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Original Article

Physiology Section

Effect of Anaemia on Sensory Nerve Conduction in Diabetic Peripheral Neuropathy: A Cross-sectional Study

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ABSTRACT

Introduction: Diabetic Peripheral Neuropathy (DPN) occurs in more than 50% of patients with Type 2 Diabetes Mellitus (T2DM). Though multifactorial pathogenesis has been claimed for the occurrence of DPN, the exact mechanism is unclear. Recently, it was found that the prevalence of anaemia is two to three times higher in diabetic patients even with preserved renal function.

Aim: To compare the sensory nerve conduction study variables such as latency (ms), amplitude (μV) and Nerve Conduction Velocity (NCV) (m/s) of the median, ulnar and sural nerves in DPN patients with anaemia to those without anaemia.

Materials and Methods: This cross-sectional study was conducted in the Department of Neurology, PSG Hospital, Coimbatore, Tamil Nadu, India, December 2017 to December 2018 with 80 DPN subjects, included both males and females of age group from 35 to 70 years, grouped into those without anaemia (n=40) and those with anaemia (n=40). Subjects were considered to have anaemia based on the World Health Organisation (WHO) classification of haemoglobin. Sensory nerve conduction studies were performed on right and left median, ulnar and sural nerves. Logistic regression was performed in DPN without and with anaemia to rule out confounding variables. Independent t-test and Mann-Whitney U test were used to compare the variables between the groups with normal and skewed distribution, respectively. The p-value <0.05 was considered to be statistically significant.

Results: Among 80 study participants, 38 (47.50%) were male and 42 (52.50%) were female. About 20 (50%) were male and 20 (50%) were female in group A (DPN without anaemia). Seventeen (42.50%) were male and 23 (57.50%) were female in group B (DPN with anaemia). Among DPN subjects with anaemia, 57.50% had mild anaemia and 42.50% had moderate anaemia. In the present study, normocytic normochromic anaemia was the predominant form of anaemia seen. NCV of right median nerve, right ulnar nerve, right sural nerve and left sural nerve were significantly reduced in DPN with anaemia when compared to DPN without anaemia with values <0.001, <0.001, 0.001 and <0.001, respectively. The amplitude of right sural nerve and left sural nerve were significantly reduced in DPN with anaemia, compared to DPN without anaemia with p-values <0.001 and 0.017, respectively.

Conclusion: The DPN patients with anaemia had lower NCV and amplitude of sensory nerves, when compared to those without anaemia. Hence, even mild to moderate anaemia could be a possible risk factor that exacerbates the severity of DPN.

Keywords: Nerve conduction velocity, Normocytic normochromic anaemia, Type 2 diabetes mellitus

INTRODUCTION

Diabetic neuropathy occurs in more than 50% of individuals with T2DM. It can manifest in the forms of polyneuropathy, mononeuropathy and/or autonomic neuropathy [1]. Among the various forms of diabetic neuropathy, Distal Symmetric Polyneuropathy (DSPN) accounts for about 75% of the caseload in diabetic neuropathies. It has been found that DSPN might be present in atleast 10-15% of newly diagnosed T2DM patients [2].Though a multifactorial pathogenesis has been claimed for the occurrence of DPN; the exact mechanism for the pathogenesis is unclear. A prevailing view for the pathogenesis of DPN is the inflammatory and oxidative stress. The inflammatory and oxidative stress that occurs as a result of metabolic dysfunction in diabetes mellitus damages the neuronal cells [2].

Anaemia is a common manifestation in diabetes mellitus. The prevalence of anaemia is two to three times higher in diabetic patients compared to the general population even with preserved renal function as opposed to the myth that end-stage renal failure in diabetes is the major cause of anaemia in diabetes [3]. Chronic anaemia results in tissue hypoxia leading to diabetes associated organ damage [4]. Recently, the association of anaemia with diabetic microvascular complications has identified anaemia as an independent risk factor for predicting the severity of diabetic nephropathy [5], diabetic retinopathy [6] and diabetic neuropathy [4]. Despite the increased prevalence of diabetes related anaemia and its well-known microvascular complications, very little research has been conducted to find the association of anaemia with diabetic neuropathy. The pathophysiology of DPN has not been fully understood. Hence, studies that emphasise the association of anaemia; which is a common manifestation even in diabetic patients having preserved renal function with DPN are necessary.

