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Research Article

CORRELATION OF AUTONOMIC FUNCTION TESTS IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHY

Kannan.G[1] and Ramya.N*[2]

[1]Department of Physiology, Government Dharmapuri Medical College, Dharmapuri
[2]Department of Neurosurgery, Government Vellore Medical College, Vellore

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ABSTRACT

Aims: To study the prevalence and correlate the autonomic function tests in peripheral neuropathy in patients with diabetes and impaired glucose tolerance comparing with normal controls
Settings and Design: Cross Sectional Study done during January 2016 to November 2017 in three groups of patients randomly selected from the Department of Medicine, Government Dharmapuri Medical College.
Material and Methods: History, clinical examination, blood sugar estimation, HbA1c, Oral Glucose Tolerance Tests, blood pressure, screening for macrovascular and microvascular complications of diabetes, bed side autonomic function tests and nerve conduction studies were done.
Statistical Analysis: SPSS software analysis.
Results: 67.2% of Diabetic Peripheral Neuropathy (DPN) patients,20% of Impaired Glucose Tolerance (IGT) patients and 2% of controls had sensory symptoms at presentation. 60% of DPN patients and 16% of IGT patients had sensory signs on clinical examination. Symptoms of autonomic dysfunction was observed in 6 0% D PN patients and 16% I GT patients. Signs of autonomic dysfunction was present in 78.6% of DPN patients and 24% IGT patients.
Conclusions: Peripheral neuropathy occurs in impaired glucose tolerance patients before diabetes develops.IGT peripheral neuropathy is primarily a painful small fiber neuropathy with dys-autonomia. Severe autonomic dysfunction occurs early in diabetes .A discordance between neuropathic symptoms and electrophysiological studies was found to occur.

INTRODUCTION

Diabetic neuropathy is defined as "the presence of symptoms and signs of peripheral nerve dysfunction in individuals with diabetes mellitus after the exclusion of other causes". This study was undertaken to analyze the clinico electrophysiological correlation in patients with diabetic peripheral neuropathy and impaired glucose tolerance neuropathy as well as to screen subclinical dysautonomia with bedside autonomic function tests.

Aim

To study the clinical symptomatology and signs of peripheral neuropathy in patients with diabetes, using appropriate scoring systems. To correlate clinical features and findings on nerve conduction studies. To analyse autonomic dysfunction in patients with diabetes and impaired glucose tolerance and determine the prevalence of peripheral neuropathy in patients with Impaired Glucose Tolerance.

MATERIALS & METHODS

Cross Sectional Study done during March 2009 to February 2011 in randomly selected three groups of patients from Department of Medicine, Government Dharmapuri Medical College. History, clinical examination, blood sugar estimation, HbA1c, Oral Glucose Tolerance Tests, blood pressure, screening for macrovascular and microvascular complications of diabetes, bed side autonomic function tests and nerve conduction studies were done in

1. 70 Patients (type 2 Diabetes Mellitus) with symptoms and / or signs peripheral neuropathy were selected for the study out 110 patients screened.
2. 50 Patients with impaired glucose tolerance.
3. 50 Euglycaemic normal controls.

*Corresponding author: **Ramya.N**
Department of Neurosurgery, Government Vellore Medical College, Vellore

Inclusive Criteria

Group I: Type 2 Diabetic patients referred to neurology outpatient clinic as well as those admitted in neurology wards with symptoms and / or signs suggestive of distal symmetric peripheral neuropathy and / or autonomic dysfunction.

Group II: Impaired glucose tolerance patients , as detected by Oral Glucose Tolerance Test (OGTT).

***Group III*:** Euglycaemic normal persons.

Exclusion Criteria

Patients with duration of diabetes > 20 years, asymmetric or focal neuropathies due to diabetes, chronic renal failure, Acquired ImmunoDeficiency Syndrome (AIDS), malignancy, drug induced peripheral neuropathy, chronic alcoholics, family h/o inherited neuropathies, exposure to heavy metals and toxins, lumbar/ cervical radiculopathy, nutritional deficiencies, collagen vascular diseases, hypothyroidism, dysproteinemia and amyloidosis were excluded.

