

AUTONOMIC NEUROPATHY AND DIABETIC FOOT SYNDROME

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Introduction

Autonomic Neuropathy in diabetics, contrary to the general belief that it is a late complication, can occur not only early in the natural course of the disease but even precede the diagnosis of diabetes, the best example being impotence. The assessment of autonomic neural involvement is usually done by evaluating cardiac autonomic reflex functions. The current evidence suggests that these tests reflect autonomic nervous damage not only in the heart but also elsewhere in the body.

In the present study ninety six diabetic patients were screened for cardiovascular autonomic dysfunction using the four standard tests of cardiac autonomic functions namely (1) The heart rate response to Valsalva manoeuvre, (2) Heart rate variation during deep breathing (3) Blood pressure response to sustained hand grip and (4) immediate blood pressure response to standing from lying. The results of the study were correlated with the clinical symptoms of autonomic neuropathy and peripheral neuropathy in the patients tested.

Materials and Methods

Ninety six diabetic patients attending the Diabetic Clinic of the Govt. General Hospital, Madras formed the subjects of this study. Out of these ninety six subjects ten were insulin dependent diabetics and the rest were non-insulin dependent diabetics. The age group of the study subjects ranged from 20-60 years and the duration of diabetes from one year to 23 years.

All were subjected to a careful clinical assessment, particular attention being given to the presence of clinical evidence of peripheral and autonomic neuropathy. A routine resting twelve lead ECG was done and detailed fundus examination was carried out. Patients with ECG evidence of IHD and those who had proliferative diabetic retinopathy were excluded from this study.

Twenty age matched healthy controls were also assessed for the presence of cardiac autonomic neural dysfunction.

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Study Protocol: All the ninety six subjects were subjected to the tests in the morning hours between 10 AM and 12 Noon. No smoking was allowed on the morning of the study and subjects were instructed not to take medications like aspirin, vitamins or anti-histamines for atleast 48 hours before the test.

The results of the four tests were categorised and depending on it the subjects were put into one of the following four groups.

1. Normal-in which the response to all the four tests were within normal limits.
2. Early parasympathetic in which one test for parasympathetic nerve involvement was abnormal the rest of the tests being normal.
3. Definite parasympathetic: Two tests of parasympathetic nerve function being abnormal.
4. Combined parasympathetic and sympathetic in which in addition to abnormal parasympathetic test results findings in one or both sympathetic tests were abnormal.

Results:

Clinical Profile:(Table-I)

Table I
Clinical Features

Clinical Features	No. of patients	Total (%)
Sexual Dysfunction	32	33.33
Peripheral Neuropathy	25	26.04
Diabetic Ulcer (Foot)	10	10.42
Background Retinopathy	11	11.45
Nephropathy (Diabetic)	3	3.12

Out of the ninety six subjects of this study 32 (33.33%) had sexual dysfunction in the form of erectile failure. Clinical features of peripheral neuropathy was found in twenty five subjects (26.04%). Ten patients (10.42%) had chronic diabetic ulcer of the foot. Eleven patients (11.45%) had evidence of

diabetic back ground retinopathy while three (3.12%) had albuminuria. Except for sexual dysfunction (in 32 subjects) no other clinical evidence (Diabetic diarrhoea, atonic bladder, urostatory sweating, and postural hypotension) of autonomic neuropathy was present in any of the study subjects.

Controls: None of the twenty healthy non-diabetic control subjects showed any abnormal response in any of the four tests of cardiac autonomic nerve functions. *Diabetics'*- 76 out of the ninety six subjects studied (79.16%) showed evidence of abnormal cardiac autonomic nerve function, one or more of the four tests being abnormal. The results of each of the four tests were categorised in to three groups as (1) normal (2) Border line and (3) abnormal. Based on this the following results were obtained (Table-2).

