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PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY (CAN) IN PATIENTS OF TYPE 2 DIABETES MELLITUS (T2DM) – A STUDY FROM EASTERN INDIA.

***[1]Dr. Sumit Kumar Chakrabarti, [2]Atindra Nath Bandopadhyay and [3]Pradip Kumar Datta**

*[1]DM (Endocrinology) Associate Profesor General Medicine NRS Medical College & Hospital 138, A.J.C. Bose Road Kolkata 700014.
[2]MD General Medicine DM (Cardiology) Post-doc Trainee Cardiology I.P.G.M.E. & R. & SSKM Hospital 244, A.J.C. Bose Road Kolkata-700020.
[3]MD General Medicine Profesor General Medicine I.P.G.M.E. & R. & SSKM Hospital 244, A.J.C. Bose Road Kolkata-700020.

*** Corresponding Author Dr. Sumit Kumar Chakrabarti**
DM (Endocrinology) Associate Profesor General Medicien NRS Medical College & Hospital 138, A.J.C. Bose Road Kolkata 700014.

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ABSTRACT

Background: Presence of symptoms along with abnormal cardiovascular function tests suggest poor prognosis with increased incidence of silent myocardial infarction & sudden cardiac death. The present study was undertaken to highlight the magnitude of the problem in Eastern India.**Materials and Methods:** Total 80 male and female subjects suffering from type 2 diabetes mellitus (T2DM) were selected. The battery of autonomic cardiovascular tests performed as bed side procedure included tests reflecting cardiac parasympathetic damage, heart rate response to deep breathing, heart rate response to standing. Tests reflecting sympathetic damage conducted were blood pressure (BP) response to standing, BP response to sustained hand grip. Other routine investigations performed included complete hemogram, serum urea, creatinine, Na, K, lipid profile, liver function test, urine analysis and albumin creatinine ratio, USG abdomen, chest x ray and echocardiography. **Results:** Cardiac Autonomic Neuropathy (CAN) was found in 50% of study subjects. Of those detected with CAN, Parasympathetic neuropathy was found in 50% cases and sympathetic neuropathy in 23.75% cases. Symptoms of CAN were less commonly encountered. Dizziness on standing was encountered in 37.5% patients. Bladder symptoms, abnormal sweating and diarrhea were other symptoms commonly encountered. With increasing duration of diabetes, HRV on standing doubled in group B (5 – 10 years duration) but unaltered in group C (>10 years duration) compared with group A (diabetes duration less than 5 years). The most significant abnormality was HRV with breathing which was absent in group and appeared in group B and significant in group C for BP response to standing but not for BP response to isometric hand grip. Very significant changes in HDL data was found between group A and C with which there was also significant change between group A and C in HRV breathing, BP response to standing and isometric hand grip. Retinopathy was detected, both non proliferative and proliferative in 10% of T2DM patients in the present study. **Conclusion:** CAN is detected by different cardiac autonomic function tests. Parasympathetic dysfunction is early to appear but does not increase linearly with duration. Sympathetic dysfunction appears late and expresses a partial liner increase. CAN symptoms are not as sensitive as autonomic function test to detect cardiac neuropathy. Assessment of autonomic cardiovascular reflexes affords a satisfactory method of evaluation of CAN. Parasympathetic cardiac autonomic function test are more sensitive for the detection of CAN than sympathetic test. HRV deep breathing is the most sensitive parasympathetic abnormality detection test, followed by HRV standing and HRV valsalva maneuver. BP response to postural hypotension is slightly more sensitive than that of BP response to isometric hand grip.

KEYWORDS: Cardiac Autonomic Neuropathy, Type 2 diabetes mellitus, India, Prevalence.

INTRODUCTION

Type 2DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose output. Its prevalence increases with age and is rising much more rapidly because of increasing obesity and reduced activity levels.[1] It constitutes a growing concern to population all over the world because of its well-known chronic complications particularly the triad of neuropathy, retinopathy and nephropathy which have close correlation with its metabolic abnormalities.

