IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 3 Ver.19 March. (2018), PP 23-27
www.iosrjournals.org

Clinical Study Of Autonomic Neuropathy In Diabetes Mellitus

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Abstract: *Diabetic autonomic neuropathy (DAN) is a serious & common complication of diabetes often overlooked & misdiagnosed. The aim of present study is to observe the presenting manifestations of autonomic neuropathy in diabetes.*
Material & Methods: *94 diabetes patients proven with blood sugar fasting & post prandial & HbA1c value of RIMS Ranchi Jharkhand India were evaluated for presence or absence of autonomic neuropathy symptoms to diagnose DAN. Battery of tests devised by Ewing & Clarke et al. was done. Tran abdominal USG was done before voiding, and then patients were directed to void urine after that USG was done to look for post-void residue urine volume.*
Observation: *out of 94 patients 67 (71%) had one or more tests positive for parasympathetic dysfunction & 44 patients (47%) was positive for sympathetic dysfunction. Advanced CAN was present in 34 patients (37%) & 38 patients (40%) had early CAN. Out of 94 patients, 50 patients (53%) had post-void residual urine volume ≥ 100 ml while 44 patients (47%) had post-void residual volume < 100 ml.*
Key words: *diabetic autonomic neuropathy, Jharkhand, post void residual urinary volume.*

Date of Submission: 12-03-2018 Date of acceptance: 03-04-2018

I. Introduction

DAN[1] was defined by 1988 San Antonio (Texas) consensus meeting[2], disorder in ANS manifesting as dysfunction of several organ systems either clinical or sub clinical in patients with diabetes. DAN is a serious & common complication of diabetes. Cardiac autonomic neuropathy (CAN) is the most studied & clinically important form DAN, other system affected are GIT, GU, Sudomotor & Metabolic. Because vague nerve (the longest nerve of ANS) accounts for ~75% of all parasympathetic activity & DAN manifests first in longer nerves, even early effects of DAN are wide spread.
A study carried by S. Agrwal et al[3] in 2011 in Madhya Pradesh showed the prevalence of DAN in 70% of diabetic patients.
Study done by Anil s .Menon et al [4] in 2015 in India showed the prevalence of possible CAN was 31% & definite CAN was in 66.2%.
The aim of present study is to highlight the magnitude of the problem of DAN and different manifestations of DAN in Jharkhand & its early detection.

II. Material & Methods

This is a cross sectional observational study done in 94 patients at Rajendra institute of medical sciences, Ranchi. The duration of this study was from October 2016 to October 2017. DAN was defined by battery of tests to look for autonomic dysfunction as devised by Ewing & Clarke et al.[5]
Diabetes was defined by ADA 2016 guidelines.

American Diabetes Association 2016 Guidelines[6]

1. HbA1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

OR

2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

OR

3. 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).

Ewing & Clarke[5] et al scoring system for diagnosis of diabetic CAN.

Cardiovascular autonomic function test	Normal (0)	Borderline (1)	Abnormal (2)
Valsalva ratio	>_1.21	1.11-1.20	<_1.10
Heart rate variation during deep breathing	>_15 bpm	11-14bpm	<_10bpm
Immediate heart rate response to standing(30^{th} :15^{th} ratio)	>_ 1.04	1.01-1.03	<_1.00
Blood pressure response to standing (fall in systolic blood pressure)	<_10 mmhg	11-29	>_30 mmhg
Blood pressure response to sustained hand grip (increase in diastolic pressure)	>_16 mm hg	11-15 mm hg	<_10 mmhg

Score < 3: no cardiac autonomic neuropathy, Score 3 to 5: border line cardiac autonomic neuropathy, Score > 5: severe cardiac autonomic neuropathy

Trans abdominal USG was done before voiding, and then patients were directed to void urine after that USG was done to look for post-void residue urine volume. Cut off value of 100ml or more (PVR vol) was taken significant in our study.
Other investigations regarding autonomic dysfunction symptoms listed below
CVS:-resting tachycardia, exercise intolerance
GI:-oesophageal dysmotility, gastro paresis, constipation
GUT:-erectile dysfunction, retrogradeejaculation, neurogenic bladder
METABOLIC: - Hypoglycemia unawareness
SUDOMOTOR: - Anhidrosis, gustatory sweating, dry skin.

