ORIGINAL RESEARCH PAPER

Medicine

A STUDY ON PREVALENCE OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES AND UTILITY OF CORRECTED QT INTERVAL FOR ITS DIAGNOSIS

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ABSTRACT

Background: cardiovascular autonomic neuropathy (CAN) in diabetes is a common but often under diagnosed & underestimated. CAN is associated with increased mortality , silent myocardial infarction ,left ventricular dysfunction, chronic kidney disease. Early recognition of CAN will help to delay or arrest its progression

Methods: A cross-sectional study to evaluate the Prevalence of CAN in Type 2 diabetes & correlate it with duration of Diabetes and to investigate the relationship between cardiac autonomic dysfunction & QTc

Results: Prevalence of definite CAN was 8%, 24% and 58% in group A, B and C of study population respectively and also prevalence increases with increase in duration of diabetes. P value <0.001 significant

Conclusions: A significant correlation is present between CAN & QTc prolongation. QTc interval in the ECG can be used to diagnose CAN with a reasonable sensitivity & specificity

INTRODUCTION

Type 2 Diabetes is one of the major health problems all over the world. Autonomic dysfunction is common in diabetics but symptomatic autonomic neuropathy is not that common. Diabetic autonomic neuropathy is a serious and common complication of diabetes, yet it is under diagnosed .The autonomic function tests are now widely used for the assessment of autonomic function.

Several studies [8,9] demonstrated an association of prolonged QTc interval with CAN in DM. This study is performed to estimate prevalence of CAN with relation to duration of diabetes in our hospital & to check the utility of QTc in diagnosing it

AIMS & OBJECTIVES

1. To evaluate the prevalence of CAN in Type 2 DM
2. To correlate prevalence of CAN with duration of diabetes
3. To investigate relationship between CAN & prolonged Qtc

MATERIALS AND METHODS
STUDY POPULATION

150 patients satisfying all inclusion & exclusion criteria were enrolled for the study from the population of Type 2 Diabetes patients who attended outpatient & Inpatient clinics of narayana medical college & hospital . Written consent was obtained from all patients participating in the study after clearly explaining study procedure. Patients were grouped into three according to the duration of diabetes. Autonomic neuropathy testing by simple bet side tests

STUDY DURATION

April 2018 to may 2019

STUDY DESIGN

Cross-sectional study

METHODS

Detailed clinical history was taken from each patient & a complete clinical examination of cardiovascular system was done. Simple bedside tests for assessing the autonomic nervous system were described by Ewing and Clarke [10]. All patients were subjected to five tests as described below

Heart rate response to Valsalva maneuver

The subject was asked to blow into empty barrel of a 20ml syringe attached to a mercury sphygmomanometer, to maintain 40 mm Hg pressure for 10 seconds

Valsalva ratio = Maximum heart rate during blowing ÷ Minimum heart rate after stopping.

Mean of 3 valsalva ratios was taken as final value

HRV during deep breathing

Subject was asked to breathe deeply at six breaths / min for one minute, average heart rate difference is calculated while the patient breaths deeply for 1 min. Results were expressed as mean of difference between maximum & minimum heart rates for six measured cycles in beats / min

Immediate heart rate response to standing

The heart rate increase is recorded 15 seconds after standing from lying position. Alternatively, ratio of the R-R interval of 30th beat after standing to that of 15th beat ('30:15') can be calculated

B.P response to standing

Postural fall in B.P was taken as difference between systolic pressure lying and systolic pressure recorded 1min after standing. Test was in repeated thrice & mean systolic B.P was calculated.

