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RESEARCH ARTICLE

Nerve conduction study in neurologically asymptomatic diabetic patients and correlation with glycosylated hemoglobin and duration of diabetes

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ABSTRACT

Background: Diabetes-induced neuropathy is one of the most challenging complications of diabetes mellitus (DM). Large number of patients has subclinical neuropathy at the time of detection of diabetes. Nerve conduction studies (NCS) remain the most reliable, accurate, and sensitive measure of peripheral nerve function. The study of F waves is particularly useful for the diagnosis of peripheral neuropathy. **Aims and Objectives:** The present study was conducted to study various nerve conduction parameters in neurologically asymptomatic diabetic patients with an attempt to evaluate their value in the early detection of subclinical diabetic neuropathy and to find out if any correlation exists. **Materials and Methods:** This case–control study was carried out on 44 neurologically asymptomatic established patients of Type II DM of both sexes, aged 40–60 years attending the medicine outpatient department (OPD). NCS parameters of various nerves were studied. Blood sugar and glycosylated hemoglobin (HbA1c) were determined. Results –a longer latency, smaller amplitude and slower conduction velocity were found in all the nerves. Persistence was found to be lower and F-wave minimum latency prolonged amongst the cases. Sensory and motor NCS were found to be inferior in those with higher HbA1c. Latency, amplitude, and Nerve conduction velocity (NCV) of sural nerve showed deterioration with the duration of diabetes. All parameters of median, ulnar and common peroneal nerves showed deterioration with the duration of diabetes with the exception of NCV in common peroneal nerve and persistence in median nerve. **Conclusions:** NCS parameters are valuable for identification and future prediction of diabetic peripheral neuropath.

KEY WORDS: Subclinical Diabetic Neuropathy; Nerve Conduction Study; F Wave; Glycosylated Hemoglobin

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by abnormalities in carbohydrate metabolism. As estimated by the international diabetes federation, there are 382 million people living with diabetes globally.[1] Individuals with diabetes are at increased risk of developing diabetic peripheral neuropathy (DPN), a debilitating microvascular complication, encountered in more than one-third of diabetic patients.[2] DPN represents a complex and progressive condition with no connection between pathological severity and development of symptoms. It may manifest heterogeneously by affecting different nerves. Distal symmetric sensorimotor polyneuropathy is the most commonly diagnosed clinical type of DPN. It is the leading cause of diabetes-related hospital admissions and is responsible for 50–75% of non-traumatic amputations. Not all patients present typical features of neuropathy, i.e., paraesthesias and weakness in upper and

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lower limbs. Up to 75% of such neurologically asymptomatic patients may have nerve conduction abnormalities that are typical of neuropathy. Subclinical diabetic neuropathy, in this context, has been defined as the presence of nerve lesions attributable to DM in the absence of abnormal clinical data but detectable through electrophysiological studies.[3]

Nerve conduction studies (NCS) are considered to be the most sensitive, reliable, non-invasive, and objective means of investigating diabetic neuropathy.[4] Routine NCS include evaluation of motor function of the median, ulnar, peroneal and tibial nerves, and sensory function of median, ulnar and sural nerves in terms of onset latency, amplitude, and conduction velocity. F waves are motor responses produced by antidromic activation of motor neurons following stimulation of motor axons peripherally. Various F-wave parameters such as minimal F-wave latency and persistence have been reported to a have a very high diagnostic reliability in diabetic patients. Plasma glycosylated hemoglobin (HbA1c) is an index of average glycemic control over the previous 2–3 months and indicates poor diabetic control; furthermore, increased HbA1c concentration is the most important risk factor for predicting DM complications. Maintaining an HbA1c level below 6.5% is critical to decreasing the incidence of diabetic complications.[5]

The transition from subclinical to clinical neuropathy in patients with DM has not been described, and despite being a gold standard for the diagnosis of all neuropathies, the value of NCS in detecting and predicting subclinical diabetic neuropathy is also not well established. It also needs to be seen which NCS parameter or combination of parameters are most valuable for this purpose.