The International Diabetes Federation has recently published reports and according to that by the year 2025,

In India, there are going to be eighty percent of all diabetics from the entire world, this makes India the diabetic capital of the world.[2]

Neuropathy is the most common complication in Type 2 DM.[3] Yet it remains the least investigated. Such prolonged lack of attention could lead to delay in diagnosing cardiac autonomic neuropathy (CAN). This is not only a frequent cause of disability & morbidity but it contributes to mortality as well.[4] One of the earliest manifestation of diabetic autonomic neuropathy is denervation of cardiovascular system[5]. Hence the assessment of cardiovascular reflexes affords a satisfactory evaluation of CAN. The prevalence of autonomic nervous system dysfunction in T2DM is not precisely known, however tests of autonomic function have shown impairment in nearly 20% - 30% of patients with diabetes.[6] So the ADA recommends for screening for autonomic neuropathy at the time of diagnosis of T2DM. Presence of symptoms along with abnormal cardiovascular function tests suggest poor prognosis with increased incidence of silent myocardial infarction & sudden cardiac death.[7]

The present study was undertaken to highlight the magnitude of the problem in Eastern India

MATERIALS AND METHODS

The study was conducted in the Department of General Medicine, OPD as well as Indoor at Institute of Post Graduate Medical Education and Research (IPGME&R), Kolkata 20. Total 80 patients suffering from T2 DM were selected. This included both male and female subjects who were available and willingly participated during study period. Patients were selected irrespective of their therapeutic status. Patients who were suffering from uncontrolled hypertension and/ or heart failure and proliferative retinopathy were excluded from the study. Necessary ethical committee approval was obtained. Mercury sphygmomanometer, electrocardiography machines and modified mouth piece were used for evaluation of cardiac reflexes.

The battery of autonomic cardiovascular tests performed as bed side procedure are described below:[8]

Tests reflecting cardiac parasympathetic damage

I. Heart rate response to valsalva maneuvers:[9] The test was performed by the patient blowing into a mouth piece connected to a sphygmomanometer and holding it at a pressure of 40 mmHg for 15 seconds while a continuous ECG was recorded. The maneuver was performed three times with interval of one minute in between. The result was expressed as the valsalva ratio which is the ratio of the longest R – R interval after the maneuvers to the shortest R – R interval during the maneuver. The mean of three valsalva ratio was taken as the final value (normal valsalva ratio 1.21, borderline between 1.11 and 1.20, abnormal ≤ 1.10).

II. Heart rate response to deep breathing:[10, 11, 12] The patient sat quietly and breathed deeply at 6 breaths a minute (5 seconds in and 5 seconds out) for one minute. An ECG was recorded throughout the period of deep breathing with a marker used to indicate the onset of inspiration and expiration. The maximum and minimum R – R intervals during each breathing cycle were measured and converted into beats/minute. The result was then expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles in beats/minute (normal response ≥ 15 beats/minute, borderline 11 – 14 beats/minute, abnormal response ≤ 10 beats/minute).

III. Heart rate response to standing.[13]. The test was performed with the patient lying quietly on a couch while heart rate was recorded continuously on ECG machine. The patient was asked to stand up unaided and the point at starting to stand was marked on ECG. The shortest R – R interval at or around the 15th beat and largest R – R interval at or around the 30th beat after starting to stand were measured with a ruler. The characteristic heart rate response was expressed by 30:15 ratio which is normal if it is ≥ 1.04, borderline between 1.01 and 1.03 and abnormal if ≤ 1.00 .

Tests reflecting sympathetic damage

1. Blood Pressure response to standing:[14.15, 16]. The test was performed by measuring the patient's BP while he was lying down quietly and again when he stood up. The postural fall after 3 minutes of standing was taken as the difference between systolic BP lying and systolic BP standing (normal response ≤ 10 mmHg, borderline 11 – 29 mmHg, abnormal response ≥ 30 mmHg).

II. Blood Pressure response to sustained hand grip: After instructions in using hand grip of an inflated BP cuff, the subject gripped maximally with his dominant arm for few seconds; this was repeated thrice. Highest of the three readings is called maximum voluntary contraction (MVC). Now the subject was instructed to maintain hand grip steadily at 30% MVC for as long as possible to a maximum of 5 minutes. BP was measured on non-exercising arm and diastolic BP (DBP) was taken at muffling of sound. The BP was recorded three times at rest & at intervals of one minute during hand grip. The result was expressed as the difference between the highest DBP during hand grip began (normal response ≥ 16 mmHg, borderline 11- 15 mmHg, abnormal response ≤ 10 mmHg). All borderline tests were interpreted as normal in the present study.

