Research Paper

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Study of Cardiac Autonomic Neuropathy(Can) And Its Correlation With Retinopathy In Type 2 Diabetes Mellitus

Medicine

KEYWORDS : cardiac autonomic neuropathy,Retinopathy,Type2 DM

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ABSTRACT

AIMS AND OBJECTIVES 1)To study the clinical features of diabetic autonomic neuropathy with special reference to cardiac autonomic neuropathy.2) To study the prevalence of cardiac autonomic neuropathy in type 2 Diabetes Mellitus. 3) To find correlation between Cardiac Autonomic Neuropathy and Retinopathy in type 2 Diabetes Mellitus MATERIAL AND METHODSThe study was carried out in the outpatient and inpatient services of tertiary care hospital. A total of 50 patients were studied. Inclusion criteria were Patients with Type-2 Diabetes Mellitus .Exclusion criteria were Presence of valvular heart disease, heart failure, cardiac arrhythmias, congenital heart disease.2 Type 1 Diabetes Mellitus.3 Acute complications of DM like Diabetic Ketoacidosis, hypoglycemia. TESTS for CAN :1) valsalva test (heart rate variation in valsalva maneuver :2). heart rate response to deep breathing 3) heart rate response to standing 4) drop in systolic blood pressure on standing. Retinopathy was assessed by fundus examination carried out for all patients with the help of ophthalmologist Nephropathy was assessed by estimating proteinuria with the help of commercially available dipsticks. It was graded as 1+ to 3+.

RESULTS- 1.) The age group commonly involved was 51-60 years.14/29(48.27%) 2.) There was equal sex distribution.Males = 15/29 (51.72%), Females = 14/29 (48.27%) . 3)Dizziness on standing was the most common symptom. (24%) 4).Heart rate variation on deep breathing was the most abnormal test to be detected in 19(38%) patients.

5). Cardiac autonomic neuropathy was detected in 29 patients (58%) 6). Age, gender and BMI had no significant correlation with the occurrence of CAN ,7) Duration of diabetes had positive correlation with presence of cardiac autonomic neuropathy. (P-value<0.001) 8.) There was a positive correlation between the occurrence of CAN and presence of retinopathy and nephropathy. (P-value<0.001)

INTRODUCTION

Autonomic neuropathies affecting the cardiovascular system cause a resting tachycardia and orthostatic hypotension(1). Cardiovascular autonomic neuropathy (CAN) has been linked to exercise intolerance, enhanced perioperative cardiovascular lability, increased incidence of asymptomatic ischemia, myocardial infarction, and decreased likelihood of survival. Regional myocardial autonomic denervation and altered vascular responsiveness in diabetic autonomic neuropathy may predispose to malignant arrhythmogenesis and sudden cardiac death.Diabetic retinopathy is an early and frequent marker of other vascular complications of Diabetes Mellitus. So, DM retinopathy can be used as early and non-invasive predictor for patients at risk of serious cardiovascular events. So, it's important to find correlation between cardiac autonomic neuropathy and retinopathy in type 2 DM.

We studied various aspects of Cardiac Autonomic Neuropathy, clinical presentation, and its relationship with other microvascular complications of diabetes like nephropathy and retinopathy. We also studied the degree of autonomic dysfunction in these patients by using bedside tests of cardiac autonomic dysfunction.

AIMS AND OBJECTIVES

1 To study the clinical features of diabetic autonomic neuropathy with special reference to cardiac autonomic neuropathy.2 To study the prevalence of cardiac autonomic neuropathy in type 2 Diabetes Mellitus. 3 To find correlation between Cardiac Autonomic Neuropathy and Retinopathy in type 2 Diabetes Mellitus.

MATERIAL AND METHODS

The study was carried out in the outpatient and inpatient services of tertiary care hospital. A total of 50 patients were studied. **Inclusion criteria were as follows:**Patients with Type-2 Diabetes Mellitus.**Exclusion criteria were as follows:**1 Presence of valvular heart disease, heart failure, cardiac arrhythmias, congenital heart disease.2 Type 1 Diabetes Mellitus.3 Acute complications of DM like Diabetic Ketoacidosis, hypoglycaemia **MATERIAL** 1 .mercury sphygmomanometer. 2 .ECG machine. 3 .urine dipsticks. 4. fundoscope. 5. modified mouth piece. 6. stethoscope.