Many investigators have examined the correlation of HbA1c levels with DM complications. However, very little research has considered the correlation between NCS parameters, HbA1c, and subclinical diabetic neuropathy. The objectives of the present study were to evaluate various nerve conduction parameters in neurologically asymptomatic Diabetic patients with an attempt to analyze their value in the early detection of subclinical diabetic neuropathy and also to see if any correlation exists between nerve conduction parameters and the levels of HbA1c.

MATERIALS AND METHODS

This case–control study was conducted in the Department of Physiology, ESIC Medical College, Faridabad, over a period of 6 months from November 2017 to April 2018. The study sample consisted of established cases of Type II DM as per criteria laid down by American Diabetes Association.[6] The cases were of both sexes, aged 40–60 years attending the medicine OPD with no signs and symptoms suggestive of autonomic dysfunction and peripheral neuropathies. The control group comprised an equal number of age-matched nondiabetic healthy individuals. The sample size was calculated using the mean values of F wave minimum latency, as shown in a previous study (95% confidence interval and 80% power).[7] Keeping the ratio of cases:controls as 1:1, the minimum sample size was calculated to be 44 in each group.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients with established diabetic neuropathy, inflammatory demyelinating neuropathies, lumbar or cervical radiculopathies or any other neurologic illness which could affect peripheral nerve conduction.
2. Chronic alcoholics, smokers, and patients with a history of occupational or environmental heavy metal exposure.
3. Patients with vitamin B_{12}, B_6 deficiency, thyroid disorders, and on medication known to cause neuropathies (Isoniazid, Anticancer, and Antiretroviral drugs).

The study was conducted after obtaining ethical clearance from the Institute's ethical committee. Written informed consent was obtained from all the participants.

NCS of the median, ulnar, tibial, peroneal, and sural nerves were done. All studies were performed with surface electrodes on physio-pac single channel polygraph with NCV, using the standardized technique.[8,9] The nerves were stimulated using 0.1 ms electrical pulses with an intensity sufficient to elicit maximal amplitude of compound muscle action potential and sensory nerve action potential. Onset latency, conduction velocity, response amplitude, and F responses were measured. For the F response, 16 stimuli were given at a frequency of 1/s. An F wave was defined as an action potential of amplitude >20 μV. The latency to onset of the first deflection from baseline was marked for each trace, and the shortest latency (minimal F-wave latency) was determined. In addition, F-wave persistence (number of stimuli eliciting F-waves) was determined. For each nerve NCS was conducted on one side only, preferably the right side.

Blood sugar and HbA1c were performed on fully automated biochemistry analyzer (Randox Daytona DX).

Statistical Analysis

The information collected was converted into a computer-based spread sheet using Microsoft Excel software. Statistical analysis of the data was done on the SPSS software 17.0. Unpaired students t-test was applied to study the difference between motor and sensory NCS parameters among cases and controls. Pearson's correlation coefficient was used to study the association between motor and sensory NCS parameters and duration of diabetes and HbA1c. $P = 0.05$ was taken to be statistically significant.

RESULTS

A total of 44 patients with DM and an equal no. of age-matched nondiabetic controls were studied. The mean duration of diabetes was 4.46 ± 2.4 years and HbA1c, 7.63 ± 2.4%. Mean age of the cases was 52.16 ± 10.12 years and mean age of controls 49.84 ± 14 years.

Table 1 shows the results of motor NCS in median, ulnar, common peroneal, and posterior tibial nerves. On applying

