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"A COMPARATIVE STUDY OF NERVE CONDUCTION VELOCITIES IN INDIVIDUALS WITH NORMAL AND IMPAIRED GLUCOSE TOLERANCE"

Physiology

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ABSTRACT

INTRODUCTION: Diabetes mellitus is a global problem. The prevalence of diabetes mellitus is growing rapidly worldwide and is reaching epidemic proportions. Diabetic neuropathy is the most common and troublesome complication of diabetes mellitus, accounting for 28%, leading to great morbidity and resulting in a huge economic burden for diabetes care.

AIMS AND OBJECTIVES: AIM To look for changes in Nerve Conduction Velocity in early stages of Glucose Intolerance i.e. in Impaired Glucose Tolerance (IGT). OBJECTIVES: To determine the Nerve Conduction Velocity of Peripheral Nerve in lower limb in Normal Glucose Tolerance (NGT) subjects, IGT patients. To compare and analyze Motor NCV of Peroneal Nerve and Sensory NCV of Sural Nerve in Normal Glucose Tolerance subjects, IGT patients.

MATERIALS AND METHODS: 50 subjects with normal glucose tolerance and 50 subjects with impaired glucose tolerance were selected and the study was conducted in Government General Hospital, Guntur.

RESULTS AND OBSERVATIONS: there are significant changes in latency, amplitude and velocity in the 2 groups.

CONCLUSION: The early detection of abnormal glucose metabolism is particularly important, as treatments will probably be most effective if administered early in the course of neuropathy,

KEYWORDS

Nerve conduction velocity, Sensory motor neuropathy, impaired glucose tolerance.

INTRODUCTION

Diabetes mellitus is a global problem. The prevalence of diabetes mellitus is growing rapidly worldwide and is reaching epidemic proportions [1]. Diabetic neuropathy is the most common and troublesome complication of diabetes mellitus, accounting for 28% [2], leading to great morbidity and resulting in a huge economic burden for diabetes care [3]. Diabetic patients have a 12 times higher risk of amputations when compared with non-diabetic subjects, due to diabetic neuropathy [4]. The most common pattern of diabetic neuropathy is a Distal Symmetric Polyneuropathy (DSP) in which sensory symptoms and deficits predominate and are initially confined to distal lower limbs, weakness is minimal or absent until much later and, sensory loss affects the distal lower limbs initially [5]. Prevalence of Diabetic peripheral neuropathy in Type 2 diabetic subjects in an Indian study was shown to be 26.1% [6]. India accounts for 23.5 % of the world's Disability Adjusted Life Years (DALYs) [7]. Prediabetes (intermediate hyperglycaemia), typically defined as blood glucose concentrations higher than normal, but lower than diabetes thresholds, is a high risk state for diabetes development. Prevalence of diabetes and prediabetes is increasing worldwide and experts have projected that more than 366 million people will have diabetes and 470 million people will have prediabetes by 2030.[8,9] Neuropathy has a metabolic component in its pathophysiology.[10,11] Hence early metabolic aberrations as seen in impaired glucose tolerance (IGT) may also lead to changes in the nerve conduction. Neuropathy occurring in impaired glucose tolerance (IGT) and early diabetes are phenotypically very similar, suggesting a continuum of glucose dysregulation in which some individuals are more sensitive to early distal neuropathic injury than others.[12] IGT and diabetic neuropathy patients share abnormal micro vascular endothelial dysfunction.[13] The prevention of diabetes and its complications are a far better strategy than dealing with its advanced complications. There is very little research on the prevalence of diabetes related complications in pre-diabetes patients. In this study we aim to look for changes in nerve conduction in the early hyperglycemic phase, i.e. IGT.

AIM AND OBJECTIVES

AIM: To look for changes in Nerve Conduction Velocity in early stages of Glucose Intolerance i.e. in Impaired Glucose Tolerance.