CARDIAC AUTONOMIC TESTS: The patient was asked to lie comfortably. Patient was asked to relax. Only limb leads were needed. Heart rate was calculated as :1500/(Number of small squares between two consecutive R-R interval)For example:1500/20=75 beats/min.

ASSESSMENT OF RETINOPATHY

Fundus examination was carried out for all patients as a part of clinical examination with the help of ophthalmologist .Patients were divided into 3 categories: [68] 1. Normal fundus. 2. Nonproliferative diabetic retinopathy. 3 .Proliferative diabetic retinopathy.

TESTS- 1) VALSALVA TEST The patient was asked to sit comfortably with all limb leads attached .Patient was given a mouth piece which was connected to Sphygmomanometer. Patient was asked to blow in this tube, so that, the pressure in the meter rose above 40 mm of Hg (Nose was closed by the other hand so that air did not leak out).The pressure was to be sustained for 15 seconds. The ECG was taken before the test was started, while blowing and after the test was over. Normally the heart rate rises during the test and comes to normal when blowing is over.

Valsalva ratio test Inference:(Heart rate during blowing)/(Heart rate at rest)For example**:** If the heart rate during blowing is 100 and at rest it is 75, then the valsalva ratio is calculated as 100/75=1.33 which is normal. If ratio is calculated as 60/65=0.92 which is abnormal. Normal was >1.21, borderline was 1.11-1.21 and abnormal was <1.1

2)HEART RATE RESPONSE TO DEEP BREATHING

A resting ECG of lead I or II was taken .The patient was made to sit comfortably. Patient was instructed to take deep breath, i.e. slow inspiration and slow expiration without holding the breath.The R-R interval was measured to calculate the heart rate.Normally heart rate increases during inspiration and decrease during expiration **Inference:**(Heart rate during deep inspiration)- (Heart rate during expiration).if Heart rate during deep inspiration is 88 and during expiration is 54 then 88-54=34 which is normal. If Heart rate during deep inspiration is 94 and during expiration is 94 then 94-94=0 which is abnormal . Normal was taken as >15 ,borderline was 11-14 and abnormal was <10

3) HEART RATE RESPONSE TO STANDING

The patient was asked to lie down comfortably. A resting ECG was taken. The patient was asked to stand up and again ECG was taken at the interval of 3 minutes. Normally the heart rate increases during standing.**Inference:**(Heart rate during standing)/ (Heart rate during lying) If heart rate during lying down position is 75 and standing it is 100 then, 100/75=1.33 which is normal. Normal was >1.04,borderline was 1.01 -1.03 and abnormal was <1.

4) FALL IN SYSTOLIC BLOOD PRESSURE ON STANDING

Blood pressure was taken at rest on lying down position. The patient was asked to stand up and remain so for three minutes and blood pressure was recorded. less than 10 mm fall was normal , borderline was 11-29 and more than 30 was abnormal.

The findings of all 4 tests for all 50 patients were compiled.

TABLE 2: The results of autonomic tests were recorded as follows:

TEST	NORMAL	BORDERLINE	ABNORMAL
Valsalva	>1.21	1.11-1.21	<1.1
HRV during deep breathing	>15	11-14	<10
HRV after standing	>1.04	1.01-1.03	<1
Fall in SBP on standing	<10	11-29	>30

ASSESSMENT OF DIABETIC RETINOPATHY:

Fundus examination was carried out for all patients as a part of clinical examination with the help of ophthalmologist .Patients were divided into 3 categories: (3) 1. Normal fundus. 2. Nonproliferative diabetic retinopathy. 3 .Proliferative diabetic retinopathy.

ASSESSMENT OF DIABETIC NEPHROPATHY:

Nephropathy was assessed by estimating proteinuria with the help of commercially available dipsticks. It was graded as 1+ to 3+

The staging of diabetic nephropathy is based on Mogensen's(14) staging .In our study patients with grade 1+ (stage 3 of Mongensen classification) protein in the urine sample were considered to be suffering from Diabetic nephropathy.

Statistical Analysis:

Data analysis done by using SPSS 17.0 statistical software. We have used chi-square test, Fisher's exact test to find the association between various parameters. P-value less than 0.05 considered as significant.

RESULTS/OBSERVATIONS

1. Distribution of patients with respect to symptoms of DAN/ CAN.

Symptoms	Number of patients	Percentage (%)
Dizziness	12	24.00
Sweating	8	16.00
Urinary Complaints	3	6.00
Diarrhoea	2	4.00
Dysphagia	1	2.00

Dizziness on standing was found to be the most common symptom.