Table 1: Comparison of motor NCS parameters between cases and controls

Parameters	Group	Mean±SD	*t* statistic	Confidence interval		*P*
				Lower limit	Upper limit	
Latency (M) ms	Case	9.14±1.14	22.94	4.48	5.33	<0.001
	Control	4.23±0.83				
Amplitude (M)* mV	Case	3.49±1.2	−19.53	−5.19	−4.23	<0.001
	Control	8.2±1.05				
NCV (M) m/s	Case	30.6±7.9	−12.9	−21.8	−16.01	<0.001
	Control	49.5±5.5				
F min Lat (M) Ms	Case	39.6±4.11	18.85	11.15	13.78	<0.001
	Control	27.15±1.5				
Persistence (M)* %	Case	54.75±8.14	−15.226	−26.27	−20.51	<0.001
	Control	78.34±6.2				
Latency (U) Ms	Case	9.09±1.15	31.96	5.68	6.44	<0.001
	Control	3.03±0.505				
Amplitude (U) mV	Case	4±1.4	−17.82	−4.8	−3.8	<0.001
	Control	8.3±0.77				
NCV (U) m/s	Case	30.07±8.21	−18.88	−28.4	−22.99	<0.001
	Control	55.7±3.7				
Persistence (U) %	Case	54.4±9.12	−14.239	−26.44	−19.96	<0.001
	Control	77.68±5.8				
F min Lat (U) Ms	Case	38.7±3.96	17.09	9.6	12.15	<0.001
	Control	27.9±1.45				
Latency (CP) Ms	Case	9.74±1.39	24.79	5.22	6.13	<0.001
	Control	4.06±0.59				
Amplitude (CP) mV	Case	3.58±0.9	−15.5	−4.48	−3.46	<0.001
	Control	7.5±1.44				
NCV (CP) m/s	Case	29±6.65	−18.32	−22.68	−18.24	<0.001
	Control	49.4±3.2				
F min Lat (CP)* Ms	Case	69.7±4.2	25.3	18.45	21.59	<0.001
	Control	49.72±3.13				
Persistence (CP) %	Case	51.15±8.9	−16.47	−29.74	−23.34	<0.001
	Control	77.7±5.8				
Latency (PT) Ms	Case	9.93±1.3	25.14	5.06	5.93	<0.001
	Control	4.4±0.62				
Amplitude (PT)* mV	Case	3.4±0.99	−17.72	−4.3	−3.45	<0.001
	Control	7.3±1.06				
NCV (PT) m/s	Case	27.8±6.33	−20.01	−23.22	−19.02	<0.001
	Control	48.9±2.98				
F min Lat (PT)* Ms	Case	70.02±2.97	28.21	18.19	20.95	<0.001
	Control	50.44±3.5				
Persistence (PT) %	Case	54.22±8.89	−14.03	−25.37	−19.07	<0.001
	Control	76.45±5.57				

*Assumption of equal variances was violated, NCS: Nerve conduction studies, SD: Standard device, NCV: Nerve conduction velocity

t-test, the assumption of equal variances was violated in cases as shown by Levene's test for the following variables: Amplitude and persistence (median nerve), amplitude and F-wave minimum latency (posterior tibial nerve), and F-wave minimum latency (common peroneal nerve). Latency was found to be significantly higher and amplitude and NCV significantly lower among cases as compared to controls ($P < 0.001$). Similarly, F-wave minimum latency was found to be significantly higher and persistence significantly lower among cases as compared to controls ($P < 0.001$).

Results of sensory NCS are reported in Table 2. On applying *t*-test, the assumption of equal variances was violated in cases as shown by Levene's test for the following variables: NCV (median and ulnar nerve) and amplitude (sural nerve). Latency in median, ulnar, and sural nerves were found to be significantly higher among cases as compared to controls ($P < 0.001$). Amplitude and NCV were found to be significantly lower among cases as compared to controls ($P < 0.001$)

On applying the Pearson correlation statistic, the parameters of sensory and motor NCS showed a weak to moderate statistically significant relationship with HbA1c. The results are summarized in Table 3.

Varied results were obtained for correlation between duration of diabetes and NCS parameters in different nerves [Table 4].

No significant correlation was observed between latency, F-wave minimum latency, amplitude, and persistence of posterior tibial nerve and the duration of diabetes. However, NCV showed a significant negative correlation. In sensory NCS, the latency of sural nerve showed a positive correlation and amplitude and NCV a negative correlation with the duration of diabetes.

