Original Research Article

Cardiac autonomic neuropathy in diabetes mellitus

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ABSTRACT

Background: The present study was conducted with an objective to study the prevalence of cardiac autonomic neuropathy (CAN) in patients with diabetes mellitus (DM) and its relation to duration, severity of DM, patient's age and BMI.

Methods: This hospital based prospective study was conducted from August 2015 to September 2017, at M.K.C.G. Medical College Hospital, Berhampur, Odisha, India. Cross sectional study was design. A total number of 100 diagnosed patients of diabetes mellitus who were admitted in hospital or attended on OPD basis were taken for the study. Detailed history, clinical evaluation, laboratory investigations were carried out. The diagnosis of CAN was made by autonomic function tests. The CAN score of each patient was analysed. Database were generated based on age, duration of diabetes, severity of DM and BMI.

Results: Out of 100 diabetic patients, 40 patients (23 males and 17 females) were selected for final analysis after excluding conditions causing cardiac autonomic neuropathy other than diabetes mellitus. All the patients were in the age group 21 to 70years. In the present study it was found that 57.5% of patients with DM had CAN and its incidence increased with severity of hyperglycemia, duration of DM, BMI and age of the patient.

Conclusions: Cardiac autonomic neuropathy is a common and early complication of DM. Proper history taking to identify the symptoms related to CAN and performing simple autonomic tests in all patients of DM can identify cardiac autonomic neuropathy.

Keywords: Autonomic function tests, Cardiac autonomic neuropathy, Diabetes mellitus

INTRODUCTION

Diabetes mellitus 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 the metabolic abnormalities, characteristic of diabetes.

It is well known that diabetes is associated with an increased cardiovascular morbidity and mortality. Cardiac autonomic neuropathy (CAN) probably contributes to the poor prognosis of cardiovascular disease in type 1 and type 2 diabetes mellitus.[1-4] The main risk factor for autonomic neuropathy was poor glycemic control, but hyperinsulinemia also had predictive role in the development of parasympathetic autonomic neuropathy. Interestingly, both parasympathetic and sympathetic neuropathies predicted 10year cardiovascular mortality independent of conventional risk factors. Diabetic individuals generally have less myocardial MIBG uptake with more pronounced regional differences from base to apex than do patients without diabetes.[5,6] Histological damage to cardiac afferent nerve fibers has been demonstrated in diabetic patients with silent myocardial infarction.

Numerous studies have documented that increased mortality in diabetic patients with CAN in type 1 diabetics, 5year mortality in patients with CAN exceeded in 5year mortality in those without CAN by five folds.[7]

Clinicians have recognized for some time that myocardial ischemia or infarction associated with less severe angina in a diabetic versus a non-diabetic patient.[8-11] CAN may explain the blunted appreciation of cardiac ischemic pain in diabetic patients. Instead of typical angina, patients may have shortness of breath, diaphoresis, gastrointestinal complaints, profound fatigue or abrupt changes in glycemic control.[12,13] In one study that used ambulatory ST segment monitoring to examine diabetic patients with documented CAD, over 90% of ischemic episodes were asymptomatic.[14]

Diabetic patients with CAN show a homogeneous distribution of myocardial infarction throughout the full 24hour period, while diabetics without CAN have a circadian pattern of ischemia like that seen in nondiabetic patients, with a typical prominence in the early morning.[14-16] The status of the ANS can affect coronary blood flow regulation independent of mechanisms mediated by endothelial cell function.[17] Diabetic patients with sympathetic nervous system dysfunction have impaired dilation of coronary resistance vessels in response to cold pressor testing when compared with diabetics without defects in cardiac adrenergic nerve density.[18]

The relationship of sudden death to glucose intolerance was examined in 8000 Japanese American men after 23years follow up in the Honolulu Heart Program. It demonstrated that diabetes was independently associated with the risk of sudden cardiac death.[19] The presence of QT dispersion on the 12 lead ECG reflects dispersion of ventricular refractoriness and increased risk for arrhythmia. When compared with a non-diabetic control group and a diabetic group without CAN, QT dispersion was greatest in diabetic patients with CAN.[20]

A series of bedside maneuvers can aid in the diagnosis of CAN and differentiate the relative contribution of parasympathetic and sympathetic dysfunction in CAN. These tests use the ECG to measure beat to beat heart rate variation during deep breathing, at assumption of an upright posture, and during the Valsalva maneuver. Recently, tests have emerged that can detect the presence of CAN before symptoms develop. A number of methods assess heart rate variability during 24hour recordings and thereby permit detection of subtle disorders in autonomic balance.[21,22]

The objective of the study was to know the prevalence of cardiac autonomic neuropathy in diabetes mellitus and to know the correlation of cardiac autonomic neuropathy with age, duration of diabetes mellitus, other systemic diabetic complications, severity of diabetes mellitus and BMI.

