 Impaired =12	3=3.8% 0=0.0%	27=33.8% 4=5.0%	31=38.8% 3=3.8%	5=6.2% 4=5.0	2=2.5% 1=1.2%	0.07	χ^2 =8.56	Not significant
Smoking Yes =15 No= 67	0=0.0 3=3.7%	4=4.9% 28=34.1%	7=8.5% 28=34.1%	2=2.4% 7=8.5%	2=2.4% 1=1.2%	0.18	χ^2 **=6.25**	Not significant
Ischemic stroke=81 Yes =7 No =74	0=0.0 3=3.7%	1=1.2% 31=38.3%	5 = 6.2% 29= 5.8%	0=0.0% 9=11.1%	1=1.2 2=2.5%	0.18	χ^2 **=6.27**	Not significant
Heart failure N=81 Yes =5 No=76	0=0.0% 3=3.7%	1=1.2% 31=38.3%	3=3.7% 31=38.3%	1=1.2% 8=9.9%	0=0.0% 3=3.7%	0.79	χ^2 =1.70	Not significant
INSULIN USE N=76 High dose= 24 Low dose =1 Nothing =51	0=0.0% 0=0.0% 3=3.9%	7=11.8% 0=0.0% 22=28.9%	9=11.8% 1=1.3% 22=28.9%	7=9.2% 0=0.0 2=2.6%	1=1.3 0=0.0 2=2.6%	0.13	χ^2 =12.57	Not significant
Vitamin D N=107 Normal =69 Low = 19 Very low = 19	65 (60.7) 6 (5.6) 8 (7.5)	4 (3.7) 13 (12.1) 11 (10.3)		0.00			χ^2 =**42.28	Lower =1.24 Upper =1.54

* Significant association $P<0.05$ ** significant association $P < 0.01$

DISCUSSION

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes .Few studies have addressed prevalence of painful peripheral neuropathy in DM patients in Arab population. In one study performed in Saudi Arabia showed high prevalence (65%) of painful peripheral neuropathy [4] and the other similar study showed an incidence of 54% patients of T2DM having painful peripheral neuropathy [5].

DPN affects the quality of life and also associated with high morbidity and mortality. It causes huge economical burden to health care providers. The exact pathogenesis of DPN remains elusive despite extensive research [6] Based on epidemiological studies and controlled clinical trials total hyperglycemic exposure has been shown to be an important risk factor for the occurrence of DPN. The Diabetes control and complication trial(DCCT) demonstrated 60% lowered incidence of clinically detected neuropathy in intensive therapy group of T1DM patients in the study [7] However which marker of chronic hyperglycemia exposure is the best and the degree of near euglycemia needed to prevent the occurrence of DPN are known only approximately [8, 9]

Apart from chronic hyperglycemia there is only weak and inconsistent evidence implicating other risk factors such as older age, height, male sex ,weight, established heart disease, hypertension, smoking, lipoprotein concentration,anaemia, vitamin deficiency, hypothyroidism, renal disease, retinopathy, insulin use , B12 deficiency. The prospective population studies for ascertaining the frequency,severity,and risk factors for developing polyneuropathy in Saudi type2 diabetes

population are scanty. The present study performed in a university hospital outpatient clinic in western area of Saudi Arabia, to identify any risk factors for developing or associated with the severity of the DPN in T2DM in this population group. Hypothyroidism is commonly associated disorder in T2DM population.

The prevalence thyroid dysfunction and thyroid immunity in T2DM was shown to be higher than other parts of the world in the study conducted by DH Akbar [10]. Sub clinical hypothyroidism was shown to be a risk factor for the development of neuropathy in T2DM patients [11] The present study did not show any significant difference in the severity in DPN T2DM patients with hypothyroidism and euthyroid state. Low hemoglobin was detected in 29% of our study population. Low hemoglobin was significantly associated with higher diabetic foot complications in Saudi T2DM patients in a study conducted in Saudi Arabia [12] The low hemoglobin level was associated with increased risk factor or contributes to severity of DPN in our study population. Also high dose of insulin showed a satirical significant result as risk factor to development of DPLN which may be related to poor glycemic control that necessitated high dose insulin rather than to be related to insulin itself, Weak and inconsistent evidence exists in literature for smoking as risk factor , and for severity of DPN [13,14].

The present study did not show any evidence to implicate smoking as risk factor or severity of DPN.In parallel to increase in the prevalence T2DM there has been increase in vitamin D deficiency worldwide [15] High prevalence of vitamin D deficiency in Saudi Arabia was reported in recent studies [16, 17]. Increasing number of studies link vitamin D deficiency and development and severity of diabetic polyneuropathy. A systemic review and meta analysis revealed that vitamin D deficiency involved in the development DPN, in T2DM patients [18]. Shehab et al in their study showed that vitamin as an independent risk factor for DPN [19]. In our study 38% of patients had vitamin D deficiency but she there was no statistical significance to indicate it as predictor or severity of DPN in type2 diabetic patients and control group. Heart failure, nephropathy, ischemic stroke and were inconsistently and weakly related as risk factors and aggravators of DPN [11, 12] in studies and again in the study population there was no increase in relative risk for severity of DPN in T2DM and control group. In conclusion, in the western Saudi population the known risk factor for developing and causing severity of DPN which were studied in this study did not show any statistical difference between the study population and the control group apart from low hemoglobin level. The limitation of our study the retrospective study design .Well designed community based multicenter studies are needed in future to establish the relation between the predicted risk factors and their effect on development and severity of DPN.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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