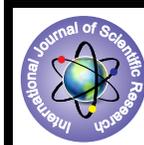


Study of Autonomic Dysfunction in Diabetes Mellitus



Medical Science

KEYWORDS : Autonomic Nervous System(ANS), Diabetic Autonomic Neuropathy(DAN), Type 1 and Type 2 DM

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ABSTRACT

Aims and objectives: To study prevalence of DAN(Diabetic Autonomic Neuropathy), evaluate and compare autonomic dysfunction with reference to cardiovascular, gastrointestinal, genitourinary, sudomotor and metabolic systems and with concurrence of other diabetic complications.

Introduction

Claude Bernard first observed and articulated scientific evidence of constant nature of milieu interieur(internal environment), homeostasis. John Newport Langley, Walter Cannon and Hans Selye suggested existence of Autonomic nervous system(ANS) independent of Central nervous system(CNS) composed of antagonistically paired subsystems necessary for optimal functioning of fundamental processes of the body⁽¹⁾. Building on the works of these gentlemen, Porges showed that ANS subsystems were indeed symbiotic and not antagonistic which moderate and coordinate internal resources of the body to maintain homeostasis⁽²⁾.

Autonomic manifestations of diabetes is associated with occurrence of broad constellation of symptoms that affect cardiac, gastrointestinal, genitourinary, sudomotor and metabolic functions resulting in significant mortality and morbidity^(3,4). Clinical symptoms of autonomic neuropathy generally do not occur until long after onset of diabetes. Subclinical ANS dysfunction, however, occur within a year of diagnosis of Type 2 DM and within two years in Type 1 DM⁽⁶⁾.

Availability of trustable noninvasive tests for ANS dysfunction will provide opportunity for early detection^(6,7) and timely intervention preventing complications of diabetes and improving quality of life.

Material and Methods

The present study was conducted in our Government medical college and attached tertiary care hospital and associated institutes between August 2012 to August 2014

Study group

Inclusion criteria

Total of 200 patients with diabetes diagnosed more than 5 years ago were enrolled. 100 patients each of Type 1 and Type 2 DM were selected.

Exclusion criteria

- Patients with clinical signs of cardiac failure, CNS abnormalities affecting peripheral nervous system, neuromuscular junction, motor neuron disease and Parkinson disease
- Patients with systemic diseases like connective tissue disorder or any long standing illness which might affect the course of ANS dysfunction
- Patients receiving drugs that interfere with functioning of ANS like beta blockers, tricyclic antidepressants, other an-

ticholinergics/adrenergics, alcohol, smoking

- Patients with electrocardiogram suggestive of arrhythmia or block
- Patients with any structural gastrointestinal abnormality and benign prostatic hypertrophy detected by ultrasonography of abdomen

Methods

- 1) Detailed history with special emphasis on autonomic symptoms were elicited from all patients
- 2) Five standard tests of autonomic functions carried out^(8,9). Patients found to have two or more tests abnormal were considered to have DAN
- 3) Simultaneously following investigations were carried out
 - Fundoscopy
 - FBS, PPBS, A1C
 - Urine analysis(Urine albumin/microalbuminuria)
 - Serum creatinine, Blood urea, Hb
 - Serum lipid profile(HDL,TG)
 - Ultrasonography of abdomen with kidney, ureter, bladder and prostate
 - 2D ECHO
- 4) Statistical analysis done for better understanding and to provide logical support to results

Results:

Prevalence of DAN was higher in Type 2 diabetes mellitus(DM) than in Type 1 DM(P0.0177). 20 out of 100 Type 1 DM patients were found to have DAN as opposed to 36 out of 100 in Type 2 DM. There was no significant age difference or sex predilection between patients with and without DAN in Type 1 or Type 2 DM. P values for age difference were 0.5507 and 0.7854 and for sex predilection were 0.4447 and 0.1753 in Type 1 and Type 2 DM respectively. Incidence was directly proportional to duration of diabetes suggested by the statistically significant difference in mean duration of diabetes between patients with and without DAN in both Type 1 and Type 2 DM with p values of 0.0010 and 0.0127 respectively. HbA1C was found to be high in patients with DAN than without DAN(p<0.0001) indicating the role of poor glycemic control in development and progression of DAN. FBS and PPBS too were found to be high in patients with DAN than without but with non-significant p value. Dyslipidemia⁽¹⁰⁾ (TG≥150 mg/dl, HDL <40 mg/dl in males and <50 mg/dl in females) was more common in patients with DAN suggesting metabolic syndrome could have significant impact on pathophysiology of autonomic neuropathy. Prevalence of chronic complications (Retinopathy, ne-

phropathy, diastolic dysfunction) were more common in patients with DAN than without DAN and in Type 2 than in Type 1 with significant p values. Alimentary system was the most commonly involved system with abdominal fullness, GERD and diarrhoea being common followed by Cardiovascular system with orthostatic hypotension as the common finding. Bladder dysfunction was more common in Type 1 diabetes(40%) than in Type 2 diabetes(33%). Clinical evidence of peripheral neuropathy in the form of tingling and numbness were found in 30% of Type 1 and 38.8% of Type 2 diabetes. Sudomotor dysfunction was seen in 30% of Type 1 and 27% of Type 2 DM.