METHODS

The present study was conducted from August 2015 to September 2017 in the Department of General Medicine, M.K.C.G. Medical College Hospital, Berhampur, Odisha, India. Cross Sectional study was design, with a sample size of 100. The work was carried out after the study protocol was approved by the Institutional Ethics Committee. Informed consent was obtained from all the participants. 100 diabetic patients attending the OPD or admitted to different wards of medicine department were screened to exclude the co-morbid conditions likely to affect the autonomic nervous system. After screening of all the 100 diabetic patients, 40 patients were selected for final analysis, who fulfilled the inclusion exclusion criteria.

A detailed medical history was obtained. Particular attention was given to duration of symptoms if any of diabetes mellitus including polyuria, polydipsia, polyphagia, unexplained weakness and weight loss. A complete physical examination including weight, height, BMI, waist hip ratio and ankle-brachial index were done and investigations including complete haemogram, urine routine and microscopy, urine for micro albumin, fasting plasma glucose, post prandial plasma glucose, HBA1c, lipid profile, renal function test, liver function test. Nephropathy was diagnosed by proteinuria >300mg/day in the absence of urinary tract infection, hypertension or cardiac failure. Retinopathy was assessed by opthalmoscopy after pupillary dilatation. BMI calculated as weight (kgs) divided by height (meters) [2].

The autonomic cardiovascular function tests were performed: Heart rate response to valsalva maneuver, Heart rate variation during deep breathing, Immediate heart rate response to standing constitutes test for parasympathetic function. BP response of standing, BP response to sustained hand grip were used for sympathetic nervous system assessment. The prevalence of CAN was assessed by Ewing's methodology, borderline test results were also taken as CAN.[23]

Inclusion criteria

Diagnosed cases of diabetes mellitus as per existing criteria, i.e.

- Symptoms of diabetes plus random blood glucose concentration ≥ 200 mg/dL or
- Fasting plasma glucose ≥126mg/dL or
- Hemoglobin A1c ≥ 6.5 % or
- 2hour plasma glucose ≥200mg/dL during an oral glucose. tolerance test.
- In the absence of unequivocal hyperglycemia and acute metabolic decompensation, the criteria confirmed by repeat testing on a different day.

Exclusion criteria

Other conditions causing cardiac autonomic neuropathy excluded such as Hypertension, Ischemic heart disease, Valvular heart disease, Hepatic cirrhosis, Prostatic enlargement, Heart failure, Urinary tract infection, Fever, Secondary hyperglycemic conditions like Cushing syndrome, pancreatitis, acromegaly, pheochromocytoma, hyperthyroidism, drug induced GDM.

Statistical analysis

Descriptive statistical analysis of data like frequency and percentages were used for categorical variables. Mean and standard deviation were used for describing continuous variables. Inferential statistical tools like Chi-Square test and Student's t-test were used. P-value of <0.05 was considered statistically significant.

RESULTS

Out of 40 patients studied with an age group of 20 to 70 years, 57.5% were males and 42.5% were females. Among them 20% cases had Type 1 DM and 80% had type 2 DM. The duration of DM varied from newly diagnosed cases (12.5%) to more than 10 years duration (25%). 37.5% cases had duration of DM from 0-5years and 25% cases had DM for 6 to 10 years. Severity of diabetes mellitus was assessed by glycosylated Hb estimation at the time of admission. Good glycemic control was seen in 25% of cases (HbA1c<7). Similarly, 25% of cases had uncontrolled DM (HbA1c>8), rest 50% had HbA1c between 7 and 8.

Patients presented with various symptoms due to autonomic dysfunction. Dizziness on standing was the most common symptom encountered in 40% of cases. Other symptoms were bladder symptoms 20%, abnormal sweating 15%, impotence 20%, diarrhoea 10% and dysphagia 5%.

A series of clinical tests to assess cardiac autonomic affection were performed.[23] It was observed that 57.5% of the case had evidence of Cardiac autonomic neuropathy.

Among the 3 tests to detect parasympathetic neuropathy, heart rate response to valsalva maneuver was abnormal in 25% cases, heart rate response to deep breathing was abnormal in 25% cases and heart rate response to standing constitutes 27.5% cases of cardiac autonomic neuropathy.

Among the sympathetic tests, abnormalities in blood pressure response to sustained handgrip was found in 20% and postural hypotension, which is least common abnormality was seen in 15% of the patients. It was also found that no significant difference in CAN between type 1 and type 2 DM. Also, there was no significant difference of prevalence of CAN between males and females.