METHODOLOGY

Detailed history with screening for neuropathic symptom taken and analysed using Michigan Neuropathy Screening Instrument (MNSI) scoring system. Clinical examination Bed side autonomic function tests, and Glycemic status assessment were done.Diabetes was diagnosed if the fasting plasma glucose value was > 126mg/dl or the 2 hour plasma glucose was > 200mg/dl. IGT was diagnosed if the 2 hour plasma glucose is > 140 < 199 mg/dl.

Electrodiagnosis: The Recorders and Medicare System (RMS) with recommended filter settings was used for Nerve Conduction Study (NCS). Median, ulnar nerves, Tibial and peroneal nerves studied. Computation of distal latency, amplitude of action potential and calculation of segmental Conduction Velocity were done. F minimum latency, F estimate, F:M Ratio and H Reflex analysis were done . In Sensory Median, ulnar nerves and Sural nerves were studied. Computation of latency, amplitude and calculation of segmental Conduction velocity were done. Heart rate variability and sympathetic skin response done bedside.

The normal values representative for nerve conduction studies of various peripheral nerves were derived at after analyzing the NCS of 50 controls.

RESULTS

52.9% of patients with DPN were above 51 years and the incidence increases as age increases. Prevalence of DPN was slightly higher in male diabetics (54.3%) compared to female diabetics (45.7%). 68% of patients under group 2 had abnormal Post Prandial Blood Sugar (PPBS) values in the IGT range. The Co-incidence of hypertension was more in the DPN patients (55.7%) compared to patients with IGT (6%) and controls (6%). Coronary Artery Disease (CAD) was more prevalent in DPN patients than the other two groups. Co-existent CerebroVascular Accident (CVA) was found in 7.1% of DPN patients. Nephropathy was found in 22.9% and Retinopathy in 24.3% of DPN patients. Peripheral vascular disease was present in 31.4% of DPN patients .Distal motor weakness was found in 41.4% of DPN patients. Deep tendon reflexes were sluggish to absent in 70% of DPN patients and 4% of IGT patients. 67.2% of DPN patients, 20% of IGT patients and 2% of controls had sensory symptoms at presentation. On Neuropathy Symptoms Scoring (NSS) , 23 patients had no symptoms, 15 patients scored < 5/15, 15 patients scored 6-10/15 and 17 patients scored 11-15/15. All of the IGT patients with sensory symptoms had NSS between 6-10. 60% of DPN patients and 16% of IGT patients had sensory signs on clinical examination.

Table 1 Normal Compound Motor Action Potential (Cmap) Values of Tested Nerves

CMAP'S	Distal Latency (ms)	Amplitude (mV)	Conduction Velocity (CV) (m/s)	F Wave latency (ms)
Median	<4	>4	>50	<31
Ulnar	<3.5	>4	>50\	<31
Tibial	<6	<4	>40	<56
Peroneal	<6	>2	>40	<56

