Prevalence of Autonomic Neuropathy in Diabetes Mellitus

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Abstract

Diabetic autonomic neuropathy is a serious and common complication of diabetes whose significance has not been fully appreciated. In this study, 50 non-cardiac diabetic patients were randomly selected to serve as cases and subjected to a standardized protocol of history, examination and a battery of autonomic function tests. 70% of them tested positive for autonomic dysfunction with its incidence increasing in direct proportion with increasing duration of the disease as well as with increasing hyperglycemia. An increase in the severity of autonomic dysfunction was also observed with high blood glucose levels. However no significant correlation of incidence with age and sex of the patient or type of the diabetes were established. The present study may help to appreciate the significance of diabetic autonomic neuropathy and its early detection as the same can encourage both the patient and the physician to improve metabolic control and use therapies such as Angiotensin- converting enzyme inhibitors, α- Lipoic acid and β- blockers proven to be effective with cardiac autonomic neuropathy.

Introduction

Diabetic autonomic neuropathy (DAN) is among the least recognized and understood complication of diabetes despite its significant negative impact on survival and quality of life in people with diabetes. DAN frequently coexists with peripheral neuropathies and other diabetic complications, but, it may be isolated, frequently preceding the detection of other complications [1]. It can involve the entire autonomic nervous system producing troubling symptoms (impotence, syncope) and lethal outcomes. DAN may occur sub clinically without any symptoms or be clinically evident sometimes occurring as early as the first year after diagnosis with its major manifestations being cardiovascular, gastrointestinal or genitourinary dysfunction.

The repeated prevalence of DAN varies widely depending on the cohort studied and the methods of assessment. Other factors that account for the marked variability include the lack of a standard accepted definition of DAN, different diagnostic methods, variable study selection criteria and referral bias. Additional complicating factors include the wide variety of clinical syndromes and confounding variables such as age and sex of the patient, duration of diabetes, glycemic control, diabetic type, height and other factors [2].

Cardiac autonomic neuropathy (CAN) is the most studied and clinically important form of DAN because of its life threatening consequences and the availability of direct non-invasive tests of cardiovascular autonomic functions. CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels and results in abnormalities in heart rate control and vascular dynamics [3]. One unifying mechanism of nervous system injury in diabetes lies in the ability of both metabolic and vascular insults to increase cellular oxidative stress and impair the function of mitochondria. Hyperglycemia and dyslipidemia are major contributors to this oxidative stress. The various pathogenic pathways leading to neuropathy become perturbed as a direct and indirect consequence of hyperglycemia-mediated superoxide overproduction by the mitochondrial electron transport chain and trigger a feed-forward system of progressive cellular dysfunction **[4].**

The association of mortality and cardiovascular autonomic dysfunction indicates that individuals with abnormal autonomic functions are candidates for close surveillance. Nevertheless some of these deaths may be avoided through early identification of these high risk patients and by slowing, with therapy, the progression of autonomic dysfunction and its associated conditions. In addition, it appears that cardiovascular autonomic function testing provides a predictive tool in identifying a group of post

myocardial infarction patients who are at a high risk for death.[5]

The present study was undertaken to find the incidence of autonomic neuropathy in diabetes and its correlation with age and sex of the patient, duration and type of diabetes and hyperglycemia.

Material and Method

The present work was undertaken in 50 cases of diabetes mellitus attending outdoor and indoor clinics of the Department of Medicine, G.R. Medical College and J.A. Group of Hospitals, Gwalior (M.P.). The permission for undertaking the study was taken from the institutional ethical committee. The diagnosis of diabetes mellitus was made as per the revised criteria laid down by the American Diabetes Association and the Expert Committee on the diagnosis and classification of diabetes mellitus, WHO (2003). The cases were randomly selected without any bias for age, sex, type, control and duration of diabetes.

A thorough history taking with special emphasis on symptoms of autonomic dysfunction and detailed examination were performed. Patients with history suggestive of heart disease, renal disease, liver disease, respiratory disease, significant anemia, electrolyte imbalance, resting abnormal electrocardiogram (E.C.G.) or familial dysautonemia were excluded from the study. The cases were subjected to five non-invasive autonomic function tests as recommended by Ewing-Clarke[6] and categorized as:

1.   Normal: all five tests normal or one borderline.

2.   Early involvement: one of the three heart rate tests abnormal or two borderline.
3.   Definite involvement: two or more of the heart rate tests abnormal.
4.   Severe involvement: two or more of the heart rate tests abnormal plus one or both blood pressure tests abnormal or both borderline.