2. Distribution of patients with respect to HRV during deep breathing test.

HRV in deep breathing	Number of patients	Percentage (%)
Normal	20	40.0
Borderline	11	22.0
Abnormal	19	38.0
Total	50	100.0

3. Distribution of patients with respect to HRV during standing

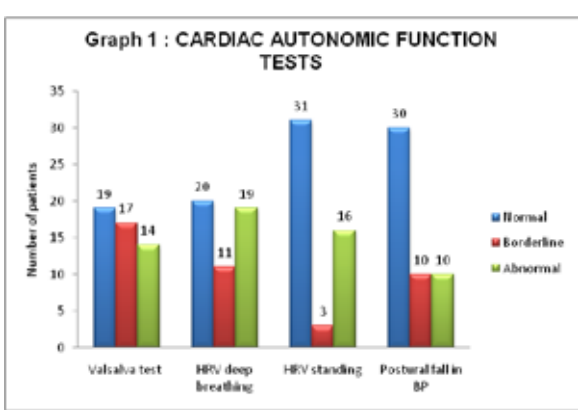
HRV in standing	Number of patients	Percentage (%)
Normal	31	62.0
Borderline	3	6.0
Abnormal	16	32.0
Total	50	100.0

4. Distribution of patients with respect to HRV during Valsalva test.

Valsalva test findings	Number of patients	Percentage (%)
Normal	19	38.0
Borderline	17	34.0
Abnormal	14	28.0
Total	50	100.0

5. Distribution of patients with respect to postural drop in systolic blood pressure

Postural drop in BP	Number of patients	Percentage (%)
Normal	30	60.0
Borderline	10	20.0
Abnormal	10	20.0
Total	50	100.0



Graph 1-Heart rate variation during deep breathing was the most abnormal test to be detected followed by heart rate variation during standing.

6. Distribution of patients with respect to occurrence of CAN.

CAN	Number of patients	Percentage (%)
Present	29	58.0
Absent	21	42.0
Total	50	100.0

7. CAN and basic characters of our patients

	CAN	N	Mean	Std. Deviation
Duration of DM	Present Absent	29 21	11.28 5.86	4.64 2.06
Age	Present Absent	29 21	57.00 54.33	6.50 6.76
BMI	Present Absent	29 21	24.34 24.94	4.92 2.63

1. Mean duration of DM in patients with CAN was 11.28 years. 2. Mean age of patients with CAN was 57 years 3. Mean BMI of the patients with CAN was 24.34kg/m2

8. Distribution of patients with respect to occurrence of CAN and age group.

Age group	CAN		Total	p-value
	Present	Absent		
41-50	8	8	16	0.650
51-60	14	10	24	
61-70	7	3	10	

Maximum number of patients with CAN were in age group of 51-60 years. By using chi-square test P value is >0.05. So, there was no significant correlation between occurrence of CAN and age group.

9. Distribution of patients with respect to occurrence of CAN and duration of diabetes (years).

Duration of DM	CAN		Total	p-value
	Present	Absent		
≤ 5	1	7	8	< 0.001
5 - 10	13	13	26	
> 10	15	1	16	

By using chi-square test p-value < 0.05 . Therefore, there was association between occurrence of CAN and duration of DM. CAN was associated with increasing duration of DM

.10. Distribution of patients with respect to occurrence of CAN and Retinopathy

Fundus	CAN		Total	p-value
	Present	Absent		
Normal	10	20	30	< 0.001
NPDR	15	1	16	
PDR	4	0	4	

By using chi-square test p-value < 0.05 . Therefore, there was association between occurrence of CAN and Retinopathy..

11. Distribution of patients with respect to occurrence of CAN and occurrence of nephropathy.

Nephropathy	CAN		Total	p-value
	Present	Absent		
Present	15	2	17	0.001
Absent	14	19	33	

By using chi-square test p-value < 0.05 therefore there was association between occurrence of CAN and occurrence of nephropathy.

DISCUSSION

The prevalence of Diabetic Neuropathy in diabetics is anywhere between 10 to 100 (16,17,2)percent depending on the criteria used to define this condition. Definite CAN defined by the strict criterion of abnormal results in > or =3 of 6 tests was detected in 16.8 %of type 1 and 22.1 % of the type 2 diabetic patients (p <0.05) by Zeigler D et al at the Heinrich-Heine-University Dusseldorf, Germany(18).

