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A STUDY OF PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN DIABETES MELLITUS PATIENTS IN A TERTIARY CARE HOSPITA

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ABSTRACT : Introduction: Cardiovascular autonomic neuropathy (CAN) in diabetes is the strongest risk factor for cardiovascular mortality. The aim of this study was to estimate the prevalence of CAN in Type1 and Type2 diabetic patients.

Methods : 50 patients were included in this study. All patients were evaluated for detection of CAN with standardised cardiovascular reflex tests and patients were categorised as per Ewing's criteria.

Results : Tests were abnormal in 62% cases. Early CAN was detected in 14% and severe CAN seen in 14%. Sympathetic dysfunctions was seen in 8%, parasympathetic dysfunctions in 16% patients . 38% cases demonstrated combined sympathetic and parasympathetic dysfunctions .

Conclusion : CAN is common in diabetes mellitus and simple bedside autonomic function tests can used for it's early detection and prevention of cardiovascular disease related morbidity and mortality.

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Keywords: Diabetes mellitus, Cardiovascular autonomic neuropathy

I. INTRODUCTION

Cardiac autonomic neuropathy(CAN) is a common underdiagnosed complications of DM. Presence CAN is associated with increased mortality and morbidity of DM[1]. Longitudinal studies have shown a 5-year mortality rate of 16%-50% in both T1DM and T2DM once CAN had been diagnosed, with most of these attributed to sudden cardiac death[6]. Several studies examined the prevalence of CAN in patients with type1 DM and type2 DM. These studies showed a large variation in CAN prevalence: 17-66% in patients with T1DM and 31-73% in patients withT2DM.

The incidence of CAN has been reported to be 6% and 2% annually in patients with T1DM and T2DM , respectively[2].The prevalence of CAN increased from 9% at the close of the DCCT study to 31% one year later[2]. Similarly, prevalence of CAN increased from 19.8% in patients with prediabetes to 32.2% in patients newly diagnosed with T2DM, with higher prevalence reported in patients with T2DM and longer diabetes duration. DCCT showed a 50% decrease in CAN incidence over a 6.5-year follow-up in its intensive therapy cohort. Participants in the DCCT intensive therapy group who were free from CAN at the end of the study had a 31% reduction in risk of incident CAN when compared to those in the control arm[3]. Pathogenesis of CAN includes is unclear and probably multifactorial. Hyperglycemia, autoimmunity and inflammation are the major contributing factors in the pathogenesis of CAN in DM.

Clinical manifestation and consequences of CAN includes:

a)Resting tachycardia which is one of the earliest signs of CAN. A fixed and unresponsive HR to breathing is associated with complete cardiac denervation and severe CAN[4].

b)reduced exercise tolerance: parasympathetic denervation and sympathetic predominance are known to impair exercise tolerance by reducing HR and blood pressure(BP) response to activity, as well as blunting the appropriate increases in cardiac output[5].

c)Orthostatic hypotension is defined as a reduction in SBP >20mmHg or DBP> 10 mmHg following a postural change from supine to standing, and is deemed to be a late sign in CAN.

d)Peri- and intraoperative complications includes intra-operative hypotension and intra-operative hypothermia.

The present study was conducted at the Department of Medicine, Fakhruddin Ali Ahmed Medical College, Barpeta from October, 2018 to March, 2019 with the aim of estimating the

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prevalence of cardiac autonomic neuropathy in diabetic patients . Documented diabetes mellitus patients as per WHO recommended criteria attending Medicine OPD or admitted in Medicine Ward were included in this study.

Inclusion criteria :

Diabetes mellitus patients of age more than 18 years of age of both sexes with duration of DM at least 5 years.

Exclusion criteria :

Patients with history of alcohol consumption, duration of DM less than 5 years, using of beta blockers, with pre-existing cardiac disease, significant anaemia and resting abnormal ECG were excluded from the study.

II. MATERIALS AND METHODS:

Permission for undertaking the study was taken from institutional ethical committee. A thorough history taking with special emphasis on symptoms of autonomic dysfunction and a detailed clinical examination was done. All the subjects were informed regarding the precautions that need to be taken before performing the tests. Both fasting and post prandial blood sugar estimation was done along with other routine investigations to quantify glycaemic control. Data was recorded in a preformed proforma.