B.P response to sustained hand grip

The B.P of patient was taken three times before the Maneuver. Patient was asked to grip the inflatable rubber of modified sphygmomanometer and apply maximum voluntary pressure. A reading from attached mercury manometer was taken during maximum voluntary contraction. Thereafter, patient was asked to maintain 30% of maximum voluntary contraction for as long as possible up to five minutes. Blood pressure was measured at one minute intervals during handgrip. The result was expressed as the difference between the highest diastolic blood pressure during handgrip exercise and the mean of the three diastolic blood pressure readings before the handgrip began. Apart from tests cardiac autonomic imbalance was also tested by detailed history suggestive of orthostatic intolerance like H/o light headedness, weakness or tiredness H/o vertigo, anxiety, palpitations, sweating abnormality, diarrhea, constipation

INTERPRETATION OF TEST WAS BASED ON WORKS OF EWING & CLARKE [10]

Score	Heart rate variability test			Blood pressure test	
	Deep breathing	Valsalva ratio	Response to standing	Response to handgrip	Response to standing
0	>15	>1.20	>15	>15	≤ 10
1	11-15	1.11-1.20	12-15	11-15	11-29
2	≤ 10	≤1.10	<12	≤ 10	>30

For grading of cardiovascular autonomic function, results are classified into normal, borderline and abnormal (scores 0, 1, and 2 respectively).

An overall score of '0' or '1' was considered normal, score 2, 3, 4 were considered borderlines and score ≥5 were judged was abnormal autonomic function. QT interval was taken from onset of QRS complex to the end of T wave. QT was then corrected for heart rate using the Bazette's formule QTc interval = QT / √(R – R). A QTc interval more than 440 Millisecond is considered prolonged.

INCLUSION CRITERIA
Type 2 diabetes patients already on treatment & newly diagnosed patients

EXCLUSION CRITERIA
• Age above 60 years
• Documented ischaemic heart disease
• Documented valvular / congenital heart disease
• Hypertension
• COPD
• Uraemia
• Parkinsonism

STATISTICAL ANALYSIS
Statistical analysis was carried out for 150 patients after categorizing each variable – Age, sex, duration of diabetes, autonomic function tests, autonomic dysfunction score; interpretation results & QTc interval were analyzed One way Analysis of variance (ANOVA) was performed for comparison of means of more than two groups. The significance of difference between the proportions was indicated by the chi-square ($x2$) statistic. The significance of difference in mean between the groups was calculated by student t-test Variables were considered to be significant if ($P<0.05$). Intervariate analysis was done by using Pearson's r- value correlation

RESULTS
POPULATION CHARACTERISTICS
The study group consists of 150 Type 2 DM patients. The patients in the groups <5yrs, 5-10 yrs & >10 yrs were taken as group A, B and C respectively.

TABLE – 1   AGE VARIATION AMONG STUDY GROUPS

Duration of DM	N	Mean age	SD
<5 years	50	50.08	4.251
5-10 years	50	52.76	3.217
>10 years	50	55.16	2.881

TABLE – 2 SEX DISTRIBUTION AMONG STUDY GROUPS

Duration of DM		<5 years		5-10 years		>10 years	
		n	%	n	%	n	%
SEX	Male	27	54	29	58	28	56
	Female	23	46	21	42	22	44
Total		50	100	50	100	50	100

Among 150 patients, 84 patients were men accounting for 56% of total patients. The remaining 66(44%) patients were women. Mean age of patients in the groups A, B and C were 50.8, 52.76 and 55.16 respectively. This shows there is no significant variation in age among the three groups.

CAN IN THE STUDY GROUP
TABLE -3 FREQUENCY DISTRIBUTION OF NORMAL (0-1), BORDERLINE (2-4), ABNORMAL (≥5)

CAN		<5YRS		5-10YRS		>10YRS		Significance
		n	%	n	%	n	%	
	0-1	36	72	24	48	13	26	
Score	2-4	10	20	14	28	8	16	P<0.001
	≥5	4	8	12	24	29	58	Significant
Total		50	100.0	50	100.0	50	100.0	

In the study population, the prevalence of definite CAN was 8%, 24% and 58% in group A, B and C respectively. The prevalence of definite CAN increases with increase in duration of diabetes. P value <0.001 significant.

TABLE – 4 MEAN QTc IN THREE STUDY GROUPS

Duration of DM	n	Mean	SD
<5YRS	50	416.84	4.251
5-10YRS	50	426.55	3.217
>10YRS	50	441.64	2.881

TABLE – 5 QTc RESULT WITH DIAGNOSIS

Screening test results	Definite CAN+	CAN-	Total
≤440	9	57	66
>440	36	16	52
Total	45	73	118

**Sensitivity = 36 / 45 x 100 = 80% Specificity = 57 / 73 x 100 = 78.08%**

The QTc values are correlated with interpretation obtained from Cardiac autonomic function tests. From the table the Sensitivity is 80% and Specificity is 78.08%.

