Accuracy of autonomic symptoms in detection of severe cardiac autonomic neuropathy

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Abstract

Autonomic neuropathy is a troublesome complication of diabetes mellitus often is not addressed by the physicians. The aim was to see the accuracy of autonomic symptoms in the detection of severe cardiac autonomic neuropathy (CAN). This study was done in BIRDEM in 62 adult patients with type 2 diabetes mellitus and cardiac autonomic neuropathy. Cardiac autonomic neuropathy was detected clinically by heart rate and blood pressure change to maneuvers such as deep breathing, valsalva and standing. Eight symptoms of autonomic neuropathy, namely exercise intolerance, dizziness, dysphagia, abdominal bloating, constipation, diarrhea, gustatory sweating and impotence were tested. In this study, impotence was the most common symptom (58%). There was no difference in the frequency of autonomic symptoms between severe and non-severe cardiac autonomic neuropathy. Taking clinical tests as gold standard, gustatory sweating had the highest specificity (96%) and constipation had the highest sensitivity (54.05%) in detection of severe cardiac autonomic neuropathy. Sensitivity increased to 78.37 when a constellation of symptoms were tested. Autonomic symptoms are common in patients with type 2 diabetes and cardiac autonomic neuropathy. Collection of symptoms was associated with a high sensitivity for detection of severe cardiac autonomic neuropathy.

Introduction

Diabetic autonomic neuropathy (DAN) is an important and often overlooked complication in patients with diabetes where different parts of the autonomic nervous system (ANS) are involved.[1] DAN involves adrenergic, cholinergic, dopaminergic autonomic fibers and peptidergic neurons.[2] Among the organ-specific manifestations of DAN, CAN usually develops early in individuals with diabetes mellitus.[3] However, the clinical signs are non-specific with complex diagnostic criteria.[4]

Traditionally, CAN occurs when autonomic nerve fibers innervating the cardiovascular system are affected due to chronic hyperglycaemia. This results in irregularities of heart rate and altered blood vessel tone.[5] It is known that diabetic complications occur after several years of disease and earlier if diabetes is uncontrolled. However, evidence from epidemiological studies revealed that the heart may be under impaired autonomic control even at the time of diagnosis of the disease.[6] Loss of parasympathetic influence and heightened sympathetic activity has detrimental effects on the heart, some of which may be arrhythmia, silent ischemia and sudden cardiac death.[7] CAN

is diagnosed after exclusion of other causes of autonomic neuropathy in patients with diabetes and results due to impaired autonomic function of the cardiovascular system.[8] The prevalence of confirmed CAN ranged from 16.6% to 65%[9, 10, 11], depending on the study population and duration of diabetes.[12, 13] Despite its prevalence and clinical impact, CAN is still widely under diagnosed in our country. Complex interactions between glycemic control, duration of disease, blood pressure, and aging-related neuronal death are responsible for CAN in diabetes.[2] Orthostatic hypotension, resting tachycardia, exercise intolerance, silent myocardial infarction and intraoperative cardiovascular complications are common symptoms in CAN.[14] Similarly, guidelines from the American Diabetes Association (ADA) recommend that diabetic patients may present with lightheadedness, weakness, palpitations and syncope on standing as symptoms of CAN if other relevant causes are excluded.[15] There are three categories of CAN based on diagnostic testing: (1) early involvement with one abnormal or two borderline heart rate test results; (2) definite involvement with two or more abnormal results; and (3) severe involvement when orthostatic hypotension is present.[5,14,16] CAN is also

divided into two stages: subclinical and clinical. The subclinical CAN is based on variations in heart rate, baroreflex sensitivity and cardiac imaging showing increased torsion of the left ventricle without any significant changes on standard cardiac autonomic reflex tests.[10, 17] The clinical stage is diagnosed when sympathetic activity is predominant and symptoms such as decreased exercise tolerance and resting state tachycardia are evident. With progression of CAN, orthostatic hypotension becomes apparent.[16, 18]

