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## The significance of autonomic symptoms in Nigerian diabetics

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### Summary

Diabetes mellitus is the most common endocrine disorder worldwide and disturbance of autonomic function is a frequent complication. Symptoms of autonomic neuropathy are however non-specific and the aetiology is multifactorial in diabetics. This study was carried out to determine the relationship between symptoms of autonomic neuropathy and pathology of the autonomic nervous system in diabetic patients. A hundred diabetics were studied, 50 with, and 50 without symptoms of autonomic neuropathy. Objective tests of autonomic function used were the heart rate responses to deep breathing, to standing and to the Valsalva manoeuvre; and the blood pressure responses to standing and to sustained handgrip. There was no significant difference between diabetics with symptoms suggestive of autonomic neuropathy, and those without, with regard to findings on autonomic function testing. While the symptoms were unreliable in determining the presence of autonomic neuropathy, they were significantly related to poor glycaemic control and to peripheral neuropathy ( $P < 0.01$ ). The symptoms of autonomic neuropathy are non-specific in Nigerian diabetics and may reflect poor glycaemic control rather than autonomic neuropathy. Autonomic function tests should be carried out in diabetics suspected of having autonomic neuropathy.

**Keywords:** *Diabetes, autonomic neuropathy, symptoms, glycaemic control*

### Résumé

Le Diabète Mellitus est le désordre endocrinien le plus commun dans le monde et les troubles de fonction autonome sont les complications fréquentes. Les symptômes de la neuropathie autonome sont cependant non-spécifiques et l'aétiologie est multifactorielle chez les diabétiques. Cette étude a été faite dans le but de déterminer la relation entre les symptômes de la neuropathie autonome et la pathologie du système nerveux autonome chez les diabétiques. 100 malades diabétiques ont été consultés, 50 avec et 50 sans symptômes de neuropathie. Les tests objectifs des fonctions autonomes utilisés étaient le toux éde réponse du Cœur à la respiration élevée. La statue debout et la manoeuvre Valsalva; et la réponse de la pression du sang à la position debout et le maintien de la maingrippes. Il n'y avait pas de différence significative entre les diabétiques aux symptômes suggestifs de la neuropathie et les autres, en relation avec les conclusions sur les tests des "fonctions autonomiques". Alors que les symptômes n'étaient pas fiables dans la détermination de la présence de la neuropathie, ils étaient significativement liés à un mauvais contrôle glycémique et la neuropathie périphérique ( $P < 0.01$ ). Les symptômes de la "neuropathie autonome" sont non-spécifiques chez les diabétiques nigérian et peuvent refléter le mauvais contrôle glycémique plutôt que la neuropathie autonome. Les tests de fonction "autonomique" doivent être faits chez les diabétiques suspects d'avoir la "neuropathie autonome".

### Introduction

Diabetes mellitus is common in Nigeria with an estimated prevalence of about 2.8% [1]. The ratio of type 2 to type 1 diabetes mellitus in Nigeria is about 11.1 [2]. Disturbance of autonomic function is a frequent long-term complication of diabetes mellitus and its important symptoms are impotence, constipation, sweating abnormalities, postural dizziness, bladder dysfunction and dysphagia. These symptoms are however often non-specific [3] and can be produced by infections, drugs, vascular and cardiac disturbances. Studies have not established the value of these symptoms as markers of autonomic neuropathy, close association and absence of association both being reported [2,4]. Impotence is however said to have the weakest association with abnormal autonomic function while postural dizziness has the strongest [5,6]. The presence of symptoms has however been established to be of prognostic significance [4,7-9].

The aims and objectives of this study were to assess the relationship of symptoms of autonomic neuropathy to objective tests of autonomic function in Nigerian diabetics.

### Materials and methods

Fifty diabetics symptomatic of autonomic neuropathy were studied along with 50 diabetics without symptoms. Symptomatic autonomic neuropathy was defined as the presence of one or more of non-bloody non-mucoid intermittent diarrhoea of more than three months duration, hard stool of less than twice a week, persistent non-physiological sweating abnormalities, impotence without nocturnal penile tumescence, postural dizziness; urinary disturbances, gastric fullness and dysphagia in the absence of any other identifiable causes. The following were excluded: patients with chronic renal failure with serum creatinine value above 177mmol/L, chronic liver disease, myelopathies, moderate or severe hypertension, cardiac failure, myocardial infarction, leprosy, porphyria, connective tissue diseases and patients on drugs that affect the autonomic nervous system.

The method of Ewing and Clarke was adopted for autonomic function testing [10]. Blood pressure readings were done by two observers and differences reconciled by a third. Supine blood pressures were taken thrice after 10 minutes rest with the cuff of a mercury sphygmomanometer applied to the right upper arm. Phases I and V Korotkoff sounds were used for systolic and diastolic blood pressure readings, respectively. Electrocardiography was done using a Mac PC computerised machine (Marquette Electronics, Jupiter, Florida, U.S.A.) to assess resting heart rate and heart rate responses using a three-lead rhythm strip. Subjects were asked to blow into a sterile mouthpiece attached to an aneroid sphygmomanometer and maintain a pressure of 40 mmHg for 15 seconds while the ECG was being recorded. The ratio of the shortest R-R interval during the procedure, to the widest R-R interval up to 20 beats immediately after the procedure, was calculated as the Valsalva ratio. The heart rate was recorded while the patient was breathing deeply at 6 breaths per minute, the mean value during expiration was subtracted from that during inspiration (the maximum-

minimum response). Blood pressures were recorded at 1-minute intervals for 5 minutes while subjects were sustaining handgrip on a handgrip dynamometer at 30% of maximum voluntary contraction, using the dominant hand. The average diastolic blood pressure was calculated, from which the resting diastolic pressure was subtracted. The ECG was recorded while subjects were standing up from a supine to the upright posture. The shortest R-R interval at the 15<sup>th</sup> beat after standing, and the widest R-R interval at the 30<sup>th</sup> beat were measured, and the 30:15 ratio was calculated. The blood pressure after 1 minute of standing up was subsequently taken. The erect systolic blood pressure was subtracted from the resting systolic blood pressure. Each normal test was scored 0, a borderline test was scored ½ and an abnormal test was scored 1. A total score of 3 and above was considered evidence of autonomic neuropathy.

Subjects were examined for the presence of other long-term diabetic complications. Peripheral somatic neuropathy was defined as 2 or more abnormalities in motor and/or sensory system clinical examination while retinopathy was defined as the presence of hard exudates, haemorrhages or retinal detachment. Leg ulcers were considered significant if they had not healed after a month of adequate treatment. Glycaemic control was assessed by the mean of three previous fasting and 2-hour post-prandial blood glucose assessments done on a monthly basis. Poor glycaemic control was defined as a mean fasting blood glucose of 6.7mmol/L or more, or a mean 2-hour post-prandial glucose of 10mmol/L or more.

The data obtained was analysed using the Epi info 6.2 computer software. The mean was used as summarising index while the standard deviation was used as index of variation. The Student's t-test was used to assess for significant differences between means of continuous variables, and the Kruskal-Wallis non-parametric test was used when the variances in the groups differed. The chi-squared test was used to test for degree of association between discrete variables. Odds ratio was used to give an estimate of risk. A p value of 0.05 or less was taken as statistically significant.

This study was approved by the joint UI (University of Ibadan/UCH University College Hospital, Ibadan) ethical committee.

## Results

Twenty-three (46%) of the subjects with symptoms of autonomic neuropