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Abnormal Nerve Conduction Parameters in Young Diabetic Patients at Diagnosis

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Abstract:

Background and Objectives: Diabetes in the young patients, less than 30 years of age, usually has sudden onset and severe hyperglycemia who are resistant to ketosis. Taking the advantage of this uniqueness of this group of patients the present study was aimed to evaluate their peripheral nerve functional status, explore its relationship with glycemic status and find out utility of nerve conduction study for detection of neuropathy at diagnosis to introduce timely intervention in the necessary cases.

Materials and Methods: A total number of 32 newly diagnosed untreated diabetic patients, age 30 years or less, consecutively attending the BIRDEM Out-patient department were recruited. Age-matched healthy subjects (n=30) with no family history of diabetes served as controls. Motor and sensory conduction velocities (NCV), distal latencies (DL), compound muscle and sensory nerve action potentials (CAMP, SNAP) of ulnar, peroneal and sural nerves were studied following standard protocol. Glucose was determined by glucose-oxidase, Fructosamine by enzymatic colorimetric method.

Results: Ulnar motor NCV (m/sec, mean±SD) was significantly slower in diabetic group compared to the controls [58.29±6.88 vs 66.56±6.13; p<0.001]. CAMP [(µv, median] of ulnar nerve was significantly lower in diabetic patients [4.5 vs 5.8; p<0.05]. Motor nerve conduction velocity of peroneal nerve was significantly slower (p<0.0001) in diabetic patients. Peroneal nerve CMAP [µv, median] amplitude showed similar trends [5.5 vs 8.7 p<0.001]. Sural sensory NCV was significantly slower [35.22±14.04 vs 42.38±8.52; p<0.05] in diabetic patients. Peroneal nerve conduction velocity showed significant negative correlation with fasting glucose (r= -0.456, p<0.001). Peroneal motor distal latency showed positive correlation with serum fructosamine value [r=0.439, p<0.05]. Peroneal and ulnar NCV was negatively correlated [p<0.001 and p<0.05 respectively] with fructosamine. Sural sensory nerve action potential was also negatively correlated [r=-0.400 p<0.05]. S. Fructosamine was negatively correlated with sensory ulnar nerve action potential.

Conclusion: The result suggest that in the newly diagnosed untreated young diabetics of Bangladesh, abnormalities of nerve conduction parameters are detected early by doing nerve conduction study; motor nerve conduction parameters are affected more than sensory ones. Abnormal nerve conduction parameters seem to be related to degree of hyperglycaemia in early neuropathic patients.

Key words: young diabetes, neuropathy, motor function, sensory function, fructosamine

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Introduction

Manifestations of diabetic neuropathy ranges from subclinical alteration of nerve conduction, affecting practically all patients with diabetes for more than a few years, to extremely severe neuropathy with life threatening autonomic dysfunction.[1] The prevalence of diabetic neuropathy (DN) found to parallel with duration and severity of hyperglycaemia in both type-1 and type-2 diabetes and ranges from 10.7% and 43% respectively.[2] This disorder is characterized by striking atrophy and loss of myelinated and unmyelinated fibres accompanied by wallerian degeneration, segmental and paranodal demyelination and blunted nerve fibre regeneration. There is a significant relationship between clinical measures of neuropathic severity and myelinated nerve fibre loss. This progressive nerve fibre damage and loss parallels the degree and/or duration of hyperglycaemia.[3]

In the pathogenesis of human DN no single cause found to fully explain its pathophysiology.[4] A wide range of factors suggested being involved in the disturbances of peripheral nerve function.[5] Several observations implicated that hyperglycaemia or its metabolic concomitants in the pathogenesis of diabetic neuropathy.[5] Patients with newly diagnosed or poorly-controlled diabetes frequently show reduced nerve conduction velocity that improves rapidly with establishment of euglycaemia.[6] Report demonstrated progressive deterioration of nerve function with time and duration of diabetes.[7] Diabetes control and complication trial has demonstrated correlation for age, duration of diabetes, diastolic blood pressure and albumin excretion (mg/24 hrs.) with diabetic neuropathy.[8] Abnormal nerve function can be due to metabolic component, which can rapidly be reversed and is greatest in the early stages of neuropathy and a structural (more permanent) component occurring later in the disease process.[7] Studies have shown that intensified metabolic control can prevent or delay the development of diabetic neuropathy. The important factor influencing motor nerve conduction parameters in young diabetic patient is their degree of recent hyperglycaemia.[9] Accumulation of sorbitol from activation of polyol pathway seems to be an early event in both human and experimental diabetic neuropathy since increased sorbitol content is usually not found in chronically affected diabetic human nerves.[10-12] It has been shown that the glycation process is enhanced in peripheral nerve in both diabetic patients and animals.[13-14] The enhanced glycation was found responisible for segmental demylination and axonal degeneration in experimental animals.[15]

Abnormalities of nerve conduction parameters are early features of diabetic nerve damage.[16] Neurological techniques and prevalence of peripheral neuropathy are specific to the population tested. So it is important to study nerve conduction parameters in different racial groups taking into consideration that various factors may influence the parameters.[17] Some studies have shown peroneal motor nerve to have the highest abnormalities.[18]

Substantial number of young diabetic patients, registered at BIRDEM, is young.[19] They present with sudden onset of the condition, marked hyperglycaemia. They are usually hypoinsulinaemic, however, resistant to ketosis.[20] Moreover, they are not prone to develop dyslipidaemia and hypertension. But these subjects are prone to develop microvascular complications.[21] Data are lacking regarding the nerve conduction parameters of these patients in the background of severe hyperglycaemia. Taking the advantage of uniqueness of this group of patients the present study was aimed to peripheral nerve functional status and explore it relationship with glycemic status and find out necessity of any nerve functional test to be introduced in the primary tests requisite of this patients to start timely intervention, in appropriate cases and avert future morbidity.

Material and Methods

Subjects

A total number of 32 newly diagnosed young diabetic subjects without any complication and non pregnant, age below 30 years, consecutively attending the Out-patient department of BIRDEM, were recruited. Age and BMI matched 30 healthy subjects with no family history of diabetes up to second generation served as controls. The nature and purpose of the study was stated to each of the participants and written consent obtained. Diabetes was diagnosed according to WHO criteria.[19]

Methods

Collection of blood

Overnight fasting blood sample (10 ml) was collected from antecubital vein following all aseptic precaution. Blood sample was allowed to clot for 30 min and centrifuged at 3000 rpm for 10 mins. Separated serum was aliquoted and preserved -40^{o}C for further biochemical analyses.

Biochemical methods

Glucose was measured by glucose-oxidase; serum fructosamine by enzymatic colorimetric method. Creatinine was measured by alkaline picrate method. Urinary albumin was determined by immunoturbiditry method using first voided morning urine sample.

Nerve conduction study

Nerve motor nerve conduction velocities (NCV), distal latencies (DL), compound muscle action potentials (CAMP) were determined following standard protocol for nerve conduction study. For upper limb, unilateral studies of motor and sensory conduction of ulnar nerve latencies were measured. For lower limbs unilateral study

of peroneal nerve for motor conduction were measured. Unilateral study of sural nerve for sensory conduction was done for sensory conduction.

Nerve conduction velocity was measured by a standard EMG machine in a room with a temperature of 37°C. Nerve conduction parameters were included according to the protocol recommended by San Antonio Conference on diabetic neuropathy.[22]

Statistical Methods

Data were expressed as mean±SD and median (range) unless otherwise stated. The comparison between the groups was made by unpaired Student's-'t' and/ or Mann Whitney Rank sum test, as appropriate, using Statistical Package for Social Science (SPSS) for Windows Version 15. P <0.05 was considered as level of significance.

Results

Baseline clinico-biochemical data were shown in table I. Age and BMI of the two groups were matched. Very high fasting glucose level in the diabetic group reflected in their significantly higher serum fructosamine (p<0.001) levels compared to the controls. Renal functional status of the diabetic subjects was normal as evidenced by albumin creatine ratio (ACR) (Table I).

Motor nerve conduction of ulnar nerve was shown in table II. Ulnar distal latency was almost similar in the two groups. In diabetic subjects ulnar compound muscle action potential and nerve conduction velocity were significantly lower compared to the Controls (p=0.017 and 0.0001 respectively). Ulnar sensory nerve conduction study in the diabetic group did not show significant difference compared to the controls (Table III).

Peroneal motor nerve conduction was shown in table IV. Peroneal distal latency in the two groups was similar. Peroneal CMAP and NCV were significantly lower in the DM subjects (p=0.001) compared to the (Table IV).

Sural distal latency and sensory SNAP in the diabetic group did not statistical difference compared to the controls. But Sural NCV was significantly lower in the diabetic (p=0.019) group compared to the counterpart (Table V).

Correlation analysis

Motor peroneal nerve conduction velocity was found to be negtively correlated with fasting glucose [r=-0.456, p=0.001]. Motor peroneal distal latency showed significant positive correlation with fasting fractosamine [r=0.439, p=0.012]. Fasting fructosamine also showed significant negative correlation with motor Peroneal NCV [r=-0.572, p=0.001], motor Ulnar NCV [r=-0.468, p=0.007], both Ulnar and Sural SNAP (p=0.02 for both] (Table VI).