In present study, 50 patients of Type 2 Diabetes Mellitus were studied and following observations were made.

AGE: (The mean age in our study was 55.66 years which is similar to the epidemiologic data from other studies such as Rochester Diabetic Neuropathy Study(5), EDS study(9), SLVDS(7).In a study conducted in Medical Institute-central clinical base, Department of Endocrinology, Sofia, Bulgaria (10) maximum number of patients were in the age group of 51-60 years. Maximum number of patients (48%) in our study were in the age group of 51 to 60 years **SEX** - In a study done in Department of Endocrinology , Sofia, Bulgaria 42 patients with DM were studied out of which 26(61.9%) were males and 16(38.1%) were females. (10) In the present study of 50 patients 30(60%) were male patients and 20(40%) were female patients. The male to female ratio was found to be 3:2.The higher male female ratio was probably because of greater number of males attending the outpatient department.

Clinical features: (Table no 1)

Dizziness on standing was the most frequently associated symptom found in 12 patients (41%) followed by abnormal sweating in 8(28%) patients. Impotence was a complaint in 7(23%) of the patients. The study conducted at Medical Institute, Department of Endocrinology, Sofia Bulgaria(10), Dizziness on standing was most frequently observed symptom being found in 42.9% of the patients followed by abnormal sweating in 19% of the patients. **Duration of Diabetes:**The mean duration of Diabetes in our patients was 8.57 years. **BMI:** The mean BMI in our study was 24.64kg/m2 indicates our subjects were mildly over-weight.

CARDIAC AUTONOMIC NEUROPATHY:

The major aspect of our study was, the assessment of cardiac autonomic dysfunction by simple bedside tests of autonomic function. One of the earliest manifestations of diabetic autonomic dysfunction is denervation of the cardiovascular system. The presence of abnormal cardiovascular function tests suggests poor prognosis of the disease (increased incidence of silent myocardial infarction, cardiac arrest, sudden cardiac death). Reduced heart rate variability is the earliest indicator of CAN (i. e., abnormalities of heart rate control and vascular dynamics). Three major syndromes (cardiac denervation, exercise intolerance, and orthostatic hypotension) are associated with dysfunction of the cardiovascular autonomic nervous system.

INTERPRETATION OF AUTONOMIC FUNCTION TESTS: The heart rate response to deep breathing was found to be the most sensitive test for autonomic neuropathy followed by heart rate variation during standing.

1) Heart rate response to deep breathing: (Table No.2)

Heart rate response to deep breathing was abnormal in 19(38%), borderline in 11(22%) and normal in 20(40%) patients.**2) Heart rate response to standing: (Table No.3)**Heart rate response to standing was abnormal in 16(32%), borderline in 3(6%) and normal in 31(62%) patients.**3) Heart rate response to Valsalva maneuver: (Table No.4)**Heart rate response to valsalva maneuver was found abnormal in 14(28%), borderline in 17(34%) and normal in 19(38%).**4) Postural drop in systolic blood pressure: (Table No.5)** Postural hypotension was detected in 10(20%) of the patients, while 10(20%) had borderline and another 30(60%)

had normal results. **Graph 1** shows combined analysis of the various autonomic tests.

The study conducted by Mehta S et al(11) at SMS Medical College and Hospital, Jaipur, 40 NIDDM patients were studied out of which abnormal heart rate response to deep breathing was found in 12(30%),abnormal heart rate response to standing in 11(27.5%),abnormal valsalva ratio in 10(25%) and orthostatic hypotension in 6(15%) of the patients. A Study was done in Department of Endocrinology, Sofia(10) found that Heart rate variability with deep breathing abnormal in 14(33.3%),Decreased heart rate response to standing abnormal 13(31%),Valsalva ratio abnormal in 12(28.6%) and postural hypotension in 8(19%) number of patients.