OBJECTIVES:

1. To determine the Nerve Conduction Velocity of Peripheral Nerve in lower limb in Normal Glucose Tolerance subjects, IGT patients
2. To compare and analyze Motor NCV of Peroneal Nerve and Sensory NCV of Sural Nerve in Normal Glucose Tolerance subjects, IGT patients.
3. To determine whether significant NCS changes are present in the study groups.
4. To compare and analyze NCV in variation with HbA1c in the study groups

MATERIALS AND METHODS

STUDY DESIGN: Cross sectional comparative study

SOURCE OF DATA:

Cases: Out Patient Department of Medicine, GGH, Guntur. SAMPLE SIZE -. The present study was conducted at Government General Hospital, Guntur. A total of 100 subjects were studied of which 50 were NGT, and 50 were IGT.

INCLUSION CRITERIA:

Men aged between 40-60 years Cases recruited according to American Diabetes Association (ADA) guidelines.

EXCLUSION CRITERIA:

Subjects who met the following criteria were excluded 1. Skin lesion or edema of lower limb that would interfere with NCS procedures 2. Symptoms of Neuropathy such as muscle cramps, numbness, tingling sensation, burning sensation, aching pain and abnormal hot or cold sensation in feet and lower limbs 3. History of regular alcohol consumption 4. History of liver diseases or thyroid disorders or Rheumatoid Arthritis.

DURATION OF THE STUDY: January 2015 to August 2016

METHODOLOGY:

1. Ethical Clearance was obtained.
2. Written informed consent was obtained from all participants.
3. A filled pre structured proforma and details of clinical examination were noted.

INVESTIGATIONS:

A detailed clinical history and clinical examination, HbA1c, FBS and PPBS. Nerve Conduction Study was done using the Electromyograph by Medicaide system in the Department of Neurology, GGH; Guntur. Filters were set at 2 Hz to 5 Hz and sweep speed was 5 millisecond per division for motor study. For sensory study filters were set at 20 Hz to 3 kilo Hz and sweep speed was 2 millisecond per division. Skin temperature was maintained within 36°C - 38°C. No skin preparation

was needed. Motor conduction study was performed on the Peroneal Nerve on left side. Sensory conduction study was performed on Sural Nerve on left side of the body. The targeted nerve was supra maximally stimulated using a square wave current with a duration of 0.2 millisecond. The length of each nerve was estimated with a flexible measuring tape. Nerve conduction study includes **1)** Motor nerve conduction study Parameters assessed: a) Distal motor latency b) Compound muscle action potential (CMAP) Amplitude c) Motor nerve conduction velocity **2)** Sensory nerve conduction study Parameters assessed: a) Sensory nerve action potential (SNAP) Amplitude b) Sensory nerve conduction velocity In the Nerve conduction study, the nerve was stimulated, with a set of surface electrodes attached to the skin. The first set of electrodes was used to send pulses of current to stimulate the nerve. The second set of electrodes transmits the electrical signal to the instrument. This was repeated for each nerve being tested .The nerve conduction velocity (speed) was then calculated by measuring the distance between electrodes and the time it took for electrical impulses to travel between electrodes.

OBSERVATION AND RESULTS

As is apparent from the table among the IGT subjects available for the study majority (60% of IGT) belong to the age group 51 – 60 years whereas for NGT individuals majority (52%) were in age group 40 – 50 years.

LATENCY: The latency of **peroneal nerve** was significantly longer in IGT (4.90 ± 0.98) when compared with the NGT group (3.98 ± 0.62); P 0.001.

AMPLITUDE: The amplitude among the IGT was significantly reduced in comparison with the NGT group (P 0.001).

VELOCITY: The IGT group exhibited a significantly lower mean MCV level when compared with the NGT subjects (P 0.001).

Table No. 1

Comparison of Peroneal Motor Nerve Parameters in the Study Groups				
	NGT		IGT	
	Mean	SD	Mean	SD
Latency (m/s)				
Knee	11.70	1.36	13.78	1.32
Ankle	3.98	0.62	4.90	0.98
Amplitude (mv)				
Knee	5.12	2.48	6.18	2.80
Ankle	8.39	1.95	6.33	3.67
Velocity (m/s)	51.00	3.67	42.86	6.80

LATENCY: The latency of the sural nerve in IGT (2.99 ± 0.47) and in NGT group (3.12 ± 3), not statistically significant.

AMPLITUDE: There was moderately significant reduction in amplitude in IGT when compared with NGT group with P value of 0.004.

VELOCITY: There is no significant difference in the mean SCV values between the NGT and IGT groups was noted.

