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A cross-sectional study to find out the prevalence of Cardiac autonomic neuropathy (CAN) in Diabetes Mellitus cases in a tertiary care hospital

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ABSTRACT

Objective: To find out the prevalence of Cardiac autonomic neuropathy (CAN) in Diabetes Mellitus cases in a tertiary care hospital.

Methods: This was a cross-sectional study conducted in a tertiary care hospital. The study was approved by the Ethical Committee of the Institute and consent was taken from each participants before enrolling in the study. A total of 128 patients with diabetes mellitus for more than 5 years were included in the study. The classification of CAN was done as per Ewings and Clarke criteria.

Results: The prevalence of CAN was found to be 47.7% (61/128). Definite CAN was among majority of patients (67.2%) followed by early (29.5%) and advance (3.3%). Valsalva, E-I and 30:15 ratio was abnormal among 43%, 71.9% and 64.8% patients respectively. The prevalence of CAN was higher among whom Valsalva was abnormal (52.7%) than borderline (45.5%) and normal (38.9%). However, the prevalence of CAN was higher among whom E-I was borderline (52.4%) than abnormal (50%) and normal (26.7%). There was no significant ($p>0.05$) association of prevalence of CAN with Ewing's criteria variables.

Conclusion: Cardiac Autonomic Neuropathy thus is most frequently asymptomatic problem which can be identified by simple bed side tests. Early identification of Cardiac Autonomic neuropathy helps in effective prevention of cardiovascular disease related morbidity and mortality.

Key words: Diabetes Mellitus–Cardiac Autonomic Neuropathy–Prevalence

1 INTRODUCTION

Diabetes mellitus (DM) is a chronic condition characterized by hyperglycemia precipitating because of the complete or partial absence of the insulin hormone. The estimates suggest that worldwide almost 350 million people suffer from diabetes and these estimates are expected to be doubled by the year 2030 if no active measures are taken. The epidemiological studies done across different settings have revealed that a significant increase in both the incidence and onset of disease has been recorded. India has been labeled as the "Diabetes capital" of the world, owing to the share of highest number of people with diabetes (Sukla et al, 2016).

The diabetic autonomic neuropathy tends to affect the functioning of multiple systems-cardiovascular, urogenital, gastrointestinal, pupillomotor, thermoregulatory, and sudomotor-resulting in a significant proportion of the mortality and morbidity associated with the disease. Poor glycemic control, long duration of diabetes, increasing age, female gender, and smoking have been identified as the potential risk factors for diabetic autonomic neuropathy and subsequent cardiac autonomic neuropathy. Findings of an epidemiological study suggested that almost 50-77% of the diabetic patients had evidence of cardiovascular autonomic neuropathy (Maser and Lenhard, 2005; Muhopadyaya and

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Ray, 2004).

Cardiac autonomic neuropathy (CAN) is described as impairment of autonomic nerve fibers that innervate the heart and blood vessels resulting in abnormalities of heart rate control and vascular dynamics (Vinik et al, 2013). The presence of CAN increases the risk for severe hypoglycemia, silent myocardial ischemia, stroke, perioperative morbidity, and mortality even in minor surgical procedures (Yun et al, 2014; Kadoi, 2010).

CAN is the impairment of cardiovascular autonomic control in the setting of diabetes after exclusion of other causes. The prevalence of confirmed CAN is ∼20% and increases up to 65% with age and diabetes duration (Stella et al, 2000; Tahrani et al, 2014). It is a frequent chronic complication of diabetes mellitus with potentially life-threatening outcomes. It is also a major source of increased cost in caring for the patient with diabetes. The metabolic disorders of diabetes lead to diffuse and widespread damage of peripheral and autonomic nerves, and small vessels. When diabetic neuropathy affects the autonomic nervous system, it can damage the cardiovascular, gastrointestinal, genitourinary and neurovascular systems and impair metabolic functions such as glucose counter-regulation (Balcioglu and Muderrisoglu, 2015; Vinik et al, 2013).

The present study was plannedto find out the prevalence of Cardiac autonomic neuropathy (CAN) in Diabetes Mellitus cases in a tertiary care hospital.

2 MATERIAL AND METHODS

This was a cross-sectional study conducted in a tertiary care hospital. The study was approved by the Ethical Committee of the Institute and consent was taken from each participant before enrolling in the study. A total of 128 patients with diabetes mellitus for more than 5 years were included in the study. Patients with symptoms of DM + RBS >200mg/dl or fasting plasma glucose >126mg/dl orHb1AC >6.5 or two hour plasma glucose >200mg/dl during on OGTT and Type 1 and 2 diabetes mellitus were included in the study. Patients with diseases like Leprosy, Syphilis, Shingles, HIV, Gullian-Barre syndrome were excluded from the study.

