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Original Research Article

A cross-sectional descriptive study of clinical autonomic dysfunction in diabetic peripheral neuropathy

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ABSTRACT

Background: Adults having type 2 diabetes mellitus satisfying inclusion and exclusion criteria will be included. Consent of those who fit into inclusion criteria taken. 100 patients were analysed on the basis of history, clinical presentations, investigations. Patients presenting with signs and symptoms of neuropathy were accessed by nerve conduction studies (NCV), autonomic testing, heart rate variation with deep breathing, blood pressure response to standing. Arterial blood gas analysis, and CT /MRI also done.
Methods: 100 patients of type 2 diabetes were taken and study of autonomic dysfunction was done for 3 months across tertiary health care centre.
Results: Out of 100 diabetic patients under study 54 patients (54%) had diabetic neuropathy. Out of these 54, distal sensory motor neuropathy- most common (77%), sensory neuropathy- 24%. Axonal neuropathy was more prevalent than demyelinating neuropathy. Out of 100, 51 (51%) patients have autonomic neuropathy. Peripheral neuropathy was most common complication in which distal sensory motor polyneuropathy were common. Most common symptom of autonomic neuropathy was postural dizziness followed by erectile dysfunction.
Conclusions: Most common complication of type 2 DM is neuropathy. Most common neuropathy was distal sensory motor polyneuropathy whereas most common symptom of diabetic neuropathy was postural dizziness. Other autonomic dysfunction was change in blood pressure and heart after standing.

Keywords: Autonomic dysfunction, Blood pressure variation, Heart rate variation, Peripheral neuropathy, Type 2 diabetes mellitus

INTRODUCTION

Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes. Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of DAN has not been fully appreciated. India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". According to the diabetes atlas 2006 published by the International Diabetes Federation, the number of people with diabetes are currently close to 80 million people with diabetes in India and this number is expected to increase to 135 million by 2045. unless urgent preventive steps are taken. Diabetic neuropathy is the most common complication of diabetes mellitus (DM), affecting as many as 50% of patients with type 1 and type 2 DM. Diabetic autonomic neuropathy (DAN) is among the least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life in people with diabetes.[1,2] A subtype of the peripheral polyneuropathies that accompany diabetes, DAN can involve the entire autonomic nervous system (ANS).

ANS vasomotor, visceromotor, and sensory fibers innervate every organ. DAN may be either clinically evident or subclinical. It is manifested by dysfunction of one or more organ systems [e.g., cardiovascular, gastrointestinal (GI), genitourinary, sudomotor, or ocular].[3] Diabetes mellitus is characterized by various neurological complications like diabetic neuropathy, coma due to metabolic complications and strokes. In type 1 DM distal polyneuropathy typically becomes symptomatic after many years of chronic prolonged hyperglycemia, whereas in type 2, it may be apparent after only a few years of known poor glycemic control or even at diagnosis. Symptoms may include sensory, motor and autonomic features. Sensory neuropathy usually is insidious in onset and shows a stocking-and-glove distribution in the distal extremities. Sensory symptoms may be negative or positive, diffuse or focal. Motor problems may include distal, proximal, or more focal weakness. Autonomic neuropathy (AN) may involve the cardiovascular, gastrointestinal, and genitourinary systems and the sweat glands. CAN is a debilitating condition that occurs mainly among diabetic patients, especially those with a long duration of diabetes, but can manifest earlier, even before the diagnosis of diabetes.[4,5] Among its clinical manifestations, resting tachycardia, orthostatic hypotension, light-headedness, visual impairment, syncope, and exercise intolerance are the most common.

AN, diabetes, and mortality

Several studies have demonstrated the relationship between AN and increased morbidity and mortality in patients with diabetes.[6] In 1991, Ewing et al investigated the association between QT interval and corrected QT interval (QTc) length and sudden death in patients with diabetes. They showed that among 71 diabetic subjects, 13 died unexpectedly within three years of follow-up, and the QT and QTc intervals were significantly increased in these 13 participants. Thus, QT and QTc interval prolongation were associated with an increased risk of unexpected death in diabetic individuals with AN. Thereafter, in 2005, the Rochester diabetic neuropathy study (RDNS) evaluated AN and the risk factors for sudden cardiac death. Suarez et al demonstrated an association between an increase in the QTc interval and sudden cardiac death *via* univariate analysis, but this significance was not observed in the multivariate analysis.[7] Thus, they suggested that other conditions could have influenced this worse prognosis, such as nephropathy. This microvascular complication could be a marker of generalized vascular dysfunction and was marked as an independent risk factor for sudden death in the RDNS study.

Despite the RDSN findings, the diabetes heart study demonstrated that QTc interval predicted all-cause and cardiovascular disease mortality in participants with type 2 diabetes mellitus, confirming the results previously obtained by Ewing et al.[8]

Aims and objectives

To study the clinical autonomic dysfunction in diabetic peripheral neuropathy. To study the prevalence of peripheral neuropathy and autonomic neuropathy in diabetic patients.