It was indicated from the present study that duration of DM had a positive correlation with CAN. Newly diagnosed cases had 7.5% prevalence whereas cases with >10years duration had 25% prevalence of CAN. Similarly, severity of disease had also positive co-relationship with CAN. Only 7.5% with HbA1c<7 had CAN, whereas it was as higher than 30% in these subjects with HbA1c>8, (p-0.043).

It was further observed that as age increases occurrence of CAN also increases (17.5% of cases in 7th decade had CAN in contrast to only 2.5% in 3rd decade).

In the present study, patients with other chronic complications like nephropathy and retinopathy had 100% association with CAN.

Body mass index also had an influence on the occurrence of CAN. Patients with higher BMI of more than 30 had prevalence of CAN 27.5% cases, whereas patients with normal BMI of 19-25 had CAN in only 12.5% of cases.

Table 1: Age and sex distribution of cases.

Age group	Male	%	Female	%	Total	%
21-30	0	0	1	2.5	1	2.5
31-40	5	12.5	3	7.5	8	20.0
41-50	5	12.5	5	12.5	10	25
51-60	8	20	5	12.5	13	32.5
61-70	5	12.5	3	7.5	8	20
Total	23	57.5	17	42.5	40	100

Table 1 shows out of 40 cases total no of males were 23 (57.5%) and females were 17 (42.5%).

Table 2: Distribution of cases as per types of DM.

Type	Male	%	Female	%	Total	%
Type-1	5	12.5	3	7.5	8	20
Type-2	18	45	14	35	32	80
Total	23	57.5	17	42.5	40	100

Table 2 shows Type-1 DM 8 cases (20%) and Type-2 DM 32 cases (80%).

Table 3 shows symptoms of autonomic dysfunction. All cases had some form of autonomic disturbance. Dizziness on standing was the most common symptom. Dysphagia was seen only in one case.

Table 4 shows moderately severe diabetes was found in 50% of cases. Table 5 shows different clinical tests performed to identify cardiac parasympathetic and sympathetic damage.

No. 1 to 3 reflects parasympathetic damage while No. 4 and 5 reflects sympathetic nervous system.

Table 3: Distribution of cases as per clinical symptoms.

Symptoms	Male	%	Female	%	Total	%
Dizziness on standing	8	20	8	20	16	40
Bladder symptoms	4	10	4	10	8	20
Abnormal sweating	3	7.5	3	7.5	6	15
Impotence	4	10	0	0	4	20
Diarrhoea	3	7.5	1	2.5	4	10
Dysphagia	1	2.5	1	2.5	2	5
Total	23	57.5	17	42.5	40	100

Table 4: Distribution of cases as per severity (taking account of HbA1c).

HbA1c level	Male	%	Female	%	Total	%
< 7	6	15	4	10	10	25
7-8	12	30	8	20	20	50
>8	5	12.5	5	12.5	10	25
Total	23	57.5	17	42.5	40	100

Table 5: Distribution of cases as per autonomic function tests.

Tests	Male	%	Female	%	Total	%
Heart rate response to valsalva maneuver	6	15	4	10	10	25
Heart rate response to deep breathing	6	15	4	10	10	25
Heart rate response to standing	7	17.5	4	10	11	27.5
Postural hypotension	3	7.5	3	7.5	6	15
B.P. Response to sustained hand grip	4	10	4	10	8	20
Combining all tests	12	30	11	27.5	23	57.5

Table 6: Distribution of can based on type of DM.

Type of DM	Total no. of cases	Male with can	%	Female with can	%	Total with can	%
Type 1	8	3	37.5	2	25	5	62.5
Type 2	32	9	28.2	9	28.2	18	56.25
Total	40	12	30	11	27.5	23	57.5

DISCUSSION

The present cross sectional study was conducted to derive the prevalence of CAN in DM. There were 23 (57.5%) males and 17 (42.5%) females (Table 1). Highest incidence of DM was seen in the 6th decade of life. 20% of cases were type I DM and rest 80% cases were type 2 DM (Table 2).

The cases were categorized into 4 groups depending upon the duration of the diseases, like newly diagnosed cases, 0-5years duration, 6-10years duration and more than 10years duration. Maximum number of cases had DM between 0-5years (37.5%). Only 12.5% cases are newly diagnosed patients. As per the severity of the diseases classified basing on HbA1c level, the cases were categorized into three groups i.e., HbA1c level less than 7, between 7 and 8 and more than 8. Maximum number of cases (50%) had glycated haemoglobin between 7-8 (Table-4).