Methods

Subjects were made to lie supine comfortably. Then they were asked to take deep breathe evenly at the rate of 6 breaths per minute i.e., 5 seconds for inspiration and 5 seconds for expiration. A continuous ECG was recorded for one minute. The maximum and minimum R-R interval during the respiratory cycle was calculated and converted to beats per minute. The difference between the two and heart rate variation of less than 10 beats per minute was taken as abnormal. Then the patient was allowed to lie quietly for another 5 minutes. The patient was made to exhale forcibly into the mouth piece of manometer sustaining a pressure of 40 mmHg for about 15 seconds and the ECG was recorded continuously. The patient was made to stop the maneuver and the ECG was further recorded post maneuver. The ratio of shortest R-R interval during the maneuver and the longest R-R post Valsalva was calculated. A ratio less than 1.10 was considered abnormal. Again the patient was made to lie supine quietly. After about 5 minute with continuous monitoring, the patient was made to stand. The R-R internal at 15^{th} beat and 30^{th} beat was calculated. The 30:15 ratio of less than 1.00 was considered abnormal.

For the assessment of the sympathetic function, patient was made to lie down and his BP recorded. Then he was made to stand up and again BP measurement was made 2 minutes after standing. A fall of systolic Blood Pressure more than 30 mmHg was considered abnormal. Based on the above standard testing patients with 2 or more abnormal test were classified as definite, one of the three heart rate variability test abnormal were classified as early. When individuals with parasympathetic dysfunction along with significant BP fall were classified as severe CAN as per Ewingsand Clarke (1986).

7 ml of venous blood specimen was collected from the antecubital vein after fasting for 8- 12 hours. Out of which, 2 ml of blood was transferred into EDTA vacutainer and 5 ml blood was transferred into a plain vacutainer. 5 ml of urine sample was collected. The blood samples were subjected to centrifugation and the sera was collected.

Statistical analysis

The results are presented in frequencies and percentages. The binary logistic regression was used to find the association of CAN with various factors. The odds ratio (OR) with its 95% confidence interval (CI) was calculated. The p-value<0.05 will be considered significant. All the analysis will be carried out on SPSS 16.0 version (Chicago, Inc., USA).

3 RESULTS

The prevalence of CAN was found to be 47.7% (61/128) (Fig.1).

Definite CAN was among majority of patients (67.2%) followed by early (29.5%) and advance (3.3%) (Table-1).

More than one third of patients were between 40-50 years (46.1%). The prevalence of CAN was higher among patients of age 51-60 years (53.6%) followed by 40-50 (50.8%) and <40 (7.7%) years. The prevalence of CAN was 12.41 times significantly higher among patients of age 40-50 years than <40 years (OR=12.41, 95%CI=1.51-101.66, p=0.01). More than half of patients were females (60.2%). The prevalence of CAN was insignificantly (p>0.05) higher females (48.1%) than males (47.1%). Smoking was present among 65.6% patients. The prevalence of CAN was insignificantly (p>0.05) higher among smokers (53.6%) than non-smokers (36.4%) (Table-2).

Valsalva, E-I and 30:15 ratio was abnormal among 43%, 71.9% and 64.8% patients respectively. The prevalence of CAN was higher among whom Valsalva was abnormal (52.7%) than borderline (45.5%) and normal (38.9%). However, the prevalence of CAN was higher among whom E-I was borderline (52.4%) than abnormal (50%) and normal (26.7%). There was no significant (p>0.05) association of

prevalence of CAN with Ewing's criteria variables (Table-3).

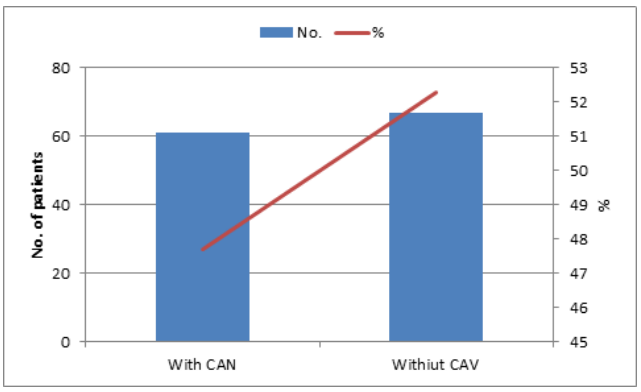

Figure 1. Prevalence of CAN

Table 1. Distribution of severity of CAN

Severity of CAN	No. (n=61)	%
Early	18	29.5
Definite	41	67.2
Advanced	2	3.3

Table 2. Association of prevalence of CAN with general characteristics

General characteristics	No. of patients (n=128) No.	%	Prevalence of CAN With CAN No.	%	Without CAN No.	%	OR (95%CI)	p-value1
Age in years								
<40	13	10.2	1	7.7	12	92.3	1.00 (Ref.)	
40-50	59	46.1	30	50.8	29	49.2	12.41 (1.51-101.66)	0.01*
51-60	56	43.8	30	53.6	26	46.4	13.84 (1.68-113.80)	0.01*
Gender								
Male	51	39.8	24	47.1	27	52.9	0.96 (0.47-1.95)	0.91
Female	77	60.2	37	48.1	40	51.9	1.00 (Ref.)	
Smoking								
Present	84	65.6	45	53.6	39	46.4	2.01 (0.95-4.27)	0.06
Absent	44	34.4	16	36.4	28	63.6	1.00 (Ref.)	