Table II
Cardiac autonomic reflex study results in diabetics

Test	Normal Response (%)	Abnormal Response	
		Border line %	Definite %
Valsalva Manoeuvre	40 (41.66)	23 (23.95%)	33 (34.27)
H.R. Variation during deep Breathing	26 (27.08)	20 (20.83)	50 (52.68)
BP response to standing	65 (67.70)	23 (23.95)	8 (8.33)
BP response to sustained hand grip	64 (66.66)	14 (14.58)	18 (18.75)

1. *Valsalva manoeuvre:* Forty subjects showed (41.66%) normal response (valsalva ratio of 1:21) while 23 subjects (23,95%) showed border line (V.R: 1.11 to 1.20) response. The rest ie. 33 subjects (34.37%) showed abnormal response V.R. 1.10).

2. *H.R. Variation during deep breathing:* Twenty six out of the 96 (27.08%) showed normal response (15 beats/mt). Twenty (20.83%) showed border line response (11-14 beats/mt) while 50 subjects should abnormal response (10 beats/mt) being 52.68% of the total.

3. *Blood Pressure response to standing*: Sixty five subjects (67.70%) had normal response (10 mm of Hg fall) whereas 23 patients (23.95%) showed border line abnormality (11-29mm of Hg fall). Eight subjects (8.33%) showed abnormal response the fall in systolic B.P. being more than 30 mm of Hg.

4. *B.P. response to sustained hand grip*: Sixty four subjects (66.66%) had normal rise of diastolic B.P. on sustained hand grip (16mm of Hg) 14 subjects (14.58%) showed border line response (11-15 mm of Hg) where as 18 subjects (18.75%) had abnormal response (10 mm of Hg).

Correlation of Autonomic Neuropathy with the clinical profile of the study subjects (Table-III)

Table III
Correlation of Autonomic Neuropathy with the Clinical features of the subjects

Clinical Feature (No. of patients)	Autonomic Neuropathy			
	Total (%):	Para sympathetic	Sympathetic	Combined
Sexual Dysfunction (32)	21 (65.62)	10	1	10
Peripheral Neuropathy (25)	16 (64)	6	5	5
Diabetic Ulcer (Foot) (10)	10 (100)	3	Nil	7

Sexual Dysfunction: Out of the 32 patients who presented with clinical features of sexual dysfunction, twenty one (65.62%) showed evidence of autonomic neuropathy. Out of these twenty one subjects, 10 had parasympathetic involvement alone, one had involvement of the sympathetic alone whereas ten showed evidence of both sympathetic and parasympathetic involvement.

Peripheral Neuropathy: Sixteen (64%) of the 25 subjects who had clinical features of peripheral neuropathy had abnormal cardiac autonomic function test results. Out of this six had parasympathetic test abnormality, 5 had sympathetic test abnormality.

Diabetes Ulcer Foot: All the ten subjects who had chronic diabetic ulcer of the foot showed abnormal response. Three out of this ten had parasympathetic test abnormality while seven had combined abnormality.

Correlation of duration of Diabetes with Autonomic Neuropathy:

From Table IV it can be seen that the duration of diabetes and the incidence of autonomic neuropathy has no direct relationship.

Table IV
Correlation of duration of Diabetes Mellitus with Autonomic Neuropathy

Duration of Diabetes	No. of patients	Autonomic Neuropathy
0-4 years	50	43 (86.0%)
5-9 years	15	11 (73.33%)
10-14 years	18	12 (70.0)
15-19 years	10	7 (70.0)
More than 20 years	3	3 (100%)

Discussion

Of late it has been recognised that autonomic neuropathy is fairly common and wide spread in patients with diabetes mellitus. It is not only common but can also occur very early in the course of diabetes.² In the past little attention has been paid to this complication of diabetes. This is perhaps because patients with autonomic neuropathy remain mostly asymptomatic and also ideal investigative techniques for autonomic neuropathy were not available.