Assessment of Autonomic function tests showed that HR response to Valsalva manoeuvre followed by HR response to deep breathing were the most common abnormal tests. Orthostatic hypotension credited to be the marker of severe disease occurred late in the course and was present in higher percentage(61%) in Type 2 DM than in Type 1(50%). DAN was Subclinical(Asymptomatic) in 4(20%) Type 1 and 8(22.2%) Type 2 DM patients.

Tables

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Current recommendations to diagnose Autonomic neuropathy include

3 tests reflecting parasympathetic function
Heart rate response to Deep breathing
Heart rate response to Standing
Heart rate response to Valsalva maneuver

2 tests reflecting sympathetic function
Blood pressure response to Standing/Passive tilting
Blood pressure response to sustained Handgrip

- HR response of deep breathing
Maximum and minimum HR during each 10 second breathing cycle are observed from RR intervals recorded by ECG and mean differences between them during three successive breathing cycles calculated
- HR response to Valsalva manoeuvre
The Valsalva ratio,i.e., the ratio of longest RR interval after the manoeuvre to shortest RR interval during the manoeuvre is calculated and mean of three successive manoeuvres taken
- HR response to standing up
The 30:15 ratio,i.e., the ratio of longest RR interval(around 30th beat) to shortest RR interval(around 15th beat) calculated. Counting of beats starts as soon as the subject attempts to stand up and not after assumption of standing posture
- BP response to standing up
Difference in BP in supine and 3 minutes after standing noted
- BP response to sustained handgrip
Subjects were asked to squeeze a handgrip dynamometer to maintain steady pressure at 30% of maximum for as long as possible(usually 3-4 minutes). Difference in diastolic BP before starting and just before releasing handgrip was taken as a measure of response.

Patients found to have two or more tests abnormal were considered to have DAN

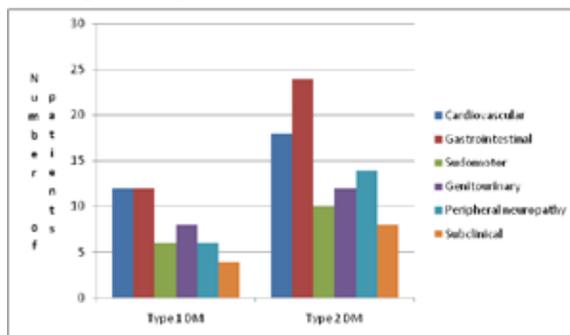
Assessment of Autonomic dysfunction

Procedure	Normal	Borderline	Abnormal
Tests assessing HR response to			
Deep breathing	≥15	11-14	≤10
Valsalva manoeuvre (Valsalva ratio)	≥1.21	1.11-1.20	≤1.10
Standing up(30:15)	≥1.04	1.01-1.03	≤1.00
Tests assessing BP response to			
Standing(Postural fall in mmHg)	≤20/10		≥20/10

Handgrip(ΔDBP in mmHg)	≥16	11-15	≤10
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3Figure

Clinical profile of patients with DAN



Discussion

Autonomic manifestations of diabetes is associated with occurrence of broad constellation of symptoms that affect cardiac, gastrointestinal, genitourinary, sudomotor and metabolic functions. Clinical symptoms of autonomic neuropathy generally do not occur until long after onset of diabetes. Subclinical ANS dysfunction, however, occur within a year of diagnosis of Type 2 DM and within two years in Type 1 DM. Even early effects of DAN are widespread as it manifests first in longer nerves and vagus nerve(the longest of the ANS nerves) accounts for ~75% of all parasympathetic activity⁽¹³⁾. Cardiac Autonomic Neuropathy(CAN) is the most prominent focus because of the life threatening consequences of this complication and availability of direct tests of cardiovascular autonomic function. However, neuropathies involving other organ systems should also be considered in the optimal care of patients with diabetes. Studies like UKPDS(United Kingdom Prospective Diabetes Study), DCCT(Diabetes Control and Complications Trial) and Kumamoto study have demonstrated that the risk of chronic complications increased as a function of duration and degree of hyperglycemia and glycemic control reduced development of microvascular complications, improved lipid profile but neither decreased nor increased CVS mortality rate. However strict blood pressure control significantly reduced both macro and microvascular complications.

In the present study duration of diabetes was significantly longer in patients with DAN than without DAN in both Type 1 and 2 diabetes. Duration of illness was more than 10 years in majority. However some manifestations of autonomic neuropathy may even precede diagnosis of diabetes mellitus by several years⁽¹⁴⁾. Study of clinical profile of patients with DAN suggests impairment of parasympathetic system followed by sympathetic system formed the pathophysiological basis. Subclinical(Asymptomatic) DAN was diagnosed in 20% of Type 1 and 22% of Type 2 DM suggesting early intervention to decrease morbidity/mortality was possible.

Conclusion

Incidence of DAN is directly proportional to duration and glycaemic index irrespective of age, sex or type of diabetes. With availability of reliable tests to detect ANS dysfunction, early identification and more intensive and appropriate treatment is possible and will help reduce morbidity and mortality improving quality of life.

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