Nerve conduction study, the most sensitive and specific method for assessing the severity of DPN [7] is utilised in the present study. Since the sensory aspects of the peripheral nervous system are more commonly affected than the motor aspects [8], sensory nerve conduction studies have been chosen. The present study was designed to compare the sensory nerve conduction study variables such as latency (ms), amplitude (μV) and (NCV) (m/s) of the median, ulnar and sural nerves in DPN patients with anaemia to those without anaemia. The present study is a part of a larger project. To the best of the knowledge, no similar studies have been reported in Indian population. The hypothesis of the present study is that, the presence of anaemia affects the sensory nerve conduction values in T2DM patients with DPN.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Neurology, PSG Hospital, Coimbatore, Tamil Nadu, India, from December 2017 to December 2018 in 80 DPN outpatients after getting Institutional Ethics Clearance with IEC number 17/351.

Sample size calculation: The sample size was calculated using Open Epi software version 3.01 using 80% power, 95% Confidence Interval (CI) and mean±SD values of nerve conduction obtained from a study conducted by Wu F et al., [9].

Formula for difference in means:

$$n=\frac{2\sigma^2(Z_\beta+Z_{\alpha/2})^2}{(d)^2}$$

n=Sample size of group

σ=Standard deviation of the outcome variable

d=difference in means

Z_β=Corresponds to desired power (0.84=80% power)

$Z_{\alpha/2}$=Corresponds to two-tailed significance level (1.96 for α=0.05)

The calculated sample size was 80 subjects, with 40 subjects in each group. Convenience sampling method was employed.

Group A included 40 DPN subjects without anaemia and group B included 40 DPN patients with anaemia. Subjects were considered to have anaemia based on the WHO classification of haemoglobin. According to the WHO, anaemia is defined as haemoglobin less than 12 g/dL in women and less than 13 g/dL in men [10].

Inclusion criteria: The study included both males and females of age group from 35 to 70 years diagnosed with DPN, with duration of diabetes more than one year, and was on treatment. DPN patients with and without anaemia were included in the study. Diagnosis of DPN was made using the criteria proposed in 19th annual NEURODIAB (Diabetic Neuropathy Study group of the European association) and 8th International Symposium on Diabetic neuropathy in Toronto, 2009 [11]. DSPN was confirmed, if nerve conduction abnormality was accompanied by either a symptom or sign of neuropathy. The symptoms include decreased sensation, asleep numbness, pricking, stabbing, burning or aching pain that predominantly occurs in toes, feet or leg. The signs include a symmetrical reduction in distal sensation or unequivocally reduced or absent ankle reflexes [11].

Exclusion criteria: The DPN patients with other potential causes of neuropathy such as thyroid disorders, connective tissue diseases, chronic inflammatory demyelinating polyneuropathy or neuromuscular disease were excluded from the present study. DPN patients with haemolytic anaemia or aplastic anaemia, with renal failure {estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 m^2} [12], with signs of peripheral vascular disease (ankle brachial index ≤0.9) [13] and with history of cerebral infarction, cervical spondylosis or lumbar spondylosis were excluded from the study. DPN patients with malignancy, with cardiac failure, hepatic failure or poor general conditions, with vitamin B12 deficiency and on chronic use of medications like amiodarone, isoniazid, metronidazole, nitrofurantoin, nucleoside reverse transcriptase inhibitors, immunosuppressants like TNFα inhibitors, interferons were excluded from the study.