All the subjects were well-informed regarding the precautions that need to be taken before performing these tests. Apart from routine investigations, blood glucose estimation, both fasting and postprandial was done to quantify glycemic levels.

For the purpose of statistical analysis, Chi-square test was applied. The level of significance was considered only when the p value is less than 0.05 ($p<0.05$).

Observations

The diabetic cohort studied constituted of 31 males (62%) and 19 females (38%) with majority of the cases being in the age group 51-60yrs with mean age 52±11.19 yrs (Table 1). Majorities (54%) of them were either newly diagnosed cases for the disease or had diabetes of ≤5yrs duration. The mean duration of the entire study group was 5.89±4.57yrs (Table 2). Out of the 50 diabetic cases selected, 74% were of NIIDM and 26% of IDDM (Table 3).

35 cases (70%) tested positive for autonomic dysfunction and there was a highly significant increase in its prevalence with increasing duration of the disease ($p<0.01$) (Table 2). In ≤5yrs. duration group, 51.85% had autonomic dysfunction with one of them being a newly detected case whereas in >10yrs. duration group, all the

Table 1. Autonomic neuropathy with reference to age and sex in diabetic subjects

*Age (yrs.)			**Males		**Females		*Total cases with DAN	Percentage (%)
Range	Mean± SD	n	n	With DAN	n	With DAN		
20-30	24±4.0	3	1	0	2	1	1	33
31-40	36±3.8	7	5	3	2	1	4	57
41-50	46.5±2.9	12	7	5	5	2	7	58
51-60	57.4±2.7	15	7	5	8	7	12	80
> 60	66.4±4.2	13	11	9	2	2	11	84
Mean±SD 52.12±11.19		50	31 (62%)	22 (70.96%)	19 (38%)	13 (68.42%)	35	70

*χ^2 = 4.766, d.f. = 3; p> 0.10, insignificant

**χ^2=0.036, d.f. = 1; p>0.50, insignificant

Table 2. *Autonomic neuropathy with relation to duration of diabetes among cases*

Duration of diabetes (in yrs)	Mean±SD	n	**Grade of autonomic neuropathy Early	Definite	Severe	*Total cases with DAN	Percentage (%)
≤ 5	2.67±1.7	27	6	6	2	14	51.85
6-10	7.23±1.6	15	5	5	3	13	86.66
> 10	14.25±2.5	8	2	3	3	8	100
Total	**5.89±4.57**	**50**	**13**	**14**	**8**	**35**	**70**

Prevalence with duration: χ^2=9.647, d.f. = 2; p<0.01, highly significant
*** Severity with duration: χ^2=3.293, d.f. = 4; p>0.5, insignificant*

Table 3. *Autonomic neuropathy with relation to type of diabetes mellitus*

Sex	Total no. of cases	Grade of autonomic neuropathy			Total cases with DAN	Percentage (%)
		Early	Definite	Severe		
NIDDM	37	12	8	6	26	70.27
IDDM	13	1	6	2	9	69.23
Total	**50**	**13**	**14**	**8**	**35**	**70**

χ^2=0.05, d.f. = 1, p>0.50 insignificant

Table 4. Relation of autonomic neuropathy with blood glucose levels

Blood glucose (mg%)	**Grade of autonomic neuropathy			*Total cases with DAN	Percentage (%)
	Early	Definite	Severe		
Fasting < 100 &/or PP < 140	1	1	0	2	5.7
Fasting b/w 100-126 &/or PP b/w 140-200	5	3	1	9	25.7
Fasting > 126 &/or PP > 200	7	10	7	24	68.6
Total	**13**	**14**	**8**	**35**	**100**

Prevalence with blood glucose levels: χ^2=16.58, d.f. = 2; p<0.001, highly significant
***Severity with blood glucose levels: χ^2= 36.1, d.f.=4; p<0.001, highly significant*

cases (100%) had autonomic dysfunction. But our study showed no increase in the severity of autonomic involvement with increasing duration of the disease (p>0.5).