Recent reports have shown that cardiovascular reflex abnormalities are useful simple tests for assessment of autonomic neural dysfunction.^{3,4,5} The commonly used tests have been the Valsalva manoeuvre, beat to beat heart rate variation, blood pressure response to sustained hand grip and postural hypotension.⁸

In the study group 79.16% of the subjects studied showed abnormal response to one or more of the tests performed. This is in close agreement with other studies in the past which have put the incidence of autonomic neuropathy in diabetics to be about 70%^{7,8}. Para sympathetic involvement was found to be more common (58.32%) for Valsalva manoeuvre testing and 73.5% for beat to beat heart rate variation testing) than sympathetic (32.28% for postural hypotension test and 33.33% for diastolic response to sustained hand grip testing).

This can be easily explained as several studies have shown that it is the parasympathetic system which is involved early in diabetes.

Impotence has been reported to occur in 30-60% of diabetics⁹ and autonomic neuropathy is believed to be the major cause. In the present study of the 32 diabetics who clinically presented with erectile dysfunction 65.62% showed evidence of autonomic neuropathy.

Peripheral Neuropathy and Autonomic Neuropathy

Diabetic Neuropathy can be classified into four major types and two of these types namely the peripheral polyneuropathy and the autonomic neuropathy are thought to have a metabolic etiology.¹⁰ If this is true then symmetrical, proportional and generalised involvement of the peripheral nerves and autonomic nerves are to be expected.

In the present study only sixteen subjects out of the ninety six screened had both autonomic dysfunction and clinical features of peripheral neuropathy, while the overall incidence of autonomic nerve dysfunction was 79.16%. If the above mentioned theory that neuropathy in Diabetes Mellitus is due to a metabolic abnormality and should involve the peripheral and autonomic nerves equally is true then the figures of the present study do not correlate with that theory. But this can be explained if the alternative hypothesis that the neural involvement in diabetes is a multifactor diffuse process and has a broad based non selective process of involvement is considered.¹⁰ If this is true (then) the autonomic nerves and the peripheral nerves may be affected individually.

In diabetic subjects with symmetrical sensory neuropathy, the relationship between large fiber (peripheral somatic nerves) and small fibre (autonomic nerves) damage is not uniform¹¹ and the predominant type of fiber damage may determine the form of the presenting clinical syndrome.

More over it is now accepted that autonomic nerve function tests tend to be abnormal very early in diabetes even within 12 months of known duration of diabetes¹² while peripheral nerve involvement is a relatively late complication.

One significant finding in this study was that all the ten patients who had chronic diabetic ulcer foot had autonomic neuropathy. This is not surprising as it is being increasingly realised that autonomic neuropathy plays an important role in initiating and propagating chronic ulcer of the foot in diabetics.¹⁸ There is evidence from experiments on dogs that somatic denervation alone is insufficient to cause ulceration and that sympathetic denervation is also necessary before ulceration occurs. Recent evidence indicates that there are marked abnor-

malities of blood flow in legs of patients with diabetic autonomic neuropathy.¹⁴ Sympathetic involvement of the blood vessels of the foot results in arterio-venous shunts being formed due to opening up of the pre-existing vessels in the tissues of the foot due to increased blood flow.¹⁵ Sympathetic involvement also results in sweating abnormalities in the legs and such abnormalities are common in diabetic feet with ulcers.¹⁶

In this study the incidence of autonomic neuropathy has no significant correlation with the duration of diabetes. Lloyd et al reported similar findings.⁸

Summary

Ninety six diabetic subjects, ten insulin dependent and the remaining non-insulin dependent and ten healthy control subjects have been studied to assess cardiovascular autonomic dysfunctions and the results were correlated with the clinical profile of the subjects.

The overall incidence of cardiac autonomic dysfunction was found to be 79%. Parasympathetic involvement being more common than sympathetic. A close association was found to exist between abnormal cardiac vascular autonomic function tests and impotence, peripheral neuropathy and chronic diabetic ulcer of the foot. No association was found to exist between the duration of diabetes and cardiac autonomic Neuropathy.

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