Other routine investigations were performed. These included complete hemogram, serum urea, creatinine, Na, K, lipid profile, liver function test, urine analysis and albumin creatinine ratio, USG abdomen, chest x ray and echocardiography.

RESULTS AND ANALYSIS

The age of the subjects varied from 30 to 78. Maximum number of patients (30%) was in the age group of 51 to 60 years followed by age group of 61 to 70 years (27.5%). Younger patents (7.5%) in the age group 31 to 40 years constituted insignificant portion. Sixty percent of the subjects were male. The maximum number of patients were suffering from type 2 diabetes mellitus (45%) for duration of 5 – 10 years and maximum of them were male (25%).

Among the symptoms studied, dizziness on standing was the most frequently encountered symptom (37.5%) followed by abnormal sweating (15%), diarrhea (15%), bladder dysfunction (7.5%), impotence (7.5%) and dysphagia (5%). Dizziness on standing was not always associated with documented postural hypotension on formal testing. (Table 1)

Table 1: Prevalence of clinical symptoms among study subjects

Symptoms	No. of cases
Dizziness	30 (37.5%)
Abnormal sweating	12 (15%)
Diarrhea	12 (15%)
Bladder dysfunction	6 (7.5%)
Impotence	6 (7.5%)
Dysphagia	4 (5%)

Among the various autonomic functions studied, heart rate response to deep breathing was found to be the most sensitive test for detecting autonomic neuropathy. It was abnormal in 27 (33.75%) patients, borderline in 14 (17.5%) of cases and normal in 39 (48.75%) of cases. This was followed by abnormal heart rate response to standing (30:15 ratios). This was found abnormal in 22 (27.5%) of cases, borderline in 8 (10%) of cases and abnormal in 50 (62.5%) of cases. Abnormal handgrip test was in 10 (12.5%) of cases, borderline in 18 (22.5%) of cases and normal in 52 (65%) of cases. Valsalva ratio was abnormal in 14 (17.5%) of cases, borderline in 28 (65%) of cases and normal in 38 (47.5%) of cases. The postural drop was abnormal in 15 (18.75%) of cases, borderline in 20 (25%) of cases and normal in 45 (56.25%) of cases. (Table 2)

Table 2: Distribution of cardiovascular abnormalities among type 2 diabetes mellitus patients

Cardiovascular tests	Normal	Borderline	Abnormal
Postural hypotension	45 (56.25%)	20 (25%)	15 (18.75%)
Sustained handgrip on BP	52 (65%)	18 (22.5%)	10 (12.5%)
HRV with respiration	39 (48.75%)	14 (17.5%)	27 (33.75%)
HRV with valsalva	38 (47.5%)	28 (35%)	14 (17.5%)
HRV with standing	50 (62.5%)	8 (10%)	22 (27.5%)

Among the neuropathies detected, parasympathetic neuropathy was seen in 40 cases (50%) which is significantly higher than the sympathetic neuropathy detected in 19 cases (23.75%), $p < 0.001$. (Figure 1) Autonomic neuropathy was significantly higher amongst insulin resistance (IR) group (assessed by HOMA-IR model), $p < 0.05$, but IR status varied insignificantly among genders.

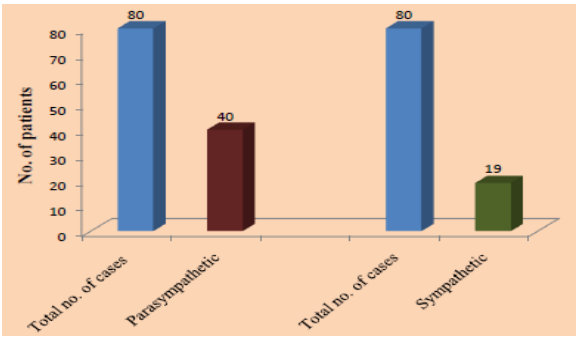

Figure 1: PREVALENCE OF NEUROPATHY

There is also an increasing prevalence of autonomic neuropathy with increasing duration of diabetes. The prevalence of parasympathetic neuropathy among patients with duration less than 5, 5-10 and greater than 10 were 3.75%, 21.25% and 25% respectively while sympathetic neuropathy being 0%, 10% and 13.75% respectively. Statistical analysis reveals a p value of < 0.05 which is significant. In our study, patients with CAN it was observed that all patients with sympathetic neuropathy (19 i.e. 23.75%) had parasympathetic neuropathy but the reverse was not true.