Observing the clinical symptoms among patients it was found that dizziness on standing was the most common symptom (40%), among them males were 20% and females were 20%. Dysphagia was least common symptom in the present series. Diarrhoea, abnormal sweating and impotence was present in 10%, 15% and 20% of patients respectively (Table-3). In 2002 at Jaipur, India, S. Mehta, D. Mathur, Krishna Verma et al, conducted a study on CAN in type 2DM where they found that dizziness on standing was the most common clinical symptom. We found that dizziness on standing

was common in both type 1 and type 2DM patients. Table 5 shows the distribution of cases as per the tests done to identify parasympathetic and sympathetic affection of cases. It revealed that CAN was present in 57.5% cases (23 out of 40). Mehta et al, also found that CAN was prevalent in 57% cases of type 2 DM.[24]

The heart rate response to valsalva was most common abnormality seen in our study group (30%). The abnormal heart rate response to valsalva was present in 20% of males and 10% females. Among other parasympathetic tests heart rate response to deep breathing was abnormal in 10% and heart rate response to standing was abnormal in 11%. Postural hypotension was the least common abnormality found in our study. This is in conformity with reports of Ewing and Nigawan, 2003, who studied association of CAN and DM with microalbuminuria.

As per distribution of CAN according to age and sex it revealed that, increase in the age had a significant association with increased prevalence of CAN. We observed that more number of CAN patients were in the age group of 61-70years (17.5%) and least in age group 21-30years (2.5%). In our study we also found that males and females had same incidence of CAN.

Taking into consideration of type of DM there is no significant difference of prevalence of CAN between type 1 DM and type 2 DM. A study design taking more number of cases may reflect the discrepancy more accurately.

We also observed that there was correlation between duration of DM and CAN. When the DM was >10years the incidence of CAN was 25% and in newly detected cases CAN was found only 7.5%. NN Guyenthi et al, also found that duration has a stronger correlation with CAN. But JR White and JH Fuller et al (Diabectologia, 2005) found no correlation between duration of DM and CAN. More studies are required to establish a clear relationship.

Severity of DM was also related to prevalence of CAN, when HbA1c is more than 8 the incidence of CAN was 30% and when less than 7 it was 7.5%. Study by E. Maeser and M. James et al, Department of Medical Technology, University of Delaware, New York (2004) also found that incidence of CAN was more in severe DM patients.

It may be due to the hyperglycemic activation of polyol pathway leading to accumulation of sorbitol and potential changes in NAD: NADH ratio may causing direct Neuronal damage and/or decrease blood flow.

When we studied the association of CAN with other complications like retinopathy and nephropathy it was seen that such complications were invariably associated with CAN. Mehta et al, also found the same result taking type 2 DM cases. We found the same observation in both type 1 DM and type 2 DM.[24]

We found that there is a linear correlation between body mass index and CAN i.e., incidence of CAN was 27.5% when body mass index (BMI) is >30 and 17.5% when BMI is 26-30 and 12.5% when BMI is 19-25.

CONCLUSION

From the above discussion it is concluded that cardiac autonomic neuropathy is a common and early complication of DM and it is associated with increased mortality due to cardiovascular related causes. Paucity of related symptoms leads to delayed detection of CAN. Proper history taking to identify symptoms related to CAN and performing simple autonomic tests in all patients of DM can identify cardiac autonomic neuropathy. Our study shows that 57.5% of the cases of diabetes mellitus had cardiac autonomic neuropathy and its incidence increased with severity of hyperglycemia, age and associated nephropathy.

REFERENCES

1. Töyry JP, Niskanen LK, Mäntysaari MJ, Länsimies EA, Uusitupa MI. Occurrence, predictors, and clinical significance of autonomic neuropathy in NIDDM: ten-year follow-up from the diagnosis. Diabetes. 1996;45(3):308-15.
2. Sampson MJ, Chambers JB, Sprigings DC, Drury PL. Abnormal diastolic function in patients with type 1 diabetes and early nephropathy. Heart. 1990;64(4):266-71.
3. O'Brien IA, McFadden JP, Corrall RJ. The influence of autonomic neuropathy on mortality in insulin-dependent diabetes. Q J Med. 1991;71:495-502.
4. Orchard TJ, Lloyd CE, Maser RE, Kuller LH. Why does diabetic autonomic neuropathy predict IDDM mortality? An analysis from the Pittsburgh Epidemiology of Diabetes Complications Study. Dia Res Clinic Pr. 1996;34:S165-71.
5. Kreiner G, Wolzt M, Fasching P, Leitha T, Edlmayer A, Korn A, et al. Myocardial m-[123I] iodobenzylguanidine scintigraphy for the assessment of adrenergic cardiac innervation in patients with IDDM:comparison with cardiovascular reflex tests and relationship to left ventricular function. Diabetes. 1995;44(5):543-9.
6. Hume L, Oakley GP, Boulton AJ, Hardisty C, Ward JD. Asymptomatic myocardial ischemia in diabetes and its relationship to diabetic neuropathy: an exercise electrocardiography study in middle-aged diabetic men. Diab Care. 1986;9(4):384-8.