Tests for assessment of cardiac autonomic neuropathy were done by five non-invasive autonomic function tests as recommended by Ewing-Clarke :

A.Tests for parasympathetic function :

1.Heart Rate response to deep breathing : The patients sit quietly and takes deep breath at 6 breaths /minute (5 seconds in, and 5 seconds out) for one minute. ECG is recorded throughout the period of deep breathing with a mark to indicate onset inspiration and expiration. Maximum and minimum R-R intervals during each breathing cycle measured and converted to beats/minute. The result is then expressed as mean of the difference between maximum and minimum heart rates for 6 measured cycles in beats/minute. Normal response >15 beats/min, borderline 11-14 beats/min, abnormal response < 10 beats/min.

2.Heart Rate response to Valsalva Manoeuver : The patients blows into a mouth piece connected to a sphygmomanometer and holding it at a pressure of 40 mmHg for 15 seconds while a continuous ECG is recorded. This manoeuvre is performed 3 times with an interval of one minute in-between. Result is expressed as Valsalva Ratio. The mean of three valsalva ratios is taken as final value. Normal valsalva ratio >1.21 ; borderline between 1.11 and 1.20; and abnormal <1.10.

3.Heart Rate response to immediate standing : Performed with patient lying quietly on a couch while heart rate is recorded continuously on ECG. The patient is asked to stand up unaided and the point at starting to stand is marked on ECG. The shortest RR interval at or around the 15^{th} beat and largest RR interval at or around the 30^{th} beat after starting to stand is measured with a ruler. The characteristic heart rate response is expressed by 30-15 ratio. Normal if >1.04; borderline between 1.01 and 1.03; and abnormal if <1.00.

B.Tests for sympathetic function :

1.Blood pressure response to standing : The test is performed by measuring patients blood pressure while he is lying down quietly and again when he stands up. The postural fall after 2 minutes in BP in standing position . Normal response <10mmHg; borderline 11-15 mmHg ; abnormal < 10 mmHg.

2.Blood response to sustained hand grip : The patient is instructed to grip an inflated BP cuff maximally and maintain the hand grip. Now difference between the highest diastolic blood pressure during hand grip exercise and mean of 3 diastolic blood pressure readings before hand grip is begun to noted. Normal response >16 mmHg ; borderline 11-15 mmHg ; abnormal <10 mmHg.

Interpretation of test results : Will be interpreted as per Ewing's criteria :

1.Normal : all test normal or one test borderline.

2.Early : one of the three Heart Rate tests abnormal or two borderline.

3.Definite : two Heart Rate tests abnormal.

4.Severe : two Heart Rate tests abnormal plus one or both blood pressure tests abnormal or borderline

5.Atypical : Any other combinations of abnormalities.

III. STATISTICAL ANALYSIS :

The results are present in mean standard deviation and percentages. The categorical variables were compared using chi-square test. The continuous variables were compared by using t-test. The $p < 0.05$ was considered statistically significant. All the analysis was carried out using SPSS 17 Version.

IV. RESULTS :

The age group of diabetic patients ranged from 37-75 years and constituted 28 males (56%) and 22 (44%) with majority of the cases being in the age group of 51-60 years with mean age 51.52±11.13. The mean age of patients with CAN

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was 55.85 ± 10.22 years and that of the patients without CAN was 54.69 ± 12.11 years.

Age (In years)		Male	Female
Range	no		
20 - 30	2	1	1
31 - 40	7	4	3
41 -50	13	6	7
51 - 60	16	9	7
>60	12	8	4

Table 1 :Age and gender distribution

In this study, it was found that 38% (19) patients had no CAN. Positive tests of autonomic dysfunction were seen in 62% (31) patients. Only sympathetic dysfunction was seen in 8% (4) patients, only parasympathetic dysfunction in 16% (8) patients (Table 2). Early CAN was seen in 14%(7), severe CAN in 14%(7), definite CAN in 8% (4) patients. Atypical CAN with other combinations of abnormalities was seen in 32% (16) patients.

Test			
	Normal	Borderline	**Abnormal**
1)E-I difference	21 (42%)	11 (22%)	18 (36%)
2)Valsalva ratio	25 (50%)	12 (24%)	13 (26%)
3)30:15 ratio	35 (70%)	9 (18%)	6 (12%)
4)BP response to standing	26 (52%)	15 (30%)	9 (18%)
5)BP response to standing handgrip	26 (52%)	10 (20%)	14 (28%)
Table-2: Cardiovascular autonomic function tests			

Pattern	Number
Normal	19 (38%)
Only sympathetic	4(8%)
Only parasympathetic	8(16%)
Both (S+PS)	19(38%)
Total	50(100%)
Table 3:Pattern of autonomic dysfunction	

Patients with CAN had a statistically significant fall in SBP on standing than patients without CAN. They also had little rise in DBP on sustained handgrip than patients without CAN. They also had a significant difference in valsalva ratio and standing 30:15 ratio than patients without CAN.