Table No. 2

Comparison of Sural Nerve Parameters in the Study Groups				
	NGT		IGT	
	Mean	SD	Mean	SD
Latency (m/s)	3.12	3.00	2.99	0.47
Amplitude (mv)	15.59	8.04	11.57	5.03
Velocity (m/s)	47.21	6.92	45.26	5.63

The mean HbA1c was significantly higher (P<0.001) in IGT (6.10 ± 0.3), when compared with the NGT (5.06 ± 0.35), group.

Table No. 3

Comparison of NCV according to HbA1c				
	NGT		IGT	
	Mean	SD	Mean	SD
HbA1c (%)	5.06	0.35	6.10	0.50

DISCUSSION

Diabetic peripheral neuropathy (DPN) is an important complication and contributes to the morbidity of diabetes mellitus. Evidence indicates early detection of DPN results in fewer foot ulcers and amputations. DPN is a complex disease of progressive nerve fiber loss. A need exists for objective, simple and reproducible assessment tools like NCS, which can be readily used in clinical practice in asymptomatic stage, is employed for screening diabetics for neuropathy in subclinical stage. Type 2 DM is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and abnormal fat metabolism. In the early stages of the disorder, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemia state. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. HbA1C levels are directly proportional to blood sugar levels so there is increase in HbA1c levels in the present study.

This study confirms the well-established fact that IGT subjects exhibit abnormal MCV and SCV readings. The major finding of the study was that the IGT subjects exhibited slower MCV when compared with the NGT. This is contrary to the findings of Eriksson et al, [14] who showed that diabetes and not IGT was associated with peripheral nerve dysfunction. The mean SCV was lower in the IGT group when compared with the NGT group. In a study by Singleton et al [15], it was shown that painful sensory neuropathy was associated with IGT. Lehtinen et al[16] had reported that clinical diabetic neuropathy is not common at diagnosis of Type 2 diabetes but disturbances in peripheral and autonomic nerve function as noted by electrophysiological and cardiovascular reflex method are often present at that stage. They reported that the prevalence of abnormal Nerve Conduction Velocity was 15.2% in newly diagnosed Type 2 diabetes. In their study they found that the prevalence of sensory and motor neuropathy was 39% and 8% in the newly diagnosed diabetic (NDD) subjects and 12% and 7% in the IGT subjects. Our study showed a significant reduction in amplitude and conduction velocity of sural nerve between NGT-IGT groups, which is in accordance with the study of Cappellari A et al [17].The abnormal conduction velocity in the sural nerve, observed in IGT subjects, suggests that the myelin dysfunction of the distal sensory fibers represents the earliest detectable nerve response to the hyperglycemia. Another finding of our study is that there is no significant reduction in sural nerve conduction between NGT and IGT groups. This is in accordance with the findings of Pourhamidi K et al [18] whose extensive findings did not support the existence of neuropathy in a pre-diabetic stage. Thrainsdottir et al had shown that increased basal membrane thickening was associated with sensory peripheral neuropathy in IGT and diabetic subjects. This may be one of the reasons for slower MCVs in the IGT subjects in our study. Insulin resistance and hyperinsulinemia with associated alteration in capillary function are hallmarks of IGT and early Type 2 diabetes; it is tempting to speculate that early endoneurial capillary microangiopathy in these groups could be attributed to insulin resistance and / or hyperinsulinemia. Studies by Graf et al [19] and Tkac et al [20] had shown that the glycemic level was associated with abnormal conduction velocities. Peripheral nerve involvement is highly frequent in diabetes mellitus and it has been documented that one third of diabetic patients have peripheral neuropathy. Our study is also in accordance with study done by Viswanathan et al [21] who observed inverse correlation between sensory conduction velocity (SCV) and motor nerve conduction velocity (MCV) and HbA1c levels.