Table 2 normal Sensory Nerve Action Potential (SNAP) values of tested nerves

SNAP's	Amplitude µV	CV m/s
Median	>10	>50
Ulnar	>10	>50
Sural	>6	>40

Symptoms of autonomic dysfunction was observed in 60% DPN patients and 16% IGT patients. Signs of autonomic dysfunction was present in 78.6% of DPN patients and 24% IGT patients. Semmes Weinstein Mono-Filament testing was abnormal in 100%DPN patients and 16% of IGT patients. Vibration and position sense testing (VPT) testing was abnormal in 100% DPN and 16% IGT patients. In motor NCS DPN patients had 22.9% abnormality in median, 40% in Ulnar,21.4% in tibial nerve. Peroneal motor NCS was abnormal in 42.9% of DPN patients, 4% of IGT patients and 2% of normal controls. Median SNAP's were abnormal in 22.9% DPN patients and 6% IGT patients.Ulnar SNAP's were abnormal in 48.6% of patients with DPN patients.Sural SNAP's were abnormal in 74.3% DPN patients, 8% IGT patients and 4 of normal controls. F Wave minimum latency was prolonged in 42.9% DPN patients.51.4% DPN patients had abnormal F estimate and F:M ratio.'H' reflex was abnormal in 74.3% DPN patients. H reflex abnormality was noticed in 78.6% of patients with DPN and 18% IGT patients. Somato-Sensory evoked Response (SSR) was abnormal in 78.6% DPN patients and 22% IGT patients. Duration of diabetes has no linear relationship with prevalence of DPN. 50% of patients in our study developed DPN within 10 years of detection of DM.16% of patients with high NSS scores of MNSI did not have sensory signs on clinical examination.20% of patients without any sensory symptoms had sensory signs on clinical examination. 84% DPN patients with high NSS scores had severe dysautonomia, 20% DPN patients without sensory symptoms also had severe dysautonomia. 92% DPN patients with high NSS scores had abnormalities in bedside Autonomic function testing (AFT), whereas 60% of patients with zero NSS scores (absent sensory symptoms) also had evidence of dysautonomia in bedside AFT. 80% DPN patients had no sensory symptoms (NSS = 0) but had abnormalities detectable on NCS. 16% of patients with intense sensory symptoms (NSS=3) had normal NCS values.

DISCUSSION

In this study, it was found that among the fifty IGT patients, 20% had significant neuropathic symptoms, 16% had sensory signs an examination, 16% had symptoms suggestive of dysautonomia, 8% had abnormal nerve conduction studies and 24% had signs of dysautonomia. Among the normal controls, 2% had sensory symptoms and 4% had abnormal sural SNAP'S. In a study done by Sumner *et al* (1) the neuropathy associated with IGT was found to be milder than the neuropathy associated with DM; OGTT is appropriate in patients with idiopathic neuropathy. Another study done by Singleton *et al*(2) on 107 sequential patients with idiopathic neuropathy revealed that IGT may cause or contribute to small-fiber neuropathy and stated that impaired glucose tolerance (IGT) serves as a marker of insulin resistance. Smith *et al*(3) stated that neuropathy associated with IGT primarily affects small fibers and is similar to early diabetes-associated neuropathy; Skin biopsy was abnormal in all neuropathy subjects and correlated poorly with NCS.

San Luis Valley Study(4) is a geographically based case-control study of Non Insulin Dependent Diabetes Melllitus (NIDDM) to ascertain distal symmetrical polyneuropathy in 1984-86. The prevalence of distal symmetrical neuropathy was associated with age and glucose tolerance status. Among patients with diabetes, the prevalence was lowest in those aged 20-44 years (10.3%) and highest in those aged 65-74 years (32.3%). Age adjusted prevalence was 3.9% for subjects with normal glucose tolerance, 11.2% for those with impaired glucose tolerance (IGT), and 25.8% in those with diabetes. Vishwanathan *et al*(6). has studied the nerve conduction abnormalities in different stages of glucose intolerance and has found that the mean motor conduction velocity of impaired glucose tolerance patients was significantly lower than normal individuals. Age, duration of diabetes, degree of hyperglycaemia, presence of other co-morbid risk factors particularly hypertension and presence of other macrovascular / microvascular complications contribute to the extent of peripheral nerve involvement in patients with diabetes. This study has revealed that the degree of hyperglycaemia rather than the duration of diabetes determines the development of DPN in diabetics. 50% of the patients in this study developed DPN within 10 years of detection of DM.