There is no single confirmatory diagnostic test for CAN. Clinically CAN is assessed from symptoms and signs. Among the symptomatic manifestations of CAN, orthostatic hypotension was found in 6%-32% of patients with diabetes mellitus based on previous studies.[11, 18, 19] As the symptoms of orthostatic hypotension are also common in hypoglycemia; screening among patients with unawareness of hypoglycemia should be considered.[11,20] Clinical manifestations of CAN usually appear in late stage and are not sensitive and specific enough for CAN diagnosis. Therefore objective autonomic tests are required to establish the diagnosis and determine the severity of autonomic dysfunction.[21] Tests for both sympathetic and vagal function should be included for assessing CAN. Cardiac autonomic reflex tests (CARTs), discovered by Ewing et al. in the 1970s are based on heart rate, blood pressure, and sudomotor responses. These tests were designed to detect autonomic dysfunction by measuring changes in heart rate variability and blood pressure to different maneuvres known to stimulate autonomic activity. Sympathetic function is tested by blood pressure response to standing and sustained hand grip and heart rate response to the valsalva maneuver. Parasympathetic function is determined by heart rate response to deep breathing, posture and valsalva.[12, 16, 19] Currently a quantitative assessment tool for diagnosing autonomic symptoms in diabetic neuropathy, Composite Autonomic Symptom Score 13 (COMPASS13) has been proposed, with a fair diagnostic value also for CAN.[21] Still, there is no consistent criteria and easy clinical bedside test for measurement of autonomic neuropathy.[10]

Detecting CAN in routine follow up is important. Despite its high incidence and impact on health, quality of life and mortality, CAN is under diagnosed due to lack of simple diagnostic tests and accurate screening criteria.[2,10] Clinical tests are accurate, but cumbersome. An easy and fast screening system is required to assess AN, especially CAN. The accuracy of autonomic symptoms for the detection of severe CAN is still to be determined. Therefore our study aims is to determine the accuracy of autonomic symptoms to diagnose severe CAN.

Methods

This cross-sectional study was done in Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) Hospital from September 2011 to August 2012 in adults with type 2 diabetes mellitus and cardiac autonomic neuropathy. Patients with disorders other than diabetes that cause autonomic neuropathy (Parkinson's disease), neurological, gastrointestinal, genitourinary diseases and on medications that cause autonomic symptoms (vasodilators and anti-depressants) were excluded from the study. The study was approved by the IRB, BIRDEM.

Symptoms of autonomic neuropathy were recorded in type 2 diabetes mellitus patients with CAN. CAN was diagnosed clinically with 3 tests - heart rate response to valsalva maneuver and deep breathing and blood pressure response to standing. When any one of two heart rate tests were abnormal or both heart rate tests were borderline/abnormal. Severe CAN was defined as definitive CAN (both heart rate tests abnormal) with postural drop.[22, 11] Clinical tests of CAN are described in Table-I. The outcome variables were symptoms of autonomic neuropathy - exercise intolerance, dizziness, dysphagia, abdominal bloating, constipation, diarrhea, gustatory sweating and impotence (only in males).

Data were analyzed by SPSS version 11.5. Chi square test was used to compare autonomic symptoms between severe and non-severe CAN. Sensitivity and specificity of autonomic symptoms for severe CAN were calculated from 2X2 contingency tables. p values less than 0.05 was taken as significant.

Table-I				
Changes of visual acuity of all 3(three) patient after injection methyl prednisolone				
Test	Measure	Abnormal	Borderline	Normal
Heart rate response to valsalva maneuver – ECG was done during and for 15 sec immediately after the maneuver .	Valsalva ratio = longest R-R interval after / shortest R-R interval during the maneuver	≤ 1.10	1.11-1.20	≥ 1.21
Heart rate response to deep breathing – Patients breathed deeply in supine position at a frequency of 6 cycles/min. Inspiration and expiration intervals were 6 s and 4 s respectively. ECG was recorded.	Difference between heart rate during rest and after deep breathing	< 10 beats/min	-	> 15 beats/min
Blood pressure response to standing - Blood pressure was recorded in supine position and 2min after standing. Each measure was repeated 3 times.	SBP fall from lying to standing	> 30 mmHg	10-29 mmHg	<10 mmHg

CG=electrocardiogram, SBP= systolic blood pressure,[23, 24, 25]

Results

The study population consisted of 62 adult individuals (mean age 55.58 years, 50% males) with cardiac autonomic neuropathy. Majority had uncontrolled diabetes and diabetic complications, especially peripheral neuropathy. Table-II shows the baseline characteristics of the study population.

