Prevalence Of Cardiac Autonomic Neuropathy In Patients With Diabetes

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Abstracts: Background: Autonomic neuropathy is a serious complication of diabetes mellitus. Cardiac autonomic neuropathy (CAN) is chronic diabetic complication with variable prevalence and clinical manifestations. Prevalence of CAN remains less explored domain among type 2 diabetic population. Aim: To analyse the prevalence of CAN in type 1 and type 2 DM. Materials and methods: A total of 152 cases with DM were selected for the study following strict inclusion and exclusion criteria. All the cases underwent a battery of cardiovascular reflex tests designed by Ewing. Results: We observed that overall prevalence of CAN was 51.9%. Prevalence of sympathetic and parasympathetic CAN was 28.9% and 44% respectively. When compared, prevalence of CAN in type 1 patients was significantly different from type 2. Further, significant difference was noted between parasympathetic and sympathetic CAN in these patients. Conclusion: Study concludes that, prevalence of CAN in type 1 DM is higher than type 2. Parasympathetic CAN prevalence is higher than sympathetic CAN in both groups. [Ramavat M et al NJIRM 2012; 3(3) : 15-19]

Key words: Diabetic autonomic neuropathy, diabetes mellitus complication, type 2 diabetes mellitus

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Introduction: While autonomic dysfunction is an established complication of diabetes, impaired autonomic function is often detected at the time of diabetes diagnosis [1]. Cardiac autonomic neuropathy (CAN) is chronic diabetic complication. It is reported with variable prevalence and clinical manifestations[2]. Several hypotheses regarding its pathogenesis include metabolic insult to axons, neurovascular insufficiency, autoimmunity, and neuro-hormonal growth factor deficiency[3]. Although clinical manifestations of CAN are not life threatening, there is increase in mortality in the diabetic patients with CAN[4]. Projected disease burden of diabetes mellitus (DM) in India by 2030 is 79.44 million[5].

Thus early detection of CAN is a necessity. Previous studies especially throw light on prevalence of CAN in overall diabetic population or type 1 DM patients. Prevalence of CAN among type 2 and its comparison with type 1 is less explored. Further, prevalence of sympathetic and parasympathetic neuropathy among both the types needs to be explored separately. With this context, present study was designed to analyze prevalence of CAN in type 1 and type 2 DM. An attempt was also made to find out prevalence of sympathetic and parasympathetic CAN in these patients.

Materials and Methods: Study was conducted at Neurophysiology Unit of Department of Physiology, in a teaching hospital in western India during 2007-2009. Cases were selected randomly from diabetic clinic. Institutional diabetic clinic adopted guidelines from 'report of a WHO consultation' on definition and classification of diabetes mellitus issued in 1999. They were diagnosed by consultant physician, for the disease and its type (Type 1 and Type 2). Patients with hypertension, cardiac failure, ECG evidence of arrhythmia, ischemia, and congenital heart diseases were excluded from the study. Patients with history of drugs known to interfere with cardiac or respiratory functions, chronic alcohol or tobacco consumption and with physical disability in maintaining erect posture were also excluded from the study.

All the patients selected for study underwent Cardiovascular Reflex Tests (CRT) for evaluation of autonomic neuropathy. Tests were performed by same examiner under constant environmental conditions and on same machine to avoid errors in data collection. An approval from institutional ethics committee was obtained. Informed consent was taken from all the subjects and the study was carried out in accordance with the World Medical Association Declaration of Helsinki.

Cardiovascular Reflex Tests (CRT) [6]

Patients were instructed to remain nil by mouth two hours before the tests. They were also instructed to avoid coffee, nicotine and alcohol intake 24 hours before the tests. Different tests designed by Ewing et al for assessment of cardiac autonomic neuropathy includes, 1) Immediate heart rate response to standing (A value of equal to 1.03 or less was considered abnormal), 2) Heart rate (R-R interval) variation during deep breathing (E/I ratio of 1.21 or less was considered as abnormal), 3) Heart rate response to Valsalva manoeuvre (VR ratio was considered abnormal if value is < 1.21), 4) Blood pressure response to sustained handgrip exercise (Value < 16 mm of Hg was considered as abnormal), and 5) Blood pressure response to cold stimulus (Value <10 mm of Hg was considered as abnormal).

First three tests were used to assess parasympathetic neuropathy and remaining two, to assess sympathetic neuropathy. Cardiac parasympathetic neuropathy was labelled if at least two tests were abnormal. Cardiac sympathetic neuropathy was labelled if at least one test was abnormal.