Study Procedure

After getting informed and written consent, the data was collected. Recorders Medicare System (RMS) EMG EPM 2K version 1.0 was used to record the sensory nerve conduction parameters such as latency, amplitude and NCV. The active, reference and ground electrodes were used. The position of the electrode in context to the skin where the threshold stimulus produces a response was identified for various nerves of interest and was noted as the site of stimulus. At the optimum site of stimulation for various nerves, the stimulus was given at the rate of one per second. Initially, minimal intensity of stimuli was provided and then increased progressively to supramaximal stimulation intensity in three to four large steps. The recommended filter setting of 10 Hz to 2 kHz, sweep speed of 1 to 2 ms/division and gain of 1 to 5 μV/division was used [14]. The signal enhancement used was proportional to the square root of the number of trials [14].

Height in cm was measured using a stadiometer. The subject was made to stand upright in the stadiometer upright four hours after the last meal and height was measured between the top of the head and the sole. Weight was measured in an electronic digital weight scale machine with the subject standing upright with feet placed close to each other. Body Mass Index (BMI) was calculated by dividing weight in kilogram by square of height in metres and expressed as kg/m^2 [15]. Blood pressure was recorded using mercury sphygmomanometer with appropriate size cuff in sitting position.

Haematological parameters, glycaemic, lipid and renal parameters were obtained from patients recent records taken less than one month back. The laboratory parameters studied and their normal values are as follows:

Haematological parameters included Haemoglobin (g/dL): 13.3-16.2 g/dL in adult male and 12.0-15.8 g/dL in adult female, Mean Corpuscular Volume (MCV) (fL): 79-93.3 fL, Mean Corpuscular Haemoglobin (MCH) (pg): 26.7-31.9 pg. Peripheral smear was used for morphological classification of anaemia. The glycaemic parameters included duration of diabetes in years, Fasting Blood Sugar (FBS) (mg/dL): 75-100 mg/dL, Post Prandial Blood Sugar (PPBS) (mg/dL): <140 mg/dL. Glycosylated haemoglobin-HbA1c (%): 4-5.6%. The renal parameters included Serum Urea (mg/dL): 7-20 mg/dL, Serum Creatinine (mg/dL): 0.7-1.4 mg/dL and estimated Glomerular Filtration Rate (eGFR) (mL/min): >60 mL/min/1.73 m^2. The lipid parameters included total cholesterol (mg/dL): <200 mg/dL, Serum High-Density Lipoproteins (HDL) (mg/dL): >60 mg/dL, Low-Density Lipoproteins (LDL) (mg/dL): <130 mg/dL and triglycerides (mg/dL): <150 mg/dL [16].

The FBS and PPBS were estimated using hexokinase, UV, kinetic methods. HbA1c was assessed using High-Pressure Liquid Chromatography (HPLC). Serum cholesterol and triglycerides were measured using enzymatic endpoint methods. HDL and LDL levels were measured using direct enzymatic assays. Serum urea and creatinine were determined using enzymatic methods. The eGFR was calculated based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2009).

STATISTICAL ANALYSIS

The data collected were analysed using Statistical Package for the Social Sciences (SPSS) IBM software version 24.0. Shapiro-Wilk test was used to test the normality of variables. Normally distributed data are presented as mean±standard deviation (SD) and variables with skewed distribution are presented as median (interquartile range). Logistic regression was performed in DPN without and with anaemia, to rule out confounding variables that could influence the results. An independent t-test was used to compare the variables with normal distribution between DPN without anaemia and those with anaemia. Mann-Whitney U test was used to compare the variables with skewed distribution. The p-value <0.05 (2-tailed) was considered to be statistically significant.

RESULTS

The gender distribution was such that, out of the 80 study participants, 38 members (47.50%) were male and 42 members (52.50%) were female. Twenty (50%) were male and 20 (50%) were female in group A (DPN without anaemia). Seventeen (42.50%) were male and 23 (57.50%) were female in group B (DPN with anaemia). Chi-square test was performed between the number of males and females in both groups, which gave p-value=0.6538, there is no statistically significant difference in number of males and females in both groups. The baseline characteristics between DPN without anaemia and DPN with anaemia are given in [Table/Fig-1].