[1]Binarylogistic regression, OR-Odds ratio, CI-Confidence interval, Ref.: Reference,*Significant

4 DISCUSSION

Cardiovascular autonomic neuropathy (CAN) is a common but often neglected diabetes mellitus complication. Based on the CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy (Spallone et al, 2011), CAN is defined as the impairment of cardiovascular autonomic control in patients with established diabetes mellitus following the exclusion of other causes. It is generally believed that CAN incidence is related to age, duration of diabetes, poor glycemic control, and microvascular disease (Martin et al, 2014). Although unpredictable, CAN progression results in a significant cardiovascular morbidity and mortality (Valensi et al 2001).

The present study was planned to find out the prevalence of Cardiac autonomic neuropathy (CAN) in Diabetes Mellitus cases in a tertiary care hospital.

In the present study, the prevalence of CAN was found to be 47.7%.Kumar et al (2000) and Veglio (1993) reported prevalence of cardiac dysautonomias 60% and 63.7% respectively. Most of the studies done among diabetic patients had a CAN prevalence of 50-60% which corresponds to the results of the present study. Gupta and Gupta (2017) found that CAN was present in 54 patients (54%) out of 100patients. Barthwal et al (1997) reported prevalence of cardiac dysautonomia as 36.2% in Indian diabetic patients whereas Mathur and Gupta (2006) reported prevalence of definite CAN as 58%.

This study found that definite CAN was among majority of patients (67.2%) followed by early (29.5%) and advanced (3.3%). Mathur and Gupta (2006) reported 58% CAN among diabetics including 20% having early CAN, 30% having definite CAN and 8% having severe CAN. Gupta and Gupta (2017) found that out of 54 (54%) patients having CAN, 16 (16%) had early CAN, 14 (14%) had definite CAN and24 (24%) had severe CAN. Another study by Ahire et al (2014) reported severe CAN as 20%. Early and definite cardiac dysautonomia was present in 33.3% and 23.3% respectively. Prevalence of severe CAN was comparatively higher in the present study which might be due to late reporting of diabetic subjects where the CAN had already set in.

As in the present study, Behera and Vishnu (2018) 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). The present study found that the prevalence of CAN was higher among females (48.1%) than males (47.1%). Zoppini (2015) reported that even though men tended to have a higher frequency of CAN, the differences were not statistically significant. Behera and Vishnu (2018) also found that there was no significant difference of prevalence of CAN between males and females. There was no significant (p>0.05) association of prevalence of CAN with smoking habit in this study.

Table 3. Association of prevalence of CAN with Cardiovascular Autonomic Function parameter- Ewing'scriteria variables

Ewing's criteria variables	No. of patients (n=128) No.	%	Prevalence of CAN With CAN No.	%	Without CAN No.	%	OR (95%CI)	p-value1
Valsalva ratio								
Normal	18	14.1	7	38.9	11	61.1	1.00 (Ref.)	
Borderline	55	43.0	25	45.5	30	54.5	1.31 (0.44-3.88)	0.62
Abnormal	55	43.0	29	52.7	26	47.3	1.75 (0.59-5.19)	0.31
E-I ratio								
Normal	15	11.7	4	26.7	11	73.3	1.00 (Ref.)	
Borderline	21	16.4	11	52.4	10	47.6	3.02 (0.72-12.63)	0.12
Abnormal	92	71.9	46	50.0	46	50.0	2.75 (0.81-9.27)	0.10
30:15 ratio								
Normal	15	11.7	8	53.3	7	46.7	1.00 (Ref.)	
Borderline	30	23.4	18	60.0	12	40.0	1.31 (0.37-4.58)	0.67
Abnormal	83	64.8	35	42.2	48	57.8	0.63 (0.21-1.92)	0.42

[1]Binarylogistic regression, OR-Odds ratio, CI-Confidence interval, Ref.: Reference,*Significant

In the present study, Valsalva, E-I and 30:15 ratio was abnormal among 43%, 71.9% and 64.8% patients respectively. The prevalence of CAN was higher among whom Valsalva was abnormal (52.7%) than borderline (45.5%) and normal (38.9%). However, the prevalence of CAN was higher among whom E-I was borderline (52.4%) than abnormal (50%) and normal (26.7%). There was no significant (p>0.05) association of prevalence of CAN with Ewing's criteria variables. The results of the present study support the findings of Mathur et al (2006) and Basu et al (2010). The findings of this regarding Ewings and Clarke (1986) parameters are in agreement with study by Gupta and Gupta (2017). Matta et al (2018) reported that an abnormal HR response to deep breathing was found in 61.2%, abnormal HR response to standing in 29.7%, abnormal Valsalva ratio or abnormal response to sustained hand grip in 12%, and, finally, orthostatic hypotension in 10.3%.

5 CONCLUSION

Cardiac Autonomic Neuropathy thus is most frequently asymptomatic problem which can be identified by simple bed side tests. Early identification of Cardiac Autonomic neuropathy helps in effective prevention of cardiovascular disease related morbidity and mortality. [1–20]

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