III. Observation

In our study Majority of the cases i.e. 82 patients (87%) were of type 2 diabetes mellitus and 12 patients (13%) were of type 1 diabetes mellitus. Majority of the patients i.e. 39 patients (41.5%) were of duration of 6-10 years. HbA1c was in range of 5.8 – 11% with mean of 8.4 (SD ± 1.4). Out of 94 patients, 41 patients (44%) had CVS symptoms, 26 (28%) had genitourinary symptoms, 18 (19%) had sudomotor symptoms, 16 (17%) had GIT symptoms and 13 patients (14%) had metabolic symptoms. Out of the 5 parameters of CAN, change in heart rate to deep breathing was most sensitive, abnormal in 58 patients (62%) closely followed by valsalva ratio, abnormal in 55 patients (58%). Least sensitive was fall in SBP on standing which was abnormal in only 10 patients (11%). 67 patients (71%) had one or more tests positive for parasympathetic dysfunction and 44 patients (47%) had one or more tests positive for sympathetic dysfunction. Prevalence of CAN was alarmingly high in the present study 34 patients (37%) had advanced CAN, 38 patients (40%) had early CAN. There was weak correlation between duration of diabetes and prevalence of CAN (r = 0.359). In the present study Heart rate response to deep breathing had best correlation with HbA1c (r = -0.656) followed by valsalva ratio (r = -0.505), SBP fall on standing was worst correlated to HbA1c (r = 0.374). In the present study relation between PVR and CAN is statistically not significant as determined by chi-square test (p value = 0.49). Relation between PVR volume and duration of diabetes mellitus is statistically significant as determined by chi-square test (p value=.029).

IV. Figures And Tables

Table No. 01: Distribution of Patients On The Basis Of Different Autonomic Symptoms.

ANS symptoms	Present	Absent
CVS symptoms	41	53
GIT symptoms	16	78
GUR symptoms	26	68
Sudomotor symptoms	18	76
Metabolic symptoms	13	81

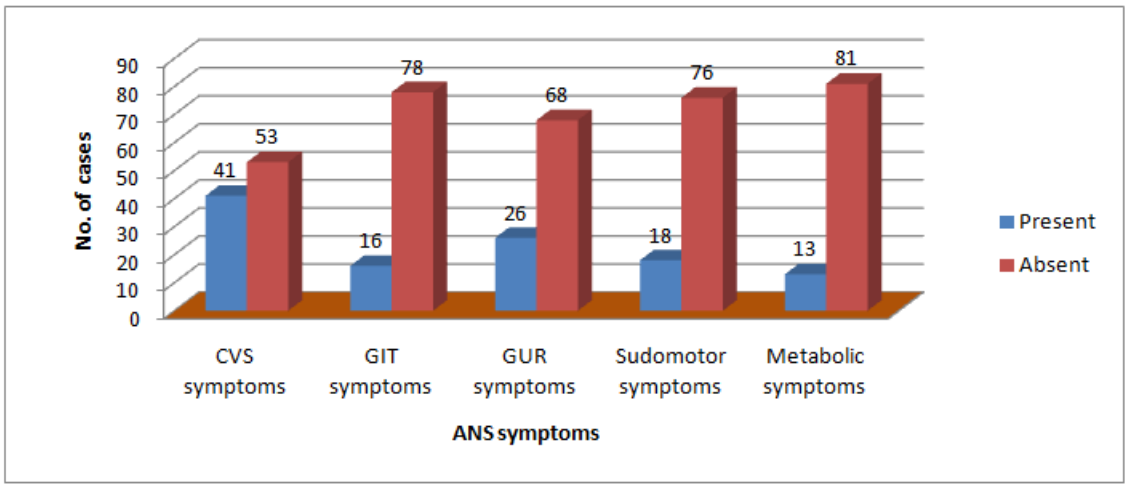

Table No. 02: Analysis of Tests for Cardiac Autonomic Neuropathy

CAN Parameters	Abnormal	Borderline	Normal
Heart rate response to deep breathing	58	8	28
Valsalva ratio	55	12	27
HR response to standing (30^{th}:15^{th}beat)	14	45	35
SBP fall on standing (mm hg)	10	38	46
DBP rise on sustained hand grip (mm hg)	42	22	30

