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Relationship of Tumor Necrosis Factor-alpha (TNF-α) with Nerve Conduction Velocity (NCV) in patients of Diabetic Neuropathy

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ABSTRACT

Introduction: Diabetic peripheral neuropathy is one of the most commonly reported long term diabetic complications. Enhanced TNF-α production in the diabetic state may promote the development of diabetic micro- and macroangiopathies through a variety of TNF-α bioactivities.

Aims and Objectives: We intend to highlight the relationship of Tumor Necrosis Factor-alpha (TNF-α) with Nerve Conduction Velocity (NCV) in patients of Diabetic Neuropathy.

Material and Methods: 52 patients of diabetic neuropathy were assessed for sensory and motor nerve conduction velocity along with serum TNF-α estimation and the results were statistically analyzed.

Results: Tingling was the most common symptom, seen in 31.1% cases. The numbers of nerve involvement increased with the duration of diabetes mellitus. A positive association of duration of disease with the number of number of nerves involved was seen in our study (p- Value <0.001). Majority of the patients showed decrease in SNCV in more than three nerves. Increasing levels of TNF-α was seen in patients with higher levels of HbA1c. Most of the patients with higher levels of TNF-α had longer duration of diabetes. Higher levels of TNF-α were seen in patients with more number of nerves involved. 34.6% patients had ≥7 nerves involvement.

Conclusion: TNF-α might be independently associated with peripheral neuropathy in type 2 diabetes mellitus, so investigative parameters like NCV and TNF- α could be used as an independent marker to assess the severity of diabetic neuropathy.

Keywords: Diabetes, Peripheral neuropathy, Nerve conduction velocity, Tumor necrosis Factor-alpha

INTRODUCTION

Diabetes Mellitus is a debilitating advance disease condition affecting a million people around the globe [1]. There is an increase in the prevalence of diabetes worldwide day by day and is also speedily gaining status of a potential epidemic in India [1].

All types of diabetes mellitus mostly leads to the development of diabetes specific microvascular pathology in the human body involving retina in the eyes, renal glomerulus in the kidneys and peripheral nerves. As a consequence of its microvascular pathology, diabetes is one of the most important leading causes of blindness (retinopathy), end stage renal disease and a variety of debilitating neuropathies [2].

There is association of diabetes with certain other complications also, like accelerated atherosclerotic macro vascular disease affecting the arteries that supply the heart, brain and lower extremities.

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Diabetic peripheral neuropathy (DPN) is one of the most commonly reported long term diabetic complication, affecting about 50.0% of type 2 diabetic patients [3]. Neuropathy in patients with diabetes is known to be heterogenous in presentation of various symptoms, pattern of neurologic involvement, course, risk covariates, pathologic alterations and underlying mechanism [4].

MATERIALS & METHODS

This prospective study was conducted on 52 patients with Diabetic Neuropathy in the Rajiv Gandhi centre for diabetes and Endocrinology, Department of Medicine, Neurophysiology section of Department of Physiology and Clinical Laboratory of Pathology, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, after approval from ethical committee of the College and taking written informed consent from the patients. The baseline characteristics were compared between age and sex matched type 2 diabetic patients having peripheral neuropathy with healthy controls.

A detailed history and thorough physical examination was carried out on every case in the study as per a pre-designed proforma. Selected cases of Type 2 Diabetes Mellitus patients were assessed for diabetic peripheral neuropathy by both sensory and motor nerve conduction velocity (Apparatus: NeuroStim4-NS4 EMG/NCV/EP, Medicaid, India) along with serum TNF-α estimation. Selected patients were assessed with neuropathy symptom score (NSS) with symptoms of paresthesias like burning/numbness/tingling/cramping/aching and clinical examination for neuropathy disability score (NDS) and were asked to report to the endocrinology laboratory after an overnight fasting of 10-12 hours. Blood samples were collected in EDTA vials for estimation of HbA1C, Sodium Fluoride vials for plasma glucose and in plain vial for TNF-α estimation by enzyme-linked immunorbent assay kit (Gen-Probe Diaclone). Blood for fasting and post prandial glucose estimation was collected on the same day. All the data was statistically analyzed using SPSS software version (20.0). Statistical analysis was performed by Chi square tests and ANOVA according to the variables and the comparisons needed. p-value of 0.05 or less was considered to be statistically significant.