Cardiac Autonomic Neuropathy: (Table No.6)
In our study those having 1 or more tests positive were considered to have cardiac autonomic neuropathy .In our study 29 out of 50(58%) fulfilled this criteria of autonomic dysfunction. This finding was similar to that of Mehta S et al SMS Medical college and hospital Jaipur(11) in which 23/40(57.5%) patients with Diabetes had CAN .Also this finding was consistent with the finding of Ashish Kumar Basu et al(3) in which 27/50(54%) of the patients had cardiac autonomic neuropathy. Study done in Department of Endocrinology, Sofia observed cardiac autonomic neuropathy in 25/42(59.5%) type 2 DM patients. (10)Majority of patients 18 (29%) with CAN 29 (58%) had 2 abnormal cardiovascular reflexes. 5 (10%) of patients had one abnormal cardiovascular reflex and the remaining 6 (12%)-3 or more abnormal.

The mean age in our study who had CAN was 57 years **(Table No.7)**.However, there was no statistically significant correlation between the age of the patient and presence of Cardiac Autonomic Neuropathy. **(Table No 8)**

Mean duration of DM in our patients was 8.57 years out of which mean duration in those having CAN was 11.28 years**(Table No 7)** indicating a long incubation period for development of Diabetic Neuropathy. In our study, we found that, duration of DM to be a very strong risk factor for CAN. There was statistically significant correlation between CAN and duration of DM **(Table No.9; p-value<0.001)**.EDS study(9) and SLVDS(7) also showed that duration of DM to be an independent risk factor for the development of CAN.D Tommaso G et al(4) found that the prevalence of CAN and retinopathy is increased with the duration of DM.

The mean BMI in our patients was 24.34 kg/m2 (**Table No.7).** CAN was not found to be associated with BMI.

The CAN was detected in 15(50%) male, while, 14(70%) female patients but, there was no significant association between occurrence of CAN and gender of the patient

Correlation between CAN and Retinopathy:
On fundus examination, we found out that, non-proliferative diabetic retinopathy was found in 16(32%), proliferative diabetic retinopathy was seen in 4(8%) of the patients, while fundus examination was normal in 30(60%) of our patients **.**

In our study, we observed that out of 29 patients who had CAN, 15(51.72%) patients had NPDR, while 4(13.79%) patients had PDR. Fundus examination was normal in 10(34.48%) patients who had CAN. On applying chi-square test, p-value was found to be significant (<0.001).So, there was association between occurrence of CAN and Retinopathy **(Table No.10)**. On comparison we found a positive correlation between CAN and retinopathy. There was a significantly greater chance of having either proliferative or non-proliferative diabetic retinopathy in patients with CAN.

Mehta S et al (11) found retinopathy in 3 patients all had cardiac autonomic neuropathy and in 0 patients without CAN. Ashish Kumar Basu et al (3) found retinopathy in 10% of the study population who also had CAN.

It was also observed previously by FONG D et al (6) who found association between proliferative diabetic retinopathy and cardiac autonomic neuropathy. **Correlation between CAN and nephropathy:** Out of 50 Diabetic patients proteinuria was positive in 17 (34%) patients . In a study, conducted by Ashish Kumar Basu et al, (3) 36% of the studied population had microalbuminuria who also had CAN. We found that, 15(51.72%) patients with CAN also had nephropathy, while 14 (48.27%) patients with CAN had no nephropathy.2 patients had nephropathy but there was no CAN. On applying chi-square test p-value (0.001) was found to be significant. So, there was association between occurrence of CAN and nephropathy **(Table No.11)**. This finding is consistent with previous studies by Mehta S et al (11) and Ashish Kumar Basu et al. (3)

The similar findings were observed in the EURODIAB IDDM complications study (8) in which CAN was associated with albuminuria.

It was observed from studies done by Mehta S et al (11) ,Ashish Kumar Basu et al (3), Department of Endocrinology, Sofia (10) that Cardiac autonomic neuropathy appears earlier than retinopathy or nephropathy.

Nevzat Bilal et al (12) in a study in Turkish type 2 diabetic patients found that, there is increased prevalence of nephropathy, retinopathy, and peripheral neuropathy with increasing severity of cardiac autonomic neuropathy.

CONCLUSIONS
1.) Cardiac autonomic neuropathy is the earliest and most common complication to be detected in type 2 Diabetes Mellitus. 2.) The presence of Cardiac autonomic neuropathy was significantly associated with Diabetic retinopathy so also with Diabetic nephropathy. 3.) This study emphasizes the need for an early screening for peripheral neuropathy, retinopathy, and nephropathy in type 2 diabetic patients with CAN, especially with severe involvement. 4). Patients with Cardiac autonomic neuropathy should undergo detailed cardiac evaluation and further work up.

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