Nerve conduction studies are performed in diabetics as screening tool to detect neuropathy in subclinical stages so that strict glycemic control (HbA1c) can prevent onset and progression of neuropathic changes .Individuals who are overweight(higher BMI) can be targeted for intensive glycemic control as it is one of the additive factor for slowing of nerve conduction velocity. Prevalence of nerve conduction abnormalities in the IGT stage calls for early screening of these subjects for complications. As IGT is a forerunner of diabetes and is easily identified by standard OGTT, it is essential to look for this early marker of several metabolic abnormalities such as impaired nerve conduction. The early detection of abnormal glucose metabolism is particularly important, as treatments will probably be most effective if administered early in the course of neuropathy, when abnormalities of

peripheral nerves are more likely to be reversible. Intensified monitoring and intervention is also needed in the NDD subjects to prevent further progression of pre-existent diabetic neuropathy and to prevent the occurrence of more debilitating consequences such as foot ulceration and amputation.

Neuropathy associated with IGT primarily affects small fibers and is similar to early diabetes-associated neuropathy. Several studies have explored different states of glucose intolerance in patients with neuropathy; however the present study has tried to evaluate nerve conduction abnormalities in patients with impaired glucose tolerance. The main limitation of the study is that we should have taken F latency to assess the proximal versus distal nerve dysfunction. The early stages of DPN are postulated to involve small fibers first; in IGT patients, this may, but not always, manifest as painful neuropathy. The methods used to measure nerve conduction in this study primarily assess the large fibers; therefore, the results do not provide information on the extent of small fiber involvement. Further studies that assess the dysfunction of small, unmyelinated fibers are warranted. This was a preliminary cross-sectional study conducted to determine the presence of nerve conduction abnormalities in different stages of glucose intolerance. There is however a limitation in this study, the presence of B12 deficiency was not excluded by biochemical tests in all the study subjects.

The presence of abnormal NCV in patients with glucose intolerance found in this study needs to be confirmed by a prospective long-term study involving a larger cohort of subjects. Large prospective population based studies, coupled with evidence that primary intervention prevents neuropathy, are needed to confirm an association between IGT and neuropathy. Further studies that assess the dysfunction of small, unmyelinated fibers are warranted. The issue whether the sensory nerves can reflect the early DPN changes in IFG group is a topic that needs to be addressed in future studies.

CONCLUSION

Clinical spectrum of Diabetic Neuropathy is variable; it may be asymptomatic, but once established as neuropathy, it is irreversible and may finally be disabling. Nerve conduction studies are the most objective and noninvasive measures of nerve function. NCS can be used as a screening tool to diagnose diabetic sensorimotor polyneuropathy in subclinical stages to prevent progression of neuropathy. Nerve conduction studies are performed in diabetics as screening tool to detect neuropathy in subclinical stages so that strict glycemic control (HbA1c) can prevent onset and progression of neuropathic changes. Prevalence of nerve conduction abnormalities in the IGT stage calls for early screening of these subjects for complications. As IGT is a forerunner of diabetes and is easily identified by standard OGTT, it is essential to look for this early marker of several metabolic abnormalities such as impaired nerve conduction. The early detection of abnormal glucose metabolism is particularly important, as treatments will probably be most effective if administered early in the course of neuropathy, when abnormalities of peripheral nerves are more likely to be reversible. Intensified monitoring and intervention is also needed in the NDD subjects to prevent further progression of pre-existent diabetic neuropathy and to prevent the occurrence of more debilitating consequences such as foot ulceration and amputation. Diabetic patients have two types of polyneuropathies: a demyelinating disease that could appear in diabetic patients with and without symptoms of polyneuropathy, and an axonal loss that is responsible for most of the symptoms.

SUMMARY

In this study we aimed to look for changes in nerve conduction velocity in early stages of glucose intolerance i.e., in IGT .The present study was conducted at Government General Hospital, Guntur. A total of 100 subjects were studied of which 50 were NGT, and 50 were IGT. Nerve conduction study was done on peroneal and sural nerves. HbA1c was estimated. The IGT group exhibited a significantly lower mean MCV level when compared with the NGT subjects (p 0.001). No significant difference in the mean SCV values between the NGT and IGT groups was noted. The mean HbA1c was also significantly higher (p 0.001) in IGT when compared with the NGT group. The study confirms the well-established fact that IGT subjects exhibit abnormal MCV and SCV readings. Slower mean MCV demonstrated by IGT subjects, calls for early screening of these subjects for complications. This study also supported the idea that IGT is a transitional state before diabetes and also the importance of nerve conduction study for early detection of neuropathy.

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