In our study neuropathy was found to occur at an younger age, the average age being 44 years in males and 47 years in females. But, the prevalence of neuropathy increased with increasing age and duration of DM. This study has not found association between either sex and neuropathy. Studies by Solomon *et al*(11) and Arindham Dutta *et al*(5) have also not found association between neuropathy and sex. Both systolic and diastolic BP was found to be associated with neuropathy in this study. Arindham Dutta *et al*, found in their study that systolic and diastolic Blood Pressure (BP) was higher in the neuropathy group but not statistically significant. Association of BP with neuropathy was found in studies done by Cohen *et al*(10), and Solomon O Ugoya. Though the mean fasting as well as post prandial blood sugar values were higher among patients with neuropathy, statistically significant association was found only between post prandial blood sugars and neuropathy. Similar findings were obtained by Ashok *et al*(13), "Young *et al*. Arindham dutta *et al* and Junani Partenan *et al*(12) in their studies. HbAlc above 7% was found to be strongly associated with neuropathy among the diabetics. Similar findings were obtained by J. Partenan *et al*(12), R. Pradeepa *et al*, Solomon O Ugoya, Cohen A *et al*, and M.L. Sands *et al*., In our study too, prolonged and poorly controlled DM were the most significant factors associated with Diabetic neuropathy as has been reported by others. But 18% of diabetics with reasonably good control of blood sugar also had evidence of neuropathy, which point to the interplay of several other risk factors in the development of Peripheral neuropathy in diabetics. Among the macrovascular complications of diabetes, there was an increased incidence of peripheral vascular disease (31.4%) in association with peripheral neuropathy followed by CAD (18.6%) and CVA (7.1%). Microvascular complications like nephropathy and retinopathy were more frequently found in patients with peripheral neuropathy. Nephropathy was found to occur in 22.9% of patients with DPN and retinopathy was found in 24.3% of patients with DPN. Sensory and motor involvement was more severe in the lower limbs when compared to upper limbs.

Sensory symptoms suggestive of neuropathy were found in 67.2% of our patients with DPN, in 20% of IGT patients and in 2% of control group. Arindham Dutta *et al*. found in his study that 32% had symptoms of neuropathy among newly diagnosed diabetics. Zsuzsanna Putz M.D.*et al*(7), found neuropathic symptoms in 12.19% of patients in their study on IGT patients. An increased prevalence of neuropathic symptoms was noted in our study group of patients with DPN and IGT patients with PN. Sensory signs suggestive of Peripheral neuropathy were found in 60% of patients with DPN, 0% of IGT patients and 0% of the control group. Arindam Dutta *et al*., found 30% of his study group having neuropathic signs. Zsuzsanna Putz M.D., *et al*., found a prevalence of impaired sensation in 12.5% of patients in her study on IGT patients. Distal motor weakness was observed in 41.4% of patients with DPN, with 30% of them having abnormal DTR in upper limbs and 70% having abnormal DTR in lower limbs. Klaus. P. Ratzmann (9) found loss of reflexes in 13.6% of patients in his study. Both MF and VPT were highly sensitive in detecting peripheral neuropathy as abnormality was observed in all patients with DPN using these modalities. Several workers have demonstrated subclinical involvement of nerve fibres in patients with diabetes by comparing conduction between patients and normal subjects. 80% of asymptomatic patients with DPN showed abnormal NCS findings in this study.

Abnormalities in motor nerve conduction study was found in 42.9% of diabetics with Peripheral neuropathy, 4% of patients with IGT and 2% of normal controls in this study. Arindan dutta *et al*. found the prevalence of motor nerve conduction abnormality in his study in new diabetics to be 27%. Klaus. P. Ratzmann in his study found that the prevalence of motor nerve conduction abnormality was 15.7% among newly diagnosed diabetics. Eugenia Roa *et al*(8), fund in her study that motor nerve involvement was present in 60% of patients who were new diabetics. Sevki Sahin *et al*., found in their study on the nerve conduction abnormalities in IGT that motor nerve conduction abnormalities were found in 39.5% of patients.

Sensory nerve conduction abnormalities were noted in 74.3% of diabetics, 14% of patients with IGT and 4% of normal controls. Eugenia Rota *et al*(8). found the prevalence of

sensory nerve abnormalities to be 56.4% among newly diagnosed diabetics. Sevki Sahin *et al*., in their study found sensory nerve conduction abnormalities in 21% of patients. Discordance between symptoms of peripheral neuropathy and findings on nerve conduction studies had been reported before by Sangiorgio *et al*., and Fedele *et al*. We found that 16% of our patients with symptomatic neuropathy had normal NCS findings, whereas 80% "of patients who were asymptomatic had abnormal NCS results. The remaining patients exhibited concordance between their symptoms and NCS findings. The discordance is due to the earlier involvement of small fibers in patients with diabetes which is not detected in routine NCS and the second phenomenon of discordance is due to the presence of asymptomatic or silent axonal neuropathy in many patients with diabetes.