Variables	DPN without anaemia Group A (n=40)	DPN with anaemia Group B (n=40)	p-value (2 tailed)
Age (years)	50.5 (40.0, 58.7)	58.5 (48.2, 65.7)	0.007*
BMI (kg/m^2)	28.1±1.5	28.7±1.5	0.110
Haemoglobin (g/dL)	14.2±1.4	10.8±1.2	<0.001*
MCV (fL)	85.3 (82.9, 88.2)	81.5 (76.1, 87.5)	0.007*
MCH (pg)	28.3 (27.1, 29.5)	27.0 (24.5, 28.5)	0.002*
Duration of diabetes (years)	4.0 (3.0, 5.7)	6.5 (5.0, 8.0)	<0.001*
FBS (mg/dL)	119.5 (99.7, 137.7)	129.0 (103.2, 151.5)	0.161
PPBS (mg/dL)	189.0 (178.5, 200.5)	190.0 (179.2, 201.0)	0.828
HbA1c (%)	6.9 (6.6, 7.2)	6.9 (6.7, 7.5)	0.308
Total cholesterol (mg/dL)	182.5±26.3	188.3±28.6	0.347
HDL (mg/dL)	29.5 (24.2, 36.5)	30.0 (23.2, 32.0)	0.736
LDL (mg/dL)	163.5 (128.5, 175.0)	162.5 (140.0, 175.0)	0.874
Triglycerides (mg/dL)	172.0 (151.7, 180.0)	175.0 (158.2, 185.0)	0.647
Serum urea (mg/dL)	22.5 (18.0, 27.0)	25.0 (18.0, 32.0)	0.327
Serum creatinine (mg/dL)	0.6±0.1	0.7±0.1	0.745
eGFR (mL/min)	105.9±15.2	97.9±14.9	0.020*
SBP (mmHg)	128.0 (124.5, 145.0)	140.0 (132.0, 146.0)	0.005*
DBP (mmHg)	84.0 (82.0, 91.5)	90.0 (88.0, 96.0)	0.001*

[Table/Fig-1]: Baseline characteristics and clinical profile between DPN without anaemia and DPN with anaemia.
Independent t-test and Mann-Whitney U test. Data are presented as mean±SD and median (interquartile range). BMI: Body mass index; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; FBS: Fasting blood sugar; PPBS: Postprandial blood sugar; HbA1c: Glycosylated haemoglobin; HDL: High density lipoproteins; LDL: Low density lipoproteins; eGFR: Estimated glomerular filtration rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure
The p-value <0.05 (2-tailed) was considered to be statistically significant*

There was no statistically significant difference in FBS, PPBS, HbA1c, total cholesterol, HDL, LDL, TGL, serum urea and creatinine between DPN patients without anaemia and those with anaemia. Though there was a statistically significant difference in eGFR between group A and B while performing independent t-test, logistic regression did not produce a significant odds ratio. Similarly, although there was a statistically significant difference in the age, duration of diabetes, systolic and diastolic blood pressure between DPN patients without anaemia and those with anaemia; logistic regression did not produce a significant odds ratio as shown in [Table/Fig-2].

Variables	Odds ratio 95% CI	p-value
Age (years)	1.022	0.841
Duration of diabetes (years)	1.051	0.773
SBP (mmHg)	1.019	0.635
DBP (mmHg)	1.083	0.187
eGFR (mL/min)	0.959	0.758

[Table/Fig-2]: Logistic regression in DPN without and with anaemia.
SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CI: Confidence interval. p-value <0.05 (2-tailed) was considered to be statistically significant*

The NCV of the right median nerve, right ulnar nerve, right sural nerve and left sural nerve were significantly reduced in DPN with anaemia when compared to DPN without anaemia. The amplitude of the right sural nerve and left sural nerve were significantly reduced in DPN with anaemia compared to DPN without anaemia as shown in [Table/Fig-3]. Out of 40 DPN subjects with anaemia, 23 (57.50%) had mild anaemia and 17 (42.50%) had moderate anaemia. In the present study, normocytic normochromic anaemia was the predominant form of anaemia seen.