Statistical analysis of data: Data was analysed using SPSS version 13. Data of the variables for comparison was skewed. Data was expressed as Mean, standard deviation, range, and percentage. Chi-square test was applied to find out difference of statistical significance. P value < 0.1 was considered statistically significant as sample size was very small. Power of the test was 67%.

Results: Table 1 shows demographic profile of diabetic population. Total 152 patients were evaluated. Out of which 78 were diagnosed for type 1 and 74 for type 2. Among type 1 patients, 40 were male (age range 17-45 years) and 38 were female (age range 15-45 years) with mean age 31.9 yrs and 28 yrs respectively. Among type 2 patients, 38 were male (age range 40-75) and 36 were females (age range 40-75) with mean age 54.6 years and 55.1 yrs respectively.

Table 2 shows prevalence of CAN among type 1 and type 2 patients. Statistically significant difference in prevalence of autonomic neuropathy was observed among type 1 patients as compared to type 2 patients (p<0.1). Statistically significant sex related difference was not observed in prevalence of autonomic neuropathy (p>0.1).

Table 1: Demographic profile of diabetic population under study

No. of Patients N=152	No of patients	Age in years Mean±SD (Age range)		Duration of diabetes in years (Mean±SD)
Type 1 diabetes N=78	Male N=40	31.9±15.97 (17-45)	29.9 (15-45)	8.05±5.12
	Female N=38	28±10.03 (15-45)		6.32±5.02
Type 2 diabetes N=74	Male N=38	54.6±10.18 (40-75)	54.9 (40-75)	7.41±6.35
	Female N=36	55.1±10.33 (40-75)		7.25±6.42

Table 2: Prevalence of CAN in diabetic population

Group	Male	Female	Total
Type 1 diabetes	52.5 (21/40)	63.1 (24/38)	57.6*(45/78)
Type 2 diabetes	44.7 (17/38)	47.2 (17/36)	45.9* (34/74)
Total	48.7** (38/78)	55.4** (41/74)	51.9 (79/152)

(Note: p value <0.1 was considered statistically significant, * shows significant difference and ** shows values are statistically not significant.)

Table 3-A and 3-B shows distribution of parasympathetic and sympathetic neuropathy among type 1 and type 2 patients. Out of 152 patients, 79 patients (51.9 %) were diagnosed to have autonomic neuropathy. Only parasympathetic CAN was observed in 35 patients, only sympathetic CAN was observed in 12 patients and 32 patients were found to have both parasympathetic and sympathetic CAN. No evidence of autonomic neuropathy was observed in 73 patients (48.03 %).

Table 3-B shows Statistically significant difference was observed in prevalence of sympathetic and parasympathetic neuropathy in overall diabetic population and in type 1, type 2 population as well (p<0.1).

Discussion: Autonomic neuropathy (AN) is often labelled as a common complication and an independent risk factor for increased morbidity and

mortality among diabetic population. It also remains the least recognized and understood complication despite its vulnerable impact on quality and survival of diabetics[7, 8]. Although wide range of tests to evaluate neurovascular function is available, poor standardization makes them of limited clinical utility. Simple, bedside and non-invasive battery of tests designed by Ewing et al holds mainstay for evaluation of CAN[9, 10].

Table: 3-A: Prevalence of sympathetic, parasympathetic and both cardiac autonomic neuropathy. (Values in parenthesis indicate number of patients)

	Type 1diabetes			Type 2 diabetes			Total=152
	Male N=40	Female N=38	Total N=78	Male N=38	Female N=36	Total N=74	
Patients having only parasympathetic neuropathy (P)	20 (8)	34.2 (13)	26.9 (21)	26.3 (10)	11.1 (4)	17.9 (14)	23 (35)
Patients having only sympathetic neuropathy (S)	10 (4)	7.8 (3)	8.9 (7)	7.8 (3)	5.5 (2)	6.4 (5)	7.8 (12)
Patients having both sympathetic and parasympathetic neuropathy (PS)	22.5 (9)	21 (8)	21.7 (17)	10.5 (4)	30.5 (11)	19.2 (15)	21 (32)

Table: 3-B: Comparison of sympathetic and parasympathetic CAN in diabetic population under study. (Values in parenthesis indicate number of patients)

	Type 1 diabetes	Type 2 diabetes	Total	p value
Total number of patients having parasympathetic neuropathy (P+PS)	48.7 (38)	39.1 (29)	44 (67)	P < 0.1
Total number of patients having sympathetic neuropathy (S+PS)	30.7 (24)	27 (20)	28.9 (44)	

(p value < 0.1 was considered statistically significant)

It is well known that prevalence of CAN varies from study to study depending upon the type of cohort and methods of assessment employed. It varies from 7.7% for newly diagnosed patients with type 1 diabetes to 90% in potential recipients of a pancreas transplant[3]. In present study, overall prevalence of CAN was 51.9%. Reported prevalence from previous studies and its comparison with present one is illustrated in Table 4.