OBSERVATIONS

Our study included 52 patients comprising of 27 males and 25 females provisionally diagnosed clinically as peripheral neuropathy were included in the present study and had given valid written consent. A group of 12 normal individuals without diabetes served as control in our study.

Tingling was the most common symptom in most of the diabetic patients constituting 31.1% cases, followed by numbness and tingling in 22.4% cases and burning sensation & tingling in 10.3% cases **(Table 1)**. The numbers of nerve involvement increased with the duration of diabetes mellitus. It was seen in 7.7% cases during 1-5 years duration of disease which increased to 32.7% cases during 11-15 years of disease **(Table 2)**.

In our study, 27 (51.9%) cases were males while 25 (48.1%) were females with a male to female ratio of 1.08. So, the gender-wise distribution of cases did not show any significant difference.

Majority of the patients were having more than 10 years duration of diabetes. The number of nerves involvement got increased as the duration of the disease prolonged. A positive association of duration of disease with the number of number of nerves involved was seen in our study (p-value<0.001) **(Table 3)**.

Most of the patients with higher levels of TNF-α had longer duration of diabetes. 32.7% patients had duration of diabetes mellitus between 11 to 15 years while 32.9 % patients had >15 years duration of diabetes. So, in total 65.4% patients had > 10 years duration of diabetes mellitus. A positive association was seen in our study with duration of diabetes and raised TNF-α levels (p-value 0.001) **(Table 4)**.

Increasing levels of TNF-α was seen in patients with higher levels of HbA1c. 28.8% patients had HbA1c levels >11.5, out of which, 93.3% patients had higher TNF-α levels in excess of 50 pg/ml **(Table 5)**. Higher levels of TNF-α were seen in patients with more number of nerves involved. 34.6% patients had ≥7 nerves involvement while 19.2% patients had involvement of 6 peripheral nerves. All these patients had higher levels of TNF-α in excess of >50 pg/ml **(Table 6)**.

Majority of the patients showed decrease in SNCV in more than three nerves; 17(32.69%), followed by three nerves in 13(25.0%) patients. Majority of the patients showed decrease in MNCV in more than 3 three nerves; 15(28.84%), followed by three nerve involvement in 13(25.0%) patients **(Table 7)**.

DISCUSSION

Majority of the patients presented with tingling, 20 (31.3%), followed by tingling and numbness, 14 (21.9%), followed by burning sensation and tingling 6 (9.4%), burning alone, 5 (7.8%), followed by weakness of limbs and cramping, 5 (7.8%). Rest of the patients, 14 (21.9%), presented with combination of above symptoms. Similar symptoms were shown in the study by Pop-Busui et al., in 2017 [6].

In our study, the age range of type 2 diabetic patients with neuropathy was 30-77 years old with average age of 56.4±11.6. Popescu et al., in 2016 reported a median age of the diabetic patients as 62 years [7]. In our study, we found the prevalence of diabetic peripheral neuropathy to be 32.2%. Tesfaye et al., in 1996; Pradeepa et al., in 2008 and Gill et al., in 2014, have stated a prevalence of 28.0%, 26.1% and 29.4% respectively [8-10].

Table 1. Distribution of cases according to presenting symptoms.

Presenting symptoms	Number of cases	Percentage
Tingling	18	31.1
Tingling and numbness	13	22.4
Burning sensation and tingling	06	10.3
Burning sensation alone	05	8.6
Limb weakness and cramping pain	04	6.9
Combination of the above symptoms	12	20.7
Total	58	100

Table 2. Number of patients having nerve involvement in relation to duration of disease.

Duration of diabetes mellitus	Number of patients having nerve involvement	Percentage
1-5 years	04	07.7
6-10 years	14	15.2
11-15 years	17	32.7
>16 years	17	32.7
Total	52	100

Table 3. Number of nerves involved in relation to duration of disease.

Numbers of nerves involved	Numbers of patients according to duration			
	≤ 10 years		>10 years	
	No.	Percentage	No.	Percentage
1	07	38.8	00	00
2	03	16.8	00	00
3	04	22.0	01	2.9
4	04	22.2	03	8.8
5	00	00	02	5.9
6	00	00	09	26.5
≥7	00	00	19	55.9
Total	18	34.6	34	65.4

Table 4. Duration of diabetes and the number of patients with raised TNF-α level.