Table-II		
Baseline characteristics of the study population (N=62)		
Characteristic	Mean ± SD	Frequency (%)
Age (years)	55.58 ± 10.73	
Sex		31 (50)
BMI (kg/m2)	25.14 ± 4.71	
Duration of diabetes (years)	14.15 ± 7.99	
HbA1c (%)	11.02 ± 2.86	
Uncontrolled diabetes		57 (91.92)
Retinopathy		32 (51.62)
Diabetic kidney disease		41 (66.13)
Peripheral neuropathy		62 (100)

Eight symptoms of autonomic neuropathy namely exercise intolerance, dizziness, dysphagia, abdominal bloating, constipation, diarrhea, gustatory sweating and impotence were determined in the study population. Impotence, exercise intolerance, constipation and dizziness were the most frequent. Values of frequency are shown in Table -III.

Table-III		
Frequency of autonomic symptoms in the study population (N=62)		
Autonomic symptoms	Frequency	Percentage
Exercise intolerance	34	54.8
Dizziness	24	40.3
Dysphagia	5	8.1
Abdominal bloating	12	19.4
Constipation	33	53.2
Diarrhea	9	14.5
Gustatory sweating	3	4.8
Impotence	18	58

**Denominator was number of males (31)

Apart from diarrhea, which was more common in cases of severe CAN, frequencies of other autonomic symptoms were similar. There was no association between autonomic symptoms and severity of CAN (Table IV).

Table-IV			
Frequency of autonomic symptoms in severe and non-severe CAN (N=62)			
Autonomic symptom	Non-severe CAN (n=25)	Severe CAN (n=37)	P value
Exercise intolerance	16 (64)	18 (48.6)	0.23
Dizziness	10 (40)	14 (37.8)	0.86
Dysphagia	2 (8)	3 (8.1)	0.99
Abdominal bloating	6 (24)	6 (16.2)	0.45
Constipation	13 (52)	20 (54.1)	0.87
Diarrhea	2 (8)	7 (18.9)	0.23
Gustatory sweating	1 (4)	2 (5.4)	0.80
Impotence	8 (32)	10 (27)	0.67

Within parentheses are percentages over column total. Chi square test was done.

Eight symptoms of autonomic neuropathy, namely exercise intolerance, dizziness, dysphagia, abdominal bloating, constipation, diarrhea, gustatory sweating and impotence were tested to determine the cases of severe cardiac autonomic neuropathy (Table-IV). Gustatory sweating had the highest specificity (96%), closely followed by dysphagia and diarrhea. Constipation, exercise intolerance and dizziness had the highest sensitivity, ranging from 37.8 to 54%. Constipation had the highest sensitivity of 54.05% and specificity of 48%. Constipation also had the highest positive and negative predictive value. When combinations of autonomic symptoms were explored, the sensitivity for detection of severe CAN increased.

Table-IV				
Accuracy of autonomic symptoms for detection of severe CAN considering clinical tests as gold standard in the study population (N=62)				
Symptom	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Exercise intolerance	48.64	36	52.94	32.14
Dizzziness	37.83	56	56	37.84
Dysphagia	8.11	92	60	40.35
Bloating	16.22	76	50	38
Diarrhoea	27.03	92	60.61	41.38
Constipation	54.05	48	77.78	43.40
Gustatory sweating	5.41	96	66.67	40.68
Impotence	18.92	68	55.56	38.64
Complex 1	75.67	32	62.22	47.06
Complex 2	78.37	16	58	33.33