METHODS

Randomly 100 patient of 16 to 65 years old patient was taken for study which was admitted in CPR hospital Kolhapur for 3 months between 1st January to 31st March 2014.all were subjected to nerve conduction study, heart rate, blood pressure was taken and analysis by cross sectional study was done.

Inclusion criteria

100 patients of diabetes mellitus-type I and II, admitted to tertiary centre were studied for autonomic dysfunction.

Exclusion criteria

Patients with following diseases were excluded: Anemia, Guillain Barre syndrome, malignancy, history of chronic alcohol consumption, poliomyelitis, botulism, diphtheria, alcohol induced neuropathy, history of hypertension, ischemic heart disease, congenital heart disease, heart failure.

Study tools

Patients presenting with signs and symptoms of neuropathy were accessed by 1) nerve conduction studies (NCV), 2) autonomic testing. Parasympathetic autonomic testing was done with 1) heart rate variation with deep breathing 2) immediate heart rate response to standing. Sympathetic autonomic testing was done by blood pressure response to standing.

Statistical analysis

Statistical analysis was done using IBM SPSS version 20. Chi-square test and for smaller frequencies fishers exact test of statistical analysis was used.

Informed verbal consent was taken. Institutional ethical committee approval was taken.

RESULTS

As shown in Table 1, in our study, most patients were in age group 46-55 years. Most common age group 45-54 years.

As shown in Table 2, in our study, out of 100 patients symptoms of peripheral neuropathy was seen in 54 patients (64%).

Table 1: Distribution of patients as per age and type of diabetes mellitus.

Age in years	Type 1		Type 2		Total
	Male	Female	Male	Female	
16-25	05	05	00	00	10
26-35	06	07	01	01	15
36-45	04	04	11	11	30
46-55	05	04	13	13	35
56-65	00	00	05	05	10
Total	20	20	30	30	100

Table 2: Symptoms and sign (ankle jerk) of peripheral neuropathy in patients.

Symptoms	Type 1		Type 2		Total
	Male	Female	Male	Female	
Tingling	06	06	08	08	26
Tingling and numbness	04	04	04	03	15
Tingling and burning	01	01	04	03	09
Burning	01	03	02	02	08
Weakness of legs	01	00	02	01	04
Tingling numbness and burning	00	00	01	01	02
Ankle jerk					
Present	03	03	06	04	16
Absent	12	08	15	13	48
Total					164

Table 3: Result of nerve conduction study.

Nerve conduction study	Type 1		Type 2		Total
	Male	Female	Male	Female	
Reduced NCV, reduced or absent SNAP and decreased CMAP (distal sensory motor neuropathy)	10	08	12	11	41
Reduced or absent SNAP (sensory neuropathy)	03	02	05	03	13
Decreased CMAP only	00	00	00	00	00
Total					54

Tingling was most common symptom (26%) followed by tingling and numbness (15%), tingling and burning feet (9%). On clinical examination ankle jerk was absent in 48% patients.

Table 4: Patients presenting with symptoms of autonomic neuropathy.

symptom	No. of patients with symptoms
Bladder dysfunction	12 (12%)
Postural dizziness	30 (30%)
Diarrhoea/constipation	10 (10%)
Erectile dysfunction	15 (30% males)

As shown in Table 3, out of 100 diabetic patients under study 54 patients (54%) had diabetic neuropathy. Out of these 54, distal sensory motor neuropathy- most common (77%) followed by sensory neuropathy in 24%. Axonal neuropathy was more prevalent than demyelinating neuropathy.

As shown in Table 4, out of 100 patients, postural dizziness was present in 30%, and bladder dysfunction-12% and gastrointestinal system symptoms- 10%. Out of 50 male patients, erectile dysfunction was present in 15 patients (30%).

As shown in Table 5, in our study out of 100 patients, postural hypotension was present in 30 patients (30%).

As shown in Table 6 in our study, out of 100 patients, abnormal response to standing was in 22% of patients.

As shown in Table 7, out of 100 patients, abnormal response of change in heart rate to deep breathing was in 25% of patients.

Table 5: Blood pressure response to standing.

Type 1				Type 2				Total abnormal response
Male		Female		Male		Female		
Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
04	05	04	03	06	12	07	10	
08				22				30

Table 6: Heart rate response to standing.

Type 1				Type 2				Total abnormal response
Male		Female		Male		Female		
Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
06	03	04	03	09	09	10	07	
03		03		09		07		22

Table 7: Heart rate response to deep breathing.

Type 1				Type 2				Total abnormal response
Male		Female		Male		Female		
Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
06	03	04	03	07	11	09	08	
03		03		11		08		25

DISCUSSION

Hypotheses concerning the multiple etiologies of diabetic neuropathy include a metabolic insult to nerve fibers, neurovascular insufficiency, autoimmune damage, and neurohormonal growth factor deficiency. Several different factors have been implicated in this pathogenic process. Hyperglycemic activation of the polyol pathway leading to accumulation of sorbitol and potential changes in the NAD:NADH ratio may cause direct neuronal damage and/or decreased nerve blood flow.[4] Activation of protein kinase C induces vasoconstriction and reduces neuronal blood flow. Increased oxidative stress, with increased free radical production, causes vascular endothelium damage and reduces nitric oxide bioavailability [9] Alternately, excess nitric oxide production may result in formation of peroxynitrite and damage endothelium and neurons, a process referred to as nitrosative stress [10] In a subpopulation of individuals with neuropathy, immune mechanisms may also be involved. Reduction in neurotrophic growth factors, deficiency of essential fatty acids, and formation of advanced glycosylation end products (localized in endoneurial blood vessels) also result in reduced endoneurial blood flow and nerve hypoxia with altered nerve function.[11,12] The result of this multifactorial process may be activation of polyADP ribosylation depletion of ATP, resulting in cell necrosis and activation of genes involved in neuronal damage.