80% of the diabetic cohort in the age group 51-60yrs. and 84% in the age group>60yrs had impairment of autonomic functions (Table 1). However, this increase in its prevalence with increasing age was found to be insignificant (p>0.5). Similarly though our results showed a slight male predominance but this variation with sex was also insignificant (p>0.5) (Table 1). Also no significant correlation between the type of diabetes and incidence of autonomic involvement was established (p>0.5) (Table 3).

However, there was an increase in prevalence as well as severity of dysautonemia with increased blood sugar levels (p<0.001) (Table 4). 68 .6% of cases with DAN had fasting blood glucose levels>126mg% and/or postprandial

levels>200mg%. And 7 out of 8 cases of severe DAN had poorly controlled blood glucose levels.

Discussion

The prevalence of DAN in the cohort studied was 70%. Amongst these, 22.9% had severe autonomic dysfunction with prevalence of definite and early neuropathy being 40% and 37% respectively.

Studies by Ewing *et al*[7] had found its prevalence as 63.93% with 39 out of 61 diabetics' examined testing positive for DAN whereas Valensi P. *et al*[8] in his French multicentre study in the year 2003 reported its prevalence as 51%. Nijhawan *et al*[9] documented its prevalence in 60% diabetics in India. The reported prevalence of DAN varies widely depending on the cohort studied and methods of assessment.

Development and degree of DAN is not an all or none phenomenon but a continuation of the progression of a disease process, its incidence increasing in direct proportion to the duration of the disease. Valensi P. *et al*[8] and Kempler *et al*[10] showed a significant correlation between prevalence of CAN and duration of diabetes (p= 0.026 and p<0.0001 respectively). **Pfeifer**[11] even concluded that after a mean duration of 25 years of diabetes almost all diabetics will have autonomic dysfunction.

Our data also suggests this correlation. A higher prevalence rate of CAN (70%) was observed with an early age of onset having mean duration of diabetes 2.67 ±1.67 yrs. This further rose with increasing duration and all the cases with mean duration 14.25 ± 2.5 yrs. had autonomic dysfunction. Studies of Tankhiwale *et al* [12] also found a linear relationship between the duration of disease and severity of dysautonemia. But in the present work, though there was an increase in the severity of autonomic dysfunction, 7.4% in ≤ 5 yrs duration group to 37.5% in > 10 yrs duration group, any significant correlation between the severity dysfunction of dysautonemia and duration of diabetes was not found (p>0.5, insignificant).

Also, no correlation of DAN could be assessed with respect to age and sex of the patient. And the increase in prevalence with age observed in this study was due to higher age distribution of the sample population which compromised of more cases of NIDDM to which Indians are more susceptible than IDDM and NIIDM predominantly affects the older age group. There is paucity of literature on the relationship between the type of diabetes and the incidence of autonomic neuropathy. This study also did not found any profound influence of the type of diabetes on the development of autonomic involvement.

In our study, the prevalence of DAN is high compared to studies of other contemporary western workers and also the mean duration of diabetes is less (5.89±4.57 yrs.). These are probably due to the fact that asymptomatic diabetes is rarely diagnosed in our setup. This is not only due to high illiteracy and ignorance about the disease but also because of non-availability of health care and medical advice to a large number of our rural-based population. Most of the patients of our setup who are diagnosed with the disease usually had the disease for sometime and most often present with one of its complications. Besides the majority of diabetics are poorly controlled.

Retrospective and prospective studies have suggested a relation between hyperglycemia and the development and severity of DAN. Study of D.R. Witte *et al*[12] confirmed the importance of exposure to hyperglycemia as a risk for CAN. Hyperglycemia is central to the development of micro- and macro-vascular complications of diabetes.

The present results indicate that cardiac autonomic neuropathy is a more common complication of diabetes mellitus than generally presumed. A long latent of diabetes before diagnosis, a high illiteracy rate and rural based health care services in our setup makes it even more common but lesser recognized and understood complication. Although it can be detected even at the time of diagnosis, both the duration and the level of hyperglycemia pose a major risk. Poorly controlled diabetes not only increases the incidence of CAN but also the extent of the autonomic involvement, may be without its obvious manifestations.

Thus in the wake of these observations, it becomes imperative to evaluate autonomic functions tests in every diabetic for any evidence of autonomic involvement, may be subclinical one as an early detection can encourage both the patient and the physician to improve metabolic control ,and use therapies such as Angiotensin-converting enzyme inhibitors, α-lipoic acid proven to be effective with CAN. And this will hopefully go a long way to help a physician to improve the quality of life of his patient.

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