Autonomic function tests	Mean±SD	CAN		P value
		Absent	Present	
BP response to standing(fall in SBP) in mm Hg	11.56±5.67	5.75±1.61	15.29±3.67	0.001
BP response to sustained hand grip (rise in DBP) in mmHg	14.36±4.17	18.38±2.22	11.93±3.28	0.002
HR response to deep breathing (bpm)	15.12±3,57	18.87±2.85	12.90±2.52	0.001
Valsalva ratio	1,14±0,12	1.27±0.06	1.06±0.07	0.018
Standing 30:15 ratio	1.02±0.11	1.12±0.10	0.96±0.09	0.513
Table-3: Interpretation of Autonomic Function Tests (unpaired students t-test)				

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V. DISCUSSION:

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease[9,10]. It is difficult to ascertain the exact prevalence of diabetic autonomic neuropathy, especially cardiac autonomic neuropathy since it is often asymptomatic or presents with vague syndrome. A total of 50 patients who were diagnosed to have type 2 diabetes mellitus based on ADA criteria were included in this study after considering the various inclusion and exclusion criteria.

In this study, positive tests of autonomic dysfunction were seen in 62% (31) patients. 38% (19) patients had no CAN. Out of the CAN positive patients 21(67.74%) were male and 10(32.25%) were female. The ACCORD trial, which included >8000 patients with T2DM, showed higher prevalence of CAN in women compared to men. A more recent study, though not statistically significant , also showed women had higher prevalence of CAN than men (65.2% vs 34.8%, p=0.059). However, the present study has shown higher CAN prevalence in men compared to women.

Early CAN was seen in 14% (7), severe CAN in 12% (6) and definite CAN in 8% (4) patients. Atypical CAN with other combinations of abnormalities was seen in 28% (14) patients. Mathur CP et al[11]. Evaluated 50 diabetics for autonomic neuropathy by Ewings criteria. Normal study was reported in 42%, early change in 20%, definite in 30%, severe in 4% and atypical in 4%. Pillai JN et al[12] evaluated 50 type 2 diabetes mellitus patients and found that 21 (42%) had severe autonomic neuropathy and 12 (24%) had early autonomic neuropathy by the autonomic functions tests. Agarwal et al[13] reported the prevalence of CAN in their study as 70%. Among them, early neuropathy was seen in 37%, definite neuropathy in 40% and severe autonomic dysfunction in 22.9% patients.

The abnormal responses were more frequently found for heart rate response to deep breathing (36%) which was consistent with the study done by Mathur et al.[14](48%). . The study conducted by Barthwalet al[15] had detected heart rate response to deep breathing and valsalva ratio to be the most sensitive while postural hypotension to be the less sensitive index. Standing 30:15 ratio was found to be least sensitive in this study with no statistically significant difference between CAN positive and negative groups of patients .

Tests for parasympathetic dysfunction were found to be the most sensitive indicators of autonomic neuropathy in the present study. Combined parasympathetic and sympathetic dysfunction was seen in 38% (19) patients. 8% (4) had sympathetic dysfunction alone and 16% (8) patients had parasympathetic dysfunction alone. Study by Ramavat[16] et al showed that 39.1% had parasympathetic neuropathy, 27% had sympathetic neuropathy and 19.2% had both parasympathetic and sympathetic neuropathy. Only parasympathetic neuropathy was seen in 17.9% of type 2 diabetes, only sympathetic neuropathy in 6.5% of type 2 diabetic patients. The results of these categories are similar to the present study. In a study of AK Basuet al[17], 50 type 2 diabetic patients were studied. Overall prevalence of CAN was 54%. Parasympathetic neuropathy was seen in 52% cases and sympathetic neuropathy was seen in 20% cases. However a study by Jyotsnaet al[20] found that sympathetic dysfunction was more prevalent than parasympathetic dysfunction. The study revealed that parasympathetic dysfunction was found in 44.2% and sympathetic dysfunction in 51.9%diabetics

VI. CONLUSION:

CAN is a serious chronic complication of diabetes and an independent predictor of cardiovascular disease mortality. Our study revealed that CAN is a common microvascular complication in diabetes mellitus . Early identification of CAN using simple bedside autonomic function tests helps in effective prevention of cardiovascular disease related morbidity and mortality. Intensive multifactorial intervention targeting lifestyle, glycemic control, and CVD risk factors prevents the development and slows the progression of CAN.

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