Duration (years)	Number of patients with different TNF-α levels							
	≤30(pg/ml)		31-50(pg/ml)		>50 (pg/ml)		Total	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
0-5	01	25.0	02	50.0	01	25.0	04	07.7
6-10	02	14.3	04	28.6	08	57.1	14	26.9
11-15	00	00	01	05.9	16	94.1	17	32.7
>15	00	00	00	00	17	100.0	17	32.7
Total	03	05.7	07	13.5	42	80.8	52	100.0

Table 5. Association of HbA1c and TNF-α level.

HbA1c levels (%)	Number of patients with different TNF-α levels							
	≤ 30(pg/ml)		31-50(pg/ml)		>50(pg/ml)		Total	
	No.	%	No.	%	No.	%	No.	%
6.6-7.5	00	00	00	00	03	100	03	5.7
7.6-8.5	02	25	02	25.0	04	50	08	15.4
8.6-9.5	00	00	01	07.7	12	92.3	13	25
9.6-10.5	00	00	02	28.6	05	71.4	07	13.5
10.6-11.5	01	16.7	01	16.7	04	66.6	06	11.5
>11.5	00	00	01	6.7	14	93.3	15	28.8
Total	03	5.7	07	13.5	42	80.8	52	100

Table 6. Association between numbers of nerves involved and different TNF-α levels.

Number of nerves involved	Number of patients with different TNF-α levels							
	≤ 30 pg/ml		31-50 pg/ml		>50 pg/ml		Total	
	No.	%	No.	%	No.	%	No.	%
1	01	14.3	05	71.4	01	14.3	07	13.5
2	00	00	00	00	02	100	02	3.8
3	01	20.0	01	20	03	60	05	9.6
4	01	12.5	01	12.5	06	75	08	15.4
5	00	00	00	00	02	100	02	3.8
6	00	00	00	00	10	100	10	19.2
≥7	00	00	00	00	18	100	18	34.6
Total	03	5.8	07	13.5	42	80.7	52	100

Table 7. Comparison between baseline characteristics of controls (n=12) v/s Type 2 Diabetic subjects (n=52).

Variable		Controls (n=12)	Diabetic subjects (n=52)	p value
Number	Male	7	27	0.689
	Female	5	25	
Age (years)		55.17±13.11	56.42± 11.58	0.743
Duration of T2 DM (years)		0	12.90± 5.02	
Fasting plasma Glucose (mg/dl)		93±10.67	167.02±25.87	<0.0001
Post prandial glucose (mg/dl)		119.75±15.43	223.18±50.72	<0.0001
TNF-α(pg/ml)		15.83±5.09	85.82±28.21	<0.0001
Right sided SNCV(m/s) of	Sural nerve	49.6±1.2	42.1±4.2	<0.0001
	Median nerve	52.7±1	46.3±6.5	0.0013
	Ulnar nerve	51.5±1	48.4±4.8	0.0306
Left sided SNCV(m/s) of	Sural nerve	49.8±1	41.8±4.2	<0.0001
	Median nerve	52.3±1	47.6±5.7	0.0063
	Ulnar nerve	52.2±1.5	48.3±4.8	0.0074
Right sided MNCV(m/s) of	Common Peroneal Nerve	48.9±2	42.5±3.4	<0.0001
	Posterior Tibial Nerve	48.8±1.5	42.7±3.5	<0.0001
	Median nerve	55.9±1	49.2±7.8	0.0045
Left sided MNCV(m/s) of	Common Peroneal Nerve	48.2±1.8	42.7±3.3	<0.0001
	Posterior Tibial Nerve	48.5±1.3	44.1±1.6	<0.0001
	Median nerve	55.2±1	51.8±2.9	0.0002

In our study we found that the duration of diabetes mellitus played an important role on the development of diabetic neuropathy. We found that with increasing age of diabetic patients, the incidence of diabetic complications of peripheral neuropathy increased. In our study the number of patients of diabetic peripheral neuropathy increased with age from 11.5% in the age group of 31-40 years old to 38.5% in the age group of >60 years old. Kennady et al reported the prevalence of diabetic neuropathy as 11.1% in the 23-40 years old age-group and 32.3% in the 60-80 years old age-group [11]. Similar results have also been reported in the study by Zoungas et al in 2014 [12].