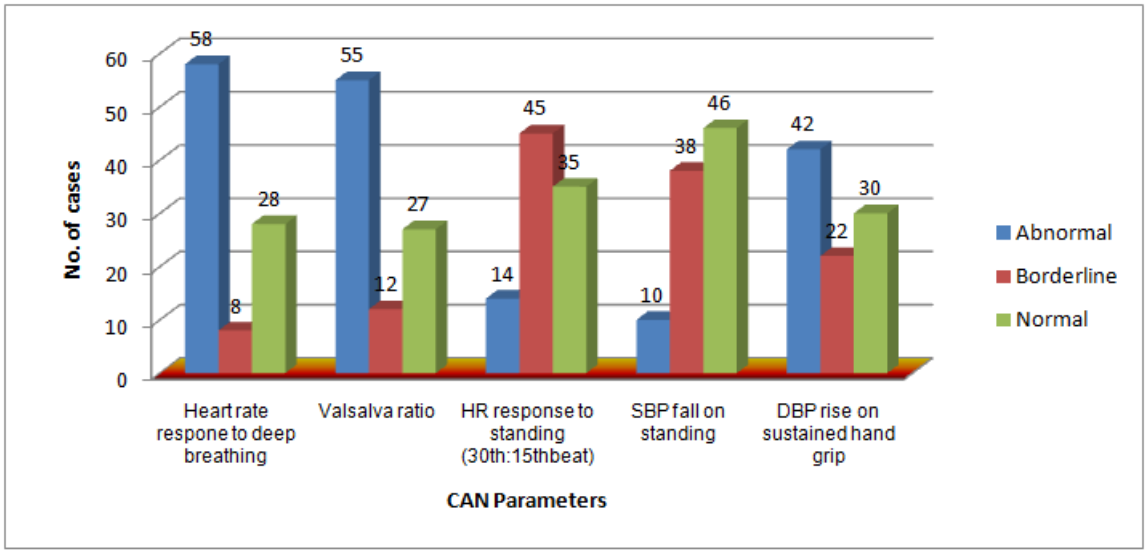

Table No. 03: Distribution of Cases on the Bias of Different Parts of ANS Involved

ANS	No. of Patients
Parasympathetic System	67
Sympathetic System	44

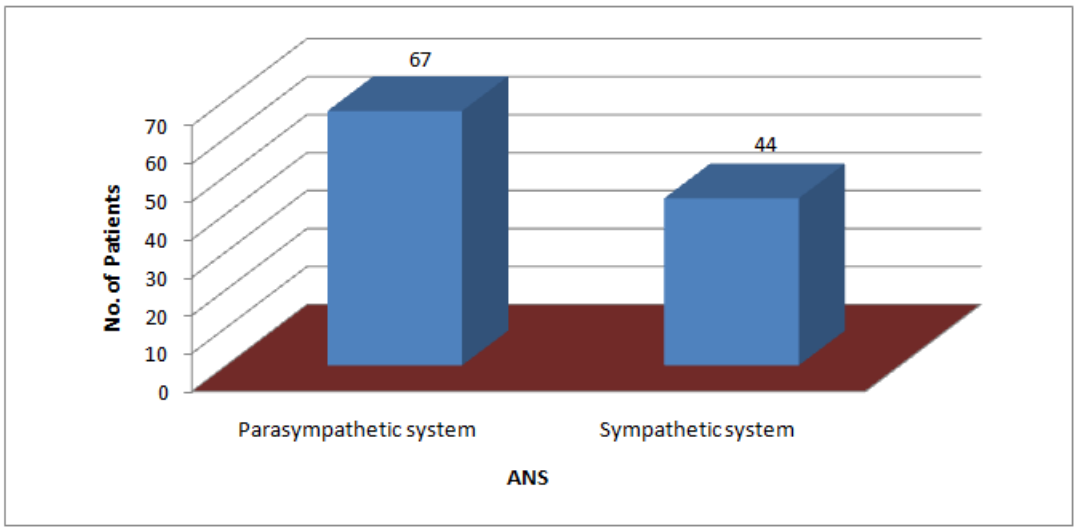

Table No.04: Distribution on the Basis of Can Severity

Can Score	No of cases	Percentage
Normal	22	23
Early	38	40
Advanced	34	37
Total	94	100.0