7. O'Brien IA, McFadden JP, Corrall RJ. The influence of autonomic neuropathy on mortality in insulin-dependent diabetes.Q J Med. 1991;71:495-502.

8. Marchant B, Umachandran V, Stevenson R, Kopelman PG, Timmis AD. Silent myocardial ischemia: role of subclinical neuropathy in patients with and without diabetes. J Amer Coll Cardiol. 1993;22(5):1433-7.

9. Faerman I, Faccio E, Milei J, Nunez R, Jadzinsky M, Fox D, et al. Autonomic neuropathy and painless myocardial infarction in diabetic patients: histologic evidence of their relationship. Diab. 1977;26(12):1147-58.

10. Ambepityia G, Kopelman PG, Ingram D, Swash M, Mills PG, Timmis AD. Exertional myocardial ischemia in diabetes: A quantitative analysis of anginal perceptual threshold and the influnce of autonomic function. J Ame Coll Cardiol. 1990;15(1):72-7.

11. Burgos LG, Ebert TJ, Asiddao C, Turner LA, Pattison CZ, Wang-Cheng R, et al. Increased intraoperative cardiovascular morbidity in diabetics with autonomic neuropathy. Anesthesiol. 1989;70(4):591-7.

12. Bradley RF, Scronfeld A. Diminished pain in diabetic patients with myocardial infarction-silent and asymptomatic. Eighteen year follow up:the Frammingham Study. Am J Cardiol. 1973;32:1-7.

13. Soler NG, Bennett MA, Pentecost BL, Fitzgerald MG, Malins JM. Myocardial infarction in diabetics. QJM: Inter J Medic. 1975;44(1):125-32.

14. Zarich S, Waxman S, Freeman RT, Mittleman M, Hegarty P, Nesto RW. Effect of autonomic nervous system dysfunction on the circadian pattern of myocardial ischemia in diabetes mellitus. J Ame Coll Cardiol. 1994;24(4):956-62.

15. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation. 1989;79:733-43.

16. Bernardi L, Ricordi L, Lazzari P, Solda P, Calciati A, Ferrari MR, et al. Impaired circadian modulation of sympathovagal activity in diabetes. A possible explanation for altered temporal onset of cardiovascular disease. Circ. 1992;86(5):1443-52.

17. Di Carli MF, Tobes MC, Mangner T, Levine AB, Muzik O, Chakroborty P, Levine TB. Effects of cardiac sympathetic innervation on coronary blood flow. N Eng J Medic. 1997;336(17):1208-16.

18. Di Carli MF, Bianco-Batlles D, Landa ME, Kazmers A, Groehn H, Muzik O, et al. Effects of autonomic neuropathy on coronary blood flow in patients with diabetes mellitus. Circulation. 1999;100(8):813-9.

19. Curb JD, Rodriguez BL, Burchfiel CM, Abbott RD, Chiu D, Yano K. Sudden death, impaired glucose tolerance, and diabetes in Japanese American men. Circulation. 1995;91(10):2591-5.

20. Kahn JK, Sisson JC, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. J Clin Endocrinol Metab. 1987;64:751-4.

21. Ziegler D, Dannehl K, Mühlen H, Spüler M, Gries FA. Prevalence of cardiovascular autonomic dysfunction assessed by spectral analysis and standard tests of heart-rate variation in newly diagnosed IDDM patients. Di Care. 1992;15(7):908-11.

22. Ewing DJ, Neilson JM, Shapiro CM, Stewart JA, Reid W. Twenty-four-hour heart rate variability: effects of posture, sleep, and time of day in healthy controls and comparison with bedside tests of autonomic function in diabetic patients. Heart. 1991;65(5):239-44.

23. Ewing DJ, Campbell IW, Clark BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. Ann Intern Med. 1980;92;308-11

24. Mehta S, Mathur D, Chaturvedi M, Verma K. Incidence of cardiac autonomic neuropathy and its correlation with retinopathy, microalbuminuria and glycated haemoglobin in non-insulin dependent diabetes mellitus. JIMA. 2002;100(3):1-2.