In our study, majority of the diabetic patients with neuropathy had duration of the disease of more than 10 years, 34 (65.4%) patients followed by 14 (26.9%) patients with 6-10 years of duration of diabetes. Similar results have been reported by Deshpande et al., in 2008 [13].

In our study, the glycemic statuses of the diabetic patients were assessed by HbA1c levels and it was seen that the glycemic status of the type 2 diabetic mellitus patients with neuropathy was higher in most of the patients. Also, as the duration of the disease increased, the HbA1c levels got increased in our patients which subsequently lead to diabetic neuropathy. So, a long duration of diabetes and poor glycemic control leads to increased occurrence of diabetic neuropathy. Oguejiofor et al and Nisar et al found a lower prevalence of polyneuropathy with duration of diabetes mellitus <5 years and high prevalence with duration of diabetes mellitus >15 years [14,15].

Diabetic peripheral neuropathy was assessed by determining the sensory and motor nerve conduction velocities of 6 pairs of peripheral nerves comprising of 3 pairs of sensory nerves and 3 pairs of motor nerves. It is considered as a gold standard for diagnosis of neuropathy. This procedure is sensitive, easier to perform, more comfortable and produces results that are easier to measure [2]. We found significant decrease in nerve conduction velocities of all the nerves assessed in the cases of neuropathy as compared to the controls, which was statistically significant ($p < 0.05$). Our findings were consistent with Tehrani et al [16].

In our study, we found that the numbers of peripheral nerve involvement was more as the duration of diabetes mellitus increased from 7.7% in the age group 1-5 years to 32.7% in the age group 11-15 years. The association between the duration of diabetes mellitus and neuropathy was also evident in several research studies by Nisar et al. and Maser et al on the epidemiology of diabetic complications [15,17].

There was early involvement of sensory nerves as compared to motor nerves in patients of diabetic neuropathy in our study, a finding consistent with the reports of Halar et al and Nascimento et al [18,19].

We also found that there was involvement of only one nerve (sural nerve) in many patients which was also the earliest and most common nerve to be affected. Similar findings have been reported in the study by Riihimaa et al. [20]. Also, the sensory nerve conduction velocity was more reduced in nerves of lower limb than the nerves of upper limb.

The mean value of serum TNF-α level in our study was found to be significantly raised in patients of diabetic neuropathy as compared to the controls. TNF-α levels showed a consistent increase with duration of diabetes mellitus. Our result is consistent with studies of Mirza et al, Swaroop et al and El Sheikh et al, who observed that this peptide contributes to the development of type 2 diabetes mellitus through insulin resistance [21-23]. Huseynova et al also showed significant increase in TNF-α levels in various stage of compensation in type 2 diabetes mellitus [24].

We also found increased level of HbA1c with increasing levels of TNF-α. Similar results have been shown by He et al., who showed that higher levels of TNF-α was significantly associated with higher levels of HbA1c in type 2 diabetic patients [25].

Our study showed a significant correlation of TNF-α level with nerve conduction velocities. 42(80.7%) patients had higher levels (>50pg/ml) of TNF-α, Out of which, 42.8% patients had ≥7 nerves involvement while 23.8% patients had involvement of 6 peripheral nerves. El Sheikh et al and Li et al also showed significant correlation of TNF- α with nerve conduction velocity [23,26].

CONCLUSION

The major problem with the development of peripheral neuropathy are very subtle changes noticed as a person gets older, which he or she tends to ignore, thinking it just to be a part of aging process which further results in reduced quality of life. As the detection of the various dormant signs of diabetic neuropathy at the earliest could minimize the damaging effects and improve the quality of life; it is recommended that nerve conduction velocity test should be performed on all diabetic patients routinely. TNF-α might be independently associated with peripheral neuropathy in type 2 diabetes mellitus, so investigative parameters like NCV and TNF- α could be used as an independent marker to assess the severity of diabetic neuropathy.

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