Table No. 05: Effect of HbA1c on CAN score

HbA1c (%)	Abnormal CAN	Normal CAN	Total
≥8.5	44	03	47
<8.5	28	19	47
Total	72	22	94

Table No. 06: Effect of Duration of Diabetes Mellitus (Years) On Post-Void Residual Urine Volume (Ml)

Duration of DM (years)	< 100 ml.	≥ 100 ml.	Total
<5 yrs.	22	9	31
6-10 yrs.	15	24	39
11-15 yrs.	8	13	21
>15 yrs.	1	2	3
Total	46	48	94

Table No. 07: Effect of Pvr Urine Vol (Ml) On Can Score

CAN Score	PVR Vol<100 ml.	PVR Vol ≥ 100 ml.	Total(94)
Normal	11	11	22
Early	15	23	38
Advance	18	16	34

Table No. 8: Relation between Hba1c and Different Parameters of Can

CAN parameters	Spearman's correlation coefficient®
Heart rate response to deep breathing	-0.656
Heart rate response to valsalva	-0.505
DBP rise on sustained hand grip(mm hg)	-0.409
30^{th} :15^{th} beat R-R ratio	-0.407
Fall in systolic BP in response to standing(mm hg)	0.374

Discussion: This study shows high prevalence of CAN (a variant of DAN) in our study. Among the 5 tests for CAN, deep breathing test was most sensitive, abnormal in 58 patients (62%), closely followed by valsalva ratio which was abnormal in 55 patients (58%).This is supported by Mathura et al[7] &Bose et al[8] study where deep breath test was the most sensitive variant. increasing the no. of tests will help in detecting CAN earlier & more correctly. In the present study 34 patients (37%) had advanced CAN & 38 patients (40%) had early CAN & 22 patients (23%) had no CAN. These findings are supported by Agrawal et al[9] & Mehta et al study[10].In the present study 67 patients (71%) for parasympathetic system & 44 patients (47%) for sympathetic system ,had one more tests positive , supported by San Antonio consensus panel which concluded that the parasympathetic dysfunction is preceded by sympathetic dysfunction . *Kempler et al.*[12] showed a significant correlation between prevalence of CAN and duration of diabetes ($p < 0.0001$). In our study There was weak correlation between

duration of diabetes and prevalence of CAN (r = 0.359). In this study heart rate response to deep breathing had best correlation with HbA1c (r = -0.656) followed by Valsalva ratio (r = -0.505). SBP fall on standing was worst correlated to HbA1c (r = 0.374).

Out of 22 patients of diabetes of less than 5 year duration, 9 patients (29%) had PVR urine volume ≥ 100 ml, out of 39 patients in the duration of 6-10 years 24 patients (56%) had PVR ≥ 100 ml. In the duration of 11-15 year, 13 patients (61%) out of 21 had PVR ≥ 100 ml, and in duration of greater than 15 year, 2 patients (66%) out of 3 had PVR ≥ 100 ml. This study is significant as determined by chi-square test (p value=0.029).
In a similar study carried by *Mona A. K. Salem et al.* in the year 2006-08 showed, the duration of diabetes was significantly related to the ultrasound residual urine volume ($p < 0.05$).
So USG can be used for evaluation of diabetic cystopathy.

V. Conclusion:

All patients with diabetes should be screened for DAN irrespective of age, sex, type and duration of DM.The screening for DAN should be done at the time of diagnosis of DM.

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Dr. Nishu Kumar. " Clinical Study Autonomic Neuropathy In Diabetes Mellitus." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 17.3 (2018): 23-27.