The incidence of autonomic symptoms was very high (60%) in patients with diabetes in this study. Clinical evidence of dysautonomia in the form of abnormalities in bedside autonomic function tests were seen in 78% of patients with diabetes. Fernandez -castaner *et al* had reported that 53% of patients with diabetes had symptoms suggestive of autonomic dysfunction, while This *et al*. reported that 67 % of diabetics have cardiac autonomic neuropathy. Motor nerve conduction studies revealed a greater involvement of peroneal nerve (42.9% abnormal) than tibial nerve (21.4% abnormal) in lower limbs and in the upper limbs, ulnar nerve (40% abnormal) was more commonly involved than median nerve (22.9% abnormal). Amplitude reduction of more than 50% was the most frequent abnormality noted. Some of our patients with sensory motor neuropathy showed a prolongation in distal motor latency which we assume is due to the loss of myelinated fibres. Also few patients with sensory motor neuropathy, in addition to prolongation in latency and reduction in amplitude, showed a minimal slowing in conduction velocity. Sensory conduction studies showed that sural SNAPs were abnormal in 74.3% of patients with DPN, followed by ulnar SNAPs which were abnormal in 48.6% of patients and median SNAPs which were abnormal in 22.9% of the patient group. Either the potentials were not obtained or the amplitude was markedly reduced. F wave latencies in lower limbs were prolonged in 42% of patients indicating significant dysfunction of proximal nerve segments. 9% of patients who showed normal F minimum latencies showed abnormal F estimate values (corrected with height). Hence it is essential to calculate F estimate values in all patients with DPN. H reflex abnormality was observed in 74% of patients. SSR abnormalities were noted in 76% of patients. The small study group and potential bias of patient referral were the limitations of our study. This was a preliminary cross sectional study done to find the degree and extent of clinico - electrophysiological correlation in patients with DPN. The increased prevalence of neuropathy in impaired glucose tolerance needs to be confirmed by a prospective long term study involving a large cohort of patients.

CONCLUSION

A reasonably significant prevalence of peripheral neuropathy is found to occur in patients with impaired glucose tolerance before they go on to develop diabetes. IGT peripheral neuropathy is primarily a painful small fiber neuropathy with dysautonomia. Autonomic neuropathy is more prevalent in patients with sensory symptoms. Severe autonomic dysfunction occurs quite early in the course of the disease even when the NCS values are normal. Since autonomic dysfunction occurs early on in the disease before symptoms and signs of peripheral neuropathy occur, screening bedside AFT should be done in all patients with newly diagnosed diabetes. Early autonomic screening is mandatory in all patients with DM to prevent serious cardiac co morbidities.84% of patients with neuropathic symptoms at presentation showed abnormalities on NCS. The remaining 16% had normal NCS inspite of sensory symptoms but these patients had evidence of dysautonomia on Heart rate variability (HRV) and SSR tests. 80% of patients with no sensory symptoms of peripheral neuropathy at presentation had abnormal NCS findings (silent asymptomatic DPN) indicating the need for NCS to be done routinely in all diabetic patients periodically. A discordance between neuropathic symptoms and NCS was found to occur. Prolonged duration of Diabetes Mellitus, presence of other macro/micro vascular complications, presence of co morbidities like hypertension, increasing age and poor blood sugar control are factors associated with more severe peripheral neuropathy. A small percentage of patients with DPN who had reasonably adequate blood sugar control, paradoxically were found to have severe peripheral neuropathy suggesting that genetic predisposition may also be a contributing factor in the development of DPN. Abnormalities of late responses in NCS do occur in a significant proportion of patients with diabetic peripheral neuropathy indicating nerve cell body dysfunction in addition to axonal damage.

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