Nerves	Nerve conduction study variables	DPN without anaemia group A (n=40)	DPN with anaemia group B (n=40)	p-value (2 tailed)
Right median nerve	Latency (ms)	4.7 (3.8,5.1)	4.8 (3.7,5.2)	0.560
	Amplitude (μV)	14.9 (13.5,20.3)	14.8 (13.6,20.8)	0.551
	NCV (m/s)	49.8 (48.1,50.2)	47.5 (42.8,49.8)	<0.001*
Left median nerve	Latency (ms)	4.5 (3.6,5.2)	4.8 (3.7,5.2)	0.312
	Amplitude (μV)	14.8 (13.6,20.4)	14.5 (13.6,20.5)	0.923
	NCV(m/s)	45.1 (43.8,50.3)	47.1 (43.3,53.2)	0.123
Right ulnar nerve	Latency (ms)	4.4±0.9	4.5±1.2	0.654
	Amplitude (μV)	14.8 (13.8,21.2)	14.7 (13.6,20.3)	0.644
	NCV (m/s)	44.6±9.8	35.9±6.9	<0.001*
Left ulnar nerve	Latency (ms)	4.5 (3.6,5.1)	4.5 (3.3,5.3)	0.732
	Amplitude (μV)	14.8 (13.8,20.3)	14.7 (13.6,21.2)	0.672
	NCV(m/s)	38.5±7.2	38.3±5.8	0.915
Right sural nerve	Latency (ms)	3.1 (2.5,4.2)	3.6 (2.8,4.2)	0.401
	Amplitude (μV)	7.5 (6.2,8.7)	4.4 (3.4,5.6)	<0.001*
	NCV (m/s)	46.7 (37.4,49.8)	32.4 (28.6,39.8)	0.001*
Left sural nerve	Latency (ms)	3.5 (2.5,4.3)	3.2 (2.5,4.2)	0.349
	Amplitude (μV)	5.7 (4.2,7.3)	4.4 (3.2,5.8)	0.017*
	NCV (m/s)	45.8 (37.8,50.8)	29.5 (25.5,38.5)	<0.001*

[Table/Fig-3]: Comparison of sensory nerve conduction study variables between DPN without anaemia (Group A) and DPN with anaemia (Group B).
Independent t-test and Mann-Whitney U test. Data are presented as mean±SD and median (interquartile range). The p-value <0.05 (2-tailed) was considered to be statistically significant*

DISCUSSION

Peripheral neuropathy is one of the most important microvascular complications of diabetes mellitus, which if not treated, at an early stage may result in significant disability and poor quality of life. The gold standard of diagnosis of DPN has been NCS [17]. Anaemia in T2DM has been attributed to erythropoietin deficiency that occurs as a result of diabetic autonomic neuropathy causing efferent sympathetic denervation of the kidneys [3]. A study conducted by Sundem L et al., has shown that in nerve crush injury, erythropoietin treatment causes functional recovery of myelin and protects myelin from the effects of nitric oxide exposure [18]. Hence, erythropoietin deficiency is hypothesised as the link between anaemia and severity of DPN in T2DM [9].

Anaemia causing reduced microvascular blood flow and oxygenation may result in endoneurial hypoxia [19], which correlates with severity of nerve fibre pathology [20] and may increase the risk of DPN. Anaemia is considered to be associated with oxidative stress which is an important mechanism of DPN [21]. Erythrocytes provide antioxidant protection to tissues and organs [22], which is weakened by anaemia resulting in increased free radical production. Imbalance between free radical and antioxidant may lead to oxidative stress and result in endothelial dysfunction resulting in development of DPN [20,21].

The severity of DPN is indicated in terms of a reduction in amplitude and NCV of the nerves [9]. In the present study, DPN patients with anaemia had lower NCV and amplitude of sensory nerves when compared to those without anaemia. Reduced amplitude denotes axonal loss. Anaemia induced low oxygen-carrying capacity exacerbates endoneurial hypoxia, thus resulting in axonal loss and a reduction in amplitude [20]. Axonal degeneration and demyelination are the major pathological changes that can affect the impulse conduction in a nerve. NCV is a measure of speed of conduction in nerve fibres. A reduction in NCV doesn't always occur, unless larger myelinated fibres are lost in random [14].