TABLE - 6 CORRELATION BETWEEN CAN & QTc PROLONGATION IN TOTAL DIABETIC PATIENTS
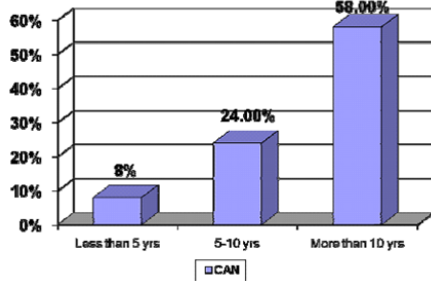
QTc in msec	Definite CAN	%	Borderline CAN	%	No CAN	%	p Value
≤440	9	20	22	68.8	58	79.5	<0.001
>440	36	80	10	31.2	15	20.5	significant

From the table, QTc interval prolongation occurs with development of CAN. Prolongation of QTc interval is well correlated with CAN . P value <0.001

DISTRIBUTION OF SYMPTOMS OF CAN AMONG CAN +ve PATIENTS
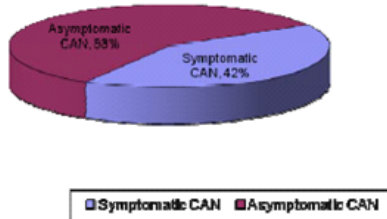
DURATION OF DIABETES & PREVALENCE OF DEFINITE CAN

DISCUSSION

This study shows that CAN is common in Diabetic patients & its prevalence increases with duration of diabetes. Similar results have been reported in previous studies conducted in India and other countries.

Andersen et al [1] assessed CAN in Danish people with screen detected diabetes in primary care at 6 year (N= 777) & 13 year(N= 443) followup. Higher BMI, Hba1c, high triglycerides were associated with prevalent CAN

Gaspar et al [2] retrospectively analyzed 187 cases (60 type -1 diabetes & 127 type -2 diabetes), orthostatic hypotension was present in 31.7 % of DM-1 and in 32.3 % OF DM-2 .

orthostatic hypotension was positively associated with prevalence of myocardial infarction in dm-1 & with prevalence of stroke in dm-2 cases. Overall 10 year mortality was higher in diabetics with orthostatic hypotension

Seung –hyun ko et al [3] did a 7 yr follow up study on 1021 patients. At follow up CAN incidence was 34.5% & higher in older patients; in those with longer duration of diabetes; with diabetic retinopathy; high levels of microalbuminuria.

Chen et al [4] did a study between 1989 & 1993. 431 men & 181 women with type 2 diabetes were given diabetic autonomic neuropathy cardiovascular reflex tests& then followed for subsequent 5-9 years to assess mortality. Prevalence rate of abnormal tests was 46.1% in patients with h/o diabetes less than 5 years & up to 69.4% when history exceeded 20 years. 8 year survival rate for patients with CAN was 63.6% in males & 76.4 % in females compared with 80.9 % & 93.3% for patients with normal tests

C P Mathur [8] studied 50 patients with diabetes with 20 normal controls to understand relationship to CAN with QTc interval. There were 15 (78.94%) cases with QTc prolongation out of 19 diabetics with CAN. None of diabetics without CAN or control subjects had QTc prolongation. It was observed to have sensitivity o9f 82.6% and specificity of 100%. In our study in ECG, out of 45 patients with definite CAN, QTc is prolonged in 36 patients, which gives a sensitivity & specificity of 80% & 78.08% respectively. There was significant correlation (p<0.001) between CAN & QTc prolongation in this study group.

CONCLUSION

Prevalence of Cardiovascular Autonomic Neuropathy is high in type 2 diabetics & will increase with increase in the duration of diabetes. A significant correlation is present between Cardiovascular Autonomic dysfunction and QTc prolongation. QTc interval in ECG can be used to diagnose CAN with a reasonable sensitivity & specificity.

DECLARATION

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