Microalbuminuria was found in 28 (35%) cases. Of 28 patients 22 (78.57%) had cardiac neuropathy and microalbuminuria and rest 6 (21.43%) had microalbuminuria without any abnormal autonomic function testing. Statistical analysis reveals a p value of 0.001 which is significant. Diabetic retinopathy was detected in 8 patients (10%), all of them had microalbuminuria and CAN. Hence, retinopathy was invariably associated with CAN but the reverse was not true.

Table 11 depicts that HRV to deep breathing is the most sensitive parasympathetic cardiac autonomic function test, which detects CAN, followed by HRV to standing and HRV to Valsalva. Blood pressure response to postural hypotension is slightly more sensitive in

sympathetic arm than that of blood pressure response to sustained 46 hand grip. HDL levels gradually came down with increasing duration of type 2 diabetes.

DISCUSSION

In this study Cardiac Autonomic Neuropathy (CAN) was found in 50% of study cases. Of those who were detected with CAN, Parasympathetic neuropathy was found in 50% cases and sympathetic neuropathy in 23.75% cases. It is in conformity with Ewing et. al[17] and Nijwawan et. al.,[18] and John et. al.[19] Heart rate response to deep breathing was the most sensitive test, 33.75% in this study. This is also in conformity with reports of John et al.[19]

Symptoms of CAN were less commonly encountered in the present study. Dizziness on standing was encountered in 37.5% patients. Bladder symptoms, abnormal sweating and diarrhea were other symptoms commonly encountered in this study. These results are also inconformity with the previous study reports by John et al.[19] The earliest marker for alteration in autonomic function available was HRV on standing which was significant. With increasing duration of diabetes this function doubles in group B (5 – 10 years duration) but unaltered in group C (>10 years duration). The most significant abnormality was HRV with breathing. The sympathetic abnormality was absent in group A (< 5 years duration) and appeared in group B and significant in group C for BP response to standing but not for BP response to isometric hand grip. Very significant changes in HDL data was found between group A and C (p 0.0000059) with which there was also significant change between group A and C in HRV breathing, BP response to standing and isometric hand grip. Retinopathy was detected, both non proliferative and proliferative in 10% of T2DM patients in the present study. Microalbuminuria was noted in 35% of patients in the above study. It was also associated with CAN.

LIMITATION OF THE STUDY

The study had few limitations of the study in the sense that the findings of the study could not be broadly generalized as it was conducted only in one selected hospital. Furthermore the study was confined to small number of subjects which further limited the generalization of the findings. Participants in the study were selected through non probability purposive sapling technique so bias might be present. The findings were restricted to the patients of type 2 diabetes mellitus. The study was confined to overt diabetes mellitus and pre-diabetics were not included

CONCLUSION:

The present study revealed the prevalence of CAN in 50% of T2DM study population. CAN is detected by different cardiac autonomic function tests. Parasympathetic dysfunction is early to appear but does not increase linearly with duration. Sympathetic dysfunction appears late and expresses a partial liner increase. CAN symptoms are not as sensitive as autonomic function test to detect cardiac neuropathy. Assessment of autonomic cardiovascular reflexes affords a satisfactory method of evaluation of CAN. Parasympathetic cardiac autonomic function test are more sensitive for the detection of CAN than sympathetic test. HRV deep breathing is the most sensitive parasympathetic abnormality detection test, followed by HRV standing and HRV valsalva maneuver. BP response to postural hypotension is slightly more sensitive than that of BP response to isometric hand grip. Statistical analysis reveals CAN is strongly associated with other microvascular complication of diabetes viz. retinopathy and microalbuminuria.

CAN is the most unpredictable life threatening complication and commonest cause of sudden cardiac death in T2 DM subjects by producing fatal arrhythmias. Though incidence of CAN at onset of T2DM is very small, but it progresses relentlessly with advancing disease process. Till now no telltale investigation to document the presence of CAN is available either to qualify or quantify the problem. Adequate therapeutic modalities are lacking except use of selective beta blockers. Thus assessment of CAN to be done routinely in all T2DM cases particularly before anesthesia and surgery. Simple clinical tests are very much predictive than sophisticated investigations and should be practiced as a routine procedure.

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