Table –I

Baseline clinical and glycemic status and renal functional status of the study subjects

Variables	DM Subjects (n=32)	Control subjects (n=30)	p value
Male (Female)	13 (19)	23 (7)	NS
Age (Yrs)	24.1±3.9	23.4±2.7	0.44
BMI (Kg/m^2)	19.1±3.5	19.4±2.2	0.76
F glucose (mmol/l)	18.65±6.73	4.80±0.55	.0001
S Fruct (mmol/l)	644±226	222±36	0.001
ACR (mg/g)	*0.84±1.09*	*1.74±3.61*	*0.20*

Results were expressed as mean±SD.

Student's unpaired't'-test was performed to calculated statistical difference between groups. P value <0.05 was taken as level of significance.

F glucose: fasting glucose; S Fruct: Serum fructosamine ACR: Albumin creatinine ratio

Table –II

Motor nerve conduction parameters of ulnar nerve

Variables	DM Subjects (n=32)	Control Subjects (n=30)	p value
U D latency (ms)	3.03±0.62	3.14±0.45	0.673
U CAMP (mv)	4.55 (1.20 - 8.70)	5.8 (3.06 -11.90)	0.017
U NCV (m/sec)	58.29±6.88	66.56±6.13	0.0001

Results have been expressed as mean±SD and median (range) as appropriate.
Student's Unpaired't'-test and Mann Whitney Ran Sum test were performed to calculated statistical difference between groups as applicable. P value <0.05 was taken as level of significance.
U D Latency: Ulnar distal latency; U CAMP: Ulnar Compound Muscle Action Potential; U NCV: Ulnar Nerve Conduction Velocity.

Table –III

Sensory nerve conduction parameters of ulnar nerve

Variables	DM Subjects (n=32)	Control Subjects (n=30)	p value
U D latency (msec)	3.05±0.48	3.09±0.28	0.689
U SNAP (mv)	10.9 (4.2–23.6)	11.05 (8.2–19.4)	0.683
U NCV (m/sec)	45.46±4.26	46.41±7.73	0.548

Results have been expressed as mean±SD and median (range) as appropriate.
Student's Unpaired't'-test and Mann Whitney Ran Sum test were performed to calculated statistical difference between groups where applicable. P value <0.05 was taken as level of significance.
U D latency: Ulnar distal latency; U SNAP: Ulnar Sensory Nerve Action Potential; U NCV: Ulnar Nerve Conduction Velocity.

Table -IV

Motor nerve conduction parameters of peroneal nerve

Variables	DM Subjects (n=32)	Control Subjects (n=30)	p value
P D latency (ms)	4.35±2.68	4.25±0.7	0.829
P CAMP (mv)	5.50 (1.40 – 12)	8.7 (4.54 – 15.50)	0.0001
P NCV (m/sec)	42.18±7.42	53.72± 6.49	0.0001

Results have been expressed as mean±SD and median (range) as appropriate.
Student's Unpaired't'-test and Mann Whitney Ran Sum test were performed to calculated statistical difference between groups as applicable. P value <0.05 was taken as level of significance.
P D latency: Peroneal distal latency; P CAMP: Peroneal compound muscle Action potential; P NCV: Peroneal nerve conduction velocity.

Table-V

Sensory nerve conduction parameters of sural nerve

Variables	DM Subjects (n=32)	Control Subjects (n=30)	p value
S D latency (ms)	3.49 ± 1.65	3.40 ± 0.48	0.766
S SNAP (mv)	12.30 (0 – 28.8)	14.05 (8.02 – 46.4)	0.075
S NCV (m/sec)	35.22 ± 14.40	42.32 ± 8.52	0.019

Results have been expressed as mean±SD and median (range) as appropriate.
Student's Unpaired't'-test and Mann Whitney Ran Sum test were performed to calculated statistical difference between groups as applicable. P <0.05 was taken as level of significance.
S D latency: Sural distal latency; S SNAP: Sural Sensory Nerve Action Potential; S NCV: Sural Nerve Conduction Velocity.

Table –VI

Correlation analysis between fasting glucose and fructosamine with different nerve conduction variables of the diabetic subjects

Variables	r	p
Fasting glucose vs		
MPNCV	-0.456	0.009
Fructosamine vs		
MPDL	0.439	0.012
MPNCV	-0.572	0.001
MUNCV	-0.468	0.007
SSNAP	-0.400	0.023
USNAP	-0.409	0.020

Pearson correlation analyses were performed. P <0.05 was taken as level of significance.