Complex 1 = exercise intolerance+dizziness+diarrhoea+sweating, complex 2 = exercise intolerance+constipation+diarrhoea+sweating, PPV=positive predictive value, NPV = negative predictive value

Discussion

Eight symptoms of autonomic neuropathy, namely exercise intolerance, dizziness, dysphagia, abdominal bloating, constipation, diarrhea, gustatory sweating and impotence were tested to determine the accuracy of severe CAN. Impotence was the most common symptom, closely followed by exercise intolerance, constipation and dizziness. There was no difference in the frequency of autonomic symptoms between severe and non-severe CAN. In detection of severe CAN, gustatory sweating had the highest specificity. Constipation had the highest sensitivity, PPV and NPV and a modest specificity. Sensitivity was low for an individual symptom, but increased when a constellation of symptoms were used.

The frequency of autonomic symptoms in this study ranged from 4.8 to 58%. The most common symptoms were cardiovagal, impotence and constipation. Based on clinical tests of autonomic function, prevalence of autonomic neuropathy ranged from 7.7 to 90%.[26] Studies reported the prevalence of autonomic neuropathy to be 54% and 73% in type 1 and 2 diabetes respectively. This prevalence was based on the Composite Autonomic Severity Score (CASS). Gastrointestinal, urinary and cardiac symptoms predominated.[27] Composite Autonomic Symptom Score (COMPASS) 31 score was 29.9 and 16.1 in patients with and without CAN respectively.[21] The prevalence of autonomic neuropathy depends on the criteria used to evaluate it, with clinical tests and laboratory investigations detecting a higher number of cases due to increased specificity. This study looked at only symptoms of autonomic neuropathy which are commonly encountered in clinical practice (either enquired by the physician or reported by the patient). It did not involve any scoring or assessment of severity. The high rate of symptoms, especially cardiovagal and impotence may be due to the fact that these patients all had uncontrolled, long standing diabetes. Moreover, all patients had CAN.

Sensitivity of individual symptoms was low in detection of severe CAN (below 55%). Among the symptoms, constipation was most sensitive in detection of severe CAN. However, when a number of symptoms were asked, the sensitivity increased to around 75%. It is interesting that instead of cardiovagal symptoms, gustatory sweating had the highest specificity (96%) in detection of severe CAN. This may be due to the fact that symptoms of autonomic neuropathy, especially exercise intolerance, dizziness and bloating are vague and nonspecific. Although other systemic diseases were ruled out clinically, these symptoms also occur in other common illnesses. It is understandable that the sensitivity was higher for several symptoms together. Questionnaires which include a number of symptoms designed to assess autonomic neuropathy such as the COMPASS 31 was significantly related to cardiovascular reflex tests score (r=0.38, P=0.0013).

The accuracy was good with an area under the curve of 0.748±0.068, 95% CI 0.599–0.861. At a cut-off of 17 for definitive CAN, the sensitivity, specificity, PPV and NPV was 70%, 66.7%, 25% and 93% respectively.[21] Another study showed a significant correlation between COMPASS and CASS scores for vasomotor (r=o.58, p<0.001), secretomotor (0.64, p<0.001) and pupillomotor (0.51, p<0.001) symptoms.[28] On the other hand, other studies showed that there was a weak correlation between symptom scores (using the Autonomic Symptom Profile) and deficits (using CASS) in diabetic autonomic neuropathy.[27] Since the symptoms have low sensitivity to identify CAN it has been suggested to use clinical tests to detect cases of CAN. The earliest clinical indicator of CAN is a decrease in heart rate variability.[29] Heart rate variability with deep breathing is the most widely used test of cardiovagal function and has a specificity of about 80%.[30] Clinical tests detect CAN at an early stage before the appearance of symptoms.[31] Although clinical tests are the gold standard to detect CAN, a combination of autonomic symptoms has an acceptable sensitivity and may be used to identify cases of severe CAN. Using symptoms to evaluate CAN in easy, convenient and plausible particularly in every day clinical practice.

A single autonomic symptom was not a good tool to detect severe CAN. However, a combination of autonomic symptoms had a high sensitivity to detect severe CAN with few false negative cases.

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