A study conducted by Wu F et al., showed a reduction in sensory NCV in DPN subjects with anaemia when compared to those without anaemia [9]. The exaggerated activity of intracellular aldose reductase in diabetic subjects leads to excess formation of sorbitol

within nerve fibres. It was previously thought that, this impermeable intraneural sorbitol accumulation causes osmosis and intraneural swelling affecting conduction velocities [23].

At present, poor energy utilisation theory has been put forth by Greene stating that with an increase in sorbitol, osmolytes such as Myo-inositol, taurine, adenosine were depleted. Phosphatidylinositol and Adenosine Triphosphate (ATP) depletion as a result of myo-inositol deficiency lead to a reduction in the activity of protein kinase C and Na^+K^+ ATPase, respectively. These derangements affect the nerve conduction velocities in diabetes [24]. In the present study, the latencies were not significantly affected between DPN without anaemia and those with anaemia. Latency represents the nerve conduction time for the largest cutaneous sensory fibres. Hence, large sensory fibres are not significantly affected by anaemia in the present study.

In a study conducted by Wu F et al., the proportions of moderate/severe neuropathy system score (42.7% vs 24.5%, p<0.001) and moderate/severe neuropathy disability score (51.5% vs 38.0%, p<0.001) were higher in the anaemic group with DPN compared to the non anaemic group [9]. Univariate logistic regression analysis indicated patients with anaemia possessed an increased risk of DPN (OR=1.906, 95% CI: 1.416, 2.567, p<0.001) and this multivariate logistic regression analysis, they noted anaemia as an independent risk factor of DPN. NCV was lower in the anaemic group with DPN. This is in concordance with the results of the present study.

In a retrospective study done by Yang J et al., on a cohort of type 2 diabetic patients, it was observed that on comparison of non DPN group, haemoglobin level in the DPN group was significantly lower (118.54±16.91 g/L vs 131.62±18.32 g/L, p-value <0.01). The prevalence of DPN increased by 50.1% (95% CI: 42.2–57.0%; p<0.001) per SD decrease in haemoglobin [24]. Compared to the highest quartile of haemoglobin, the lower quartiles were associated with a significantly increased risk of DPN in the entire T2DM population (p<0.01) [24].

In the present study, normocytic normochromic anaemia was the predominant form of anaemia. The morphological classification was done based on MCV and MCH in the present study. MCV, MCH values <80 fL and <27 pg was considered to be microcytic hypochromic. MCV, MCH values between 80-100 fL and 27-32 pg were considered to be normocytic normochromic [25]. Similar to this, normocytic normochromic anaemia was the most common form of anaemia seen in patients with DPN in a study done by SinhaBabu A et al., [26]. In their study, anaemia was found in 68% of diabetic peripheralneuropathy patients. It has been postulated that efferent sympathetic denervation of kidneys as a result of diabetic autonomic neuropathy damages the renal interstitium, with resultant erythropoietin deficiency [27].

Limitation(s)

The limitations of the study include the bias of selection and information could not be avoided, as the study participants were selected from a single centre. Confounding factors were avoided to the best of abilities. The authors could not measure erythropoietin levels of patients, even though EPO deficiency may be a mechanism linking anaemia and DPN in T2DM. Further studies comparing the nerve conduction variables before and after treating anaemia with erythropoietin supplementation must be done. Association of anaemia with DPN subjects without renal compromise needs to be studied further to unravel the pathophysiology.

CONCLUSION(S)

In the present study, DPN patients with anaemia had lower NCV and amplitude of sensory nerves, when compared to those without anaemia. Special attention is required to prevent DPN in diabetic patients with low haemoglobin levels. Mild to moderate anaemia with normocytic normochromic morphology was the predominant type of anaemia seen. It is seen that, even mild to moderate anaemia could exacerbate the severity of DPN. Anaemia in DPN patients should be recognised early and treated to prevent progression to severe DPN.

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