Neurological complications of diabetes are common, affecting up to 50% of people with diabetes. In these patients, diabetic sensorimotor neuropathy (DSPN) is by far the most frequent complication.[13] Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes, often overlooked and misdiagnosed. It is a systemic-wide disorder that may be asymptomatic in the early stages.[14]

In our study, most patients were in age group 46-55 years. Most common age group 45-54 years. A study by Hussein et al, the mean age affected was found to be 50 years. Most of our patients showed evidence of DAN (70%). This is comparable with our study. [15]

Diabetic peripheral neuropathy (DPN), can lead to significant complications ranging from paresthesia to loss of limb and life. Patients with peripheral neuropathy often present with varying degrees of numbness, tingling, aching, burning sensation, weakness of limbs, hyperalgesia, allodynia, and pain. This pain has been characterized as superficial, deep-seated, or severe, unremitting pain with exacerbation at night.[16] In our study, out of 100 patients, symptoms of peripheral neuropathy was seen in 64 patients (64%). Tingling was most common symptom (26%) followed by tingling and numbness (15%), tingling and burning feet (9%). On clinical examination ankle jerk was absent in 48% patients.

Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes. Major clinical manifestations of DAN include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, "brittle diabetes", and hypoglycemic autonomic failure. DAN may affect many organ systems throughout the body [e.g., gastrointestinal (GI), genitourinary, and cardiovascular]. GI disturbances (e.g., esophageal enteropathy, gastroparesis, constipation, diarrhea, and fecal incontinence) are common. Gastroparesis should be suspected in individuals with erratic glucose control.[17] In our study, postural dizziness was present in 30%, and bladder dysfunction- 12% and gastrointestinal system symptoms- 10%. Out of 50 male patients, erectile dysfunction was present in15 patients (30%).

Heart rate response to deep breathing is for the most part a function of parasympathetic activity, although the sympathetic nervous system may affect this measure.[18] Similarly, it is parasympathetic activity that plays the greatest role in the heart rate regulation for short-term standing, where the act of standing involves low-level exercise and parasympathetic tone is withdrawn to produce a sudden tachycardic response.[19] In response to subsequent underlying blood pressure changes while standing, a baroreceptor-mediated reflex involves the sympathetic nerves for further heart rate control. Heart rate response to the Valsalva Maneuver is influenced by both parasympathetic and sympathetic activity. Measurements of blood pressure response to standing and blood pressure response to sustained handgrip are used to assess sympathetic activity.

As shown in Table 6 in our study, out of 100 patients abnormal response to standing was in 22% of patients. As shown in Table 7, out of 100 patients, abnormal response of change in heart rate to deep breathing was in 25% of patients. So, there was abnormal heart rate response in standing in 22% of patients and to dee breathing in 25% of patients.

Autonomic dysfunction is a prevalent and serious complication for individuals with diabetes. The clinical manifestations of autonomic dysfunction can affect daily activities (e.g., exercise), produce troubling symptoms (e.g., syncope), and cause lethal outcomes. The patient's history and physical examination are ineffective for early indications of autonomic nerve dysfunction. Early detection and management at earliest can prevent serious cardiovascular and neurological complications.

The overall results of this study can be summarized as follows:

Diabetes mellitus was common in 46-55 years of age. type I- 40% type II- 60%.

Neuropathy was the most common complication- 54% patients had peripheral neuropathy.

Out of 100 diabetic patients under study 54 patients (54%) had diabetic neuropathy. Out of these 54, distal sensory motor neuropathy- most common (77%) followed by sensory neuropathy in 24%. Axonal neuropathy was more prevalent than demyelinating neuropathy.

Tingling was most common symptom- 26% tingling and numbness- 15%.

Most common symptom of autonomic neuropathy was postural dizziness followed by erectile dysfunction.

Postural hypotension was present in 30%. Abnormal heart rate response to standing- 22% abnormal heart rate response to deep breathing- 25%.

In the study, 30% patients had cardiac autonomic neuropathy.

In type 1 DM patients, 20% patients had cardiac autonomic neuropathy.

In type 2 DM patients 36% patients had cardiac autonomic neuropathy.

It is important to note that these observations are based on small sample size and may not be generalized to large population.

CONCLUSION

Most common complication of type 2 DM was neuropathy. Most common neuropathy was distal sensory motor polyneuropathy whereas most common symptom of diabetic neuropathy was postural dizziness. Other autonomic dysfunction was change in blood pressure and heart after standing.

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