MPNCV: Motor Peroneal nerve conduction velocity; MPDL: Motor Peroneal distal latency; MUNCV: Motor Ulnar nerve conduction velocity; SSNAP: Sural Sensory nerve action potential; USNAP: Ulnar Sensory nerve action potential.

Discussion

Diabetic neuropathy is an area of ongoing interest for the researchers and clinicians, not only for the diagnosing and managing it earlier but also for understanding the disease which is still under exploration. Nerve conduction studies have been accepted as an essential part of diagnosis for diabetic neuropathy. The present study was undertaken to evaluate the functional status of the peripheral nerves in newly diagnosed, untreated, nonketotic under-30 diabetic subjects of Bangladesh by electrodiagnosis and to explore which conduction parameters are affected early. Data from healthy control subjects have given the idea about the normal range of nerve conduction parameters in this study.

The healthy controls and diabetic subjects were of comparable age and similar BMI. Among the diabetic subjects females predominated (59.38%) over males (40.63%). Like other previous studies these subjects were severely hyperglycaemic, and hypoinsulinaemic with significantly high fasting serum fructosamine level (Table I. This high glycaemic state can be explained by the fact that these patients were newly diagnosed and did not get any treatment. Moreover one of the characteristic findings of these young diabetic subjects in this region is moderate to severe hyperglycaemia.[20]

One objective of the study was to see the influence of hyperglycaemia on functional status of peripheral nerves. Ulnar motor nerve conduction velocity (UNCV) was significantly slowed (p <0.001) in diabetic subjects (Table-II). Since compound muscle action potential (CAMP) distributes in a non-gausserian manner, median range was calculated and ulnar CAMP differed significantly (p<0.05) in diabetic subjects having lower amplitudes (Table II). Peroneal motor nerve conduction velocity (MPNCV) was significantly (p<0.001) slowed in diabetic subjects. Significant difference was found in peroneal CAMP values in diabetic patients having lower amplitudes than control subjects (Table IV). None of the distal latencies in either ulnar or peroneal nerve did show any significant difference (Table II, IV). Motor peroneal nerve conduction velocity was found negatively correlated with fasting blood glucose. Both the motor peroneal and ulnar nerve conduction velocity was found negatively correlated with serum fructosamine value. Peroneal distal latency had positive correlation with serum fructosamine value (Table VI). Abnormalities of motor function in diabetic neuropathy have been observed earlier and were found to increase in frequency with the duration of the disease.[23] Sural sensory nerve conduction velocity (SSNCV) was found significantly (p<0.05) prolonged in diabetic subjects (Table V). Other parameters of sensory function did not show any significant difference among the groups (Tables III, V). Fructosamine level has negative correlations with sural and ulnar sensory nerve action potential (Table VI).

Predominantly sensory or sensorimotor distal polyneuropathy is the most common form of diabetic polyneuropathy and involvement of Sural nerves in the study subjects indicate that polyneuropathy may starts very early in diabetic patients and frequently involves sensory fibers distally.

Most of the nerve conduction parameters tended to differ significantly in diabetic subjects from those of control subjects. Dysfunction of peripheral nerves was reported previously in newly detected diabetic subjects. Our findings provide supportive evidence for the existence of an acute metabolic component of diabetic neuropathy.[24] Findings of abnormalities of motor nerve

function parameters support the hypothesis that abnormalities of motor nerve conduction velocities are related to their level of hyperglycaemia in young diabetic subjects.[25] It also supports the view that peroneal nerve has the highest abnormalities in diabetic subjects.[18] High fructosamine levels of diabetic subjects in this study indicate enhanced glycation. Correlation with fructosamine also supports the notion that the important factor influencing motor nerve conduction parameters in these young diabetic patients is their degree of recent hyperglycaemia.[23] Correlation with nerve parameters implies that there is demylination as well as axonal degeneration in young diabetic patients. Prolonged sural sensory nerve conduction velocity supports distal to proximal gradient of abnormality in diabetic sensory somatic neuropathy.

Conclusions

Data of the present study conclude that abnormalities of nerve conduction parameters are present early in young diabetic subjects of Bangladesh though these patients had recent onset of diabetes mellitus. Both motor and sensory conduction parameters are affected and motor nerve conduction parameters are affected more than sensory ones. Nerve conduction study can be done at diagnosis in young diabetic patients for detection of neuropathic changes early and thus can prevent further complications and morbidity.

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