DISCUSSION

Nerve conduction changes associated with diabetic neuropathy include declining response amplitude and conduction velocity. In the present study, a significant difference was found between the NCS parameters of cases and controls. A longer latency with smaller amplitude and slower conduction velocity was found in all the nerves in both sensory and motor NCS of neurologically asymptomatic diabetic patients. Smaller amplitude reflects axonal loss and slowing of conduction velocity could be the result of a combination of segmental demyelination, loss of fastest conducting axons, and metabolic alterations.[10,11]

Panayiotopoulos and Chroni have demonstrated different patterns of F-wave abnormality in various peripheral nerve disorders. They have also reported significant and measurable changes in F-wave even before conventional NCS are informative.[12] In our study, persistence was found to be lower and F-wave minimum latency prolonged amongst the cases. Similar results have been reported by Andersen *et al.* and could be due to selective loss of fastest axons or a decreased excitability of anterior horn cells.[13] In the present study, results of sensory and motor NCS were

Table 2: Comparison of sensory NCS parameters between cases and controls

Dependent variable	Group	Mean±SD	t statistic	Confidence interval		*P*
				Lower limit	Upper limit	
Latency (M) Ms	Case	9.3±1.12	34.98	6.09	6.83	<0.001
	Control	2.9±0.47				
Amplitude (M) mV	Case	3.3±0.96	−21.34	−6.73	−5.58	<0.001
	Control	9.4±1.6				
NCV (M)* m/s	Case	28±5.5	−18.96	−22.6	−18.31	<0.001
	Control	48.5±4.5				
Latency (U) Ms	Case	9.5±1	40.09	6.3	7.05	<0.001
	Control	2.7±0.44				
Amplitude (U) mV	Case	3.2±0.99	−18.59	−5.3	−4.3	<0.001
	Control	8.11±1.4				
NCV (U)* m/s	Case	26.9±4.9	−21.69	−23.98	−19.95	<0.001
	Control	48.9±4.4				
Latency (S) Ms	Case	10.13±1.2	34.59	6.5	7.3	<0.001
	Control	3.15±0.54				
Amplitude (S)* mV	Case	3.36±1.17	−21.35	-5.2	-4.3	<0.001
	Control	8.19±0.93				
NCV (S)	Case	24.1±5.5	−19.91	−21.11	−17.28	<0.001
m/s	Control	43.34±3.03				

*Assumption of equal variances was violated, NCS: Nerve conduction studies, NCV: Nerve conduction velocity

Table 3: Correlation between HbA1c and various parameters of sensory and motor NCS

Motor NCS	Nerve	Correlation coefficient	*P*
Latency Ms	Median nerve	0.689	<0.001
	Ulnar nerve	0.568	<0.001
	Common peroneal nerve	0.642	<0.001
	PT	0.539	<0.001
Amplitude mV	Median nerve	–0.567	<0.001
	Ulnar nerve	–0.635	<0.001
	Common peroneal nerve	–0.548	<0.001
	PT	–0.394	0.008
NCV m/s	Median nerve	–0.555	<0.001
	Ulnar nerve	–0.533	<0.001
	Common peroneal nerve	–0.586	<0.001
	PT	–0.437	0.003
F min latency ms	Median nerve	0.468	0.001
	Ulnar nerve	0.573	<0.001
	Common peroneal nerve	0.554	<0.001
	PT	0.468	0.001
Persistence %	Median nerve	–0.627	0.001
	Ulnar nerve	–0.699	<0.001
	Common peroneal nerve	–0.631	<0.001
	PT	–0.525	0.001
Sensory NCS			
Latency Ms	Median nerve	0.439	<0.001
	Ulnar nerve	0.404	<0.001
	Sural nerve	0.257	<0.001
Amplitude mV	Median nerve	–0.456	<0.001
	Ulnar nerve	–0.328	<0.001
	Sural nerve	–0.165	<0.001
NCV m/s	Median nerve	–0.487	<0.001
	Ulnar nerve	–0.424	<0.001
	Sural nerve	–0.188	<0.001