Our findings were in agreement with Ewing[12] et al and Pappachan[13] et al but were different from O' Brien[14] et al and Zeigler[15] et al. Further we could also delineate the prevalence of CAN among both insulin dependent and nondependent patients as 57.6% and 45.9% respectively which were different from previous studies[14]. It may be attributed to the differences in sample size, tests employed and diagnostic criteria used for labelling CAN[3]. Factors like duration of diabetes at the time of referral and rural Indian origin of cohort as against western in previous studies, may have affected the outcome of results.

We observed that prevalence of CAN among type 1 domain of study group is higher as compared to type 2 domain. Although finding is not corroborative with Zeigler[15] et al, probable explanation for higher prevalence among type 1 patients may be attributed to autoimmune background of CAN. Granberg[16] et al proposed that autoantibodies to autonomic nerves (ANabs) are frequent phenomenon in type 1. ANabs may play primary role in pathogenesis and progression of the CAN in type I diabetics.

Another striking feature is higher prevalence of parasympathetic dysfunction as compared to sympathetic dysfunction. Ewing's criteria and San Antonio Consensus Panel[17] assumed that parasympathetic fibres involve far early due to their longer length as compared to sympathetic fibres.

Sympathetic fibres are damaged after about five years of pneumogastric (vagus) nerve damage. Prevalence of sympathetic and parasympathetic neuropathy was similar in type 1 versus type 2 diabetic patients in a study conducted by Freccero[18] et al. A recent retrospective analysis by Khandelwal[19] et al, higher prevalence of sympathetic neuropathy was observed in diabetic patients. With variable prevalence and pattern of sympathetic and parasympathetic dysfunction observed in diabetics in previous studies, extensive research with larger sample size becomes essentiality. Currently, approaches to treatment are limited due lack of evidence on exact pattern, prevalence and etiopathogenesis of this condition. To develop novel and evidence-based strategies for the prevention and treatment of diabetic autonomic neuropathy, it is therefore essential to evaluate parasympathetic and sympathetic CAN in depth.

Table 4: Reported CAN prevalence and its comparison with present study

Study and year	Type of diabetic population	No of autonomic function tests applied	No of participants	Percentage abnormality	Criteria for diagnosis
Ewing[12] et al 1980	Mixed with autonomic symptoms	Valsalva manoeuvre. Handgrip test Postural BP	61	54	
O' Brien[14] et al 1991	Type 1 DM	HRV in response to 1) rest 2) single deep breath, 3) Valsalva manoeuvre 4) standing	506	17	At least two test must be abnormal to label CAN
Ziegler[15] et al 1992	Type 1 DM Type 2 DM	Coefficient of variation of HRV, Spectral analysis, MCR, Valsalva manoeuvre, supine to standing	647 524	25.3 34.3	Greater than two tests must be abnormal to label CAN
Pappachan[13] JM et al 2008	Type 1 DM Type 2 DM	Ewing's battery of autonomic function tests	100 152	60 51.9	
Present study	Type 1 DM Type 2 DM	Parasympathetic function: HRV in response to 1) standing, 2) single deep breath, 3) Valsalva manoeuvre Sympathetic function: BP response to 1) Sustained handgrip 2) cold stimulus	78 74	57.6 45.9	Parasympathetic CAN was labelled if at least two tests were abnormal. Sympathetic CAN was labelled if at least one test was abnormal

(IDDM=Insulin dependent diabetes mellitus, NIDDM= Non-insulin dependent diabetes mellitus, BP= Blood pressure, CAN= cardiac autonomic neuropathy, HRV=Heart rate variability, MCR= mean circular resultant)

Limitations and strengths: Present study is distinct in the context that it evaluated prevalence of CAN in type 1 and type 2 DM separately. It also evaluated sympathetic and parasympathetic CAN among DM patients. Deficient data collection with respect to glycaemia, clinical features and investigations suggesting micro and macro vascular complications remain obvious limitation of this study.

Conclusion: DAN and especially its entity CAN deserve special attention due to its silent but life threatening Consequences. Present study concluded that prevalence of CAN among type 1 DM is higher ascompared to type 2 DM. Prevalence of parasympathetic neuropathy is higher as compared to sympathetic neuropathy.

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