NCS: Nerve conduction studies, NCV: Nerve conduction velocity, HbA1c: Glycosylated hemoglobin

found to be inferior in those with higher HbA1c. Lee *et al.* in a previous study have reported that poor glycemic control (HbA1c > 6.5%) reflects the severity of polyneuropathy as well as increased risk for its occurrence in DM patients by more than 5-fold.[14] Parkhad and Palve have reported a progressive decrease in NCV with HbA1c levels in controls, in diabetics with normal HbA1c levels and diabetics with raised HbA1c levels, respectively.[15] Previous studies have not shown any consistent relationship between the parameters of sensory and motor NCS and duration of diabetes. In the present study latency, amplitude and NCV of sural nerve showed deterioration with the duration of diabetes. This is in consistence with the results of Lee *et al.* who reported that sural sensory amplitude was significantly associated with the risk of developing clinical neuropathy.[14] Except for NCV,

Table 4: Correlation between duration of diabetes and various parameters of sensory and motor NCS

Motor NCS	Nerve	Correlation coefficient	*P*
Latency ms	Median nerve	0.366*	0.014
	Ulnar nerve	0.534**	<0.001
	Common peroneal nerve	0.348*	0.021
	PT	0.267	0.08
Amplitude mV	Median nerve	–0.545**	<0.001
	Ulnar nerve	–0.587**	<0.001
	Common peroneal nerve	–0.543**	<0.001
	PT	–0.285	0.061
NCV m/s	Median nerve	–0.549**	<0.001
	Ulnar nerve	–0.676**	<0.001
	Common peroneal nerve	–0.634	<0.001
	PT	–0.541**	0.003
F min latency ms	Median nerve	0.612**	<0.001
	Ulnar nerve	0.483**	0.001
	Common peroneal nerve	0.595**	<0.001
	PT	0.282	0.064
Persistence %	Median nerve	–0.524	<0.001
	Ulnar nerve	–0.527**	<0.001
	Common peroneal nerve	–0.425**	0.004
	PT	–0.213	0.165
Sensory NCS	Nerve	Correlation coefficient	p value
Latency ms	Median nerve	0.159	0.303
	Ulnar nerve	0.169	0.273
	Sural nerve	0.373*	0.013
Amplitude mV	Median nerve	–0.398**	0.007
	Ulnar nerve	–0.227	0.139
	Sural nerve	–0.314*	0.038
NCV m/s	Median nerve	–0.379*	0.011
	Ulnar nerve	–0.287	0.059
	Sural nerve	–0.437**	0.003

*Correlation is significant at 0.05 level (2-tailed), **Correlation is significant at 0.01 level (2-tailed), NCS: Nerve conduction studies, NCV: Nerve conduction velocity

none of the parameters of posterior tibial nerve showed any correlation with the duration of diabetes. However, all parameters of median, ulnar, and common peroneal nerves showed deterioration with the duration of diabetes with the exception of NCV in common peroneal nerve and persistence in median nerve. The correlations though statistically significant are weak to moderate. This may be because the mean duration of disease in our cases was 4.46 ± 2.4 years only. A long duration of diabetes is associated with increased

production of glycosylation end products, metabolic derangements, endothelial injury, and oxidative products. Oguejiofor *et al.* found a lower prevalence of neuropathy in those with duration of DM <5 years and highest in those with a duration of DM >15 years.[16] The association between the duration of DM and severity of neuropathy was also evident in a research study on the epidemiology of diabetic complications.[17]

The strength of our study is that a consistent deterioration in electrophysiological parameters has been observed with respect to HbA1c levels and duration of diabetes. This establishes the role of NCS as a routine investigation in all cases of subclinical DPN so that appropriate management is initiated to prevent possible neuropathic complications. However, relatively small cohort size and small number of outcomes are the limitations of this study.

CONCLUSION

The present study shows significant changes in sensory and motor NCS of neurologically asymptomatic patients and thereby confirms the findings of previous epidemiological studies. Since DPN is associated with significant morbidity, early identification of the neuropathic process offers the patient with diabetes, a crucial opportunity to actively alter the course of disease with optimal glycaemic control. We strongly believe that further studies, especially prospective models with large cohort and long-term evaluations, would be beneficial in understanding the role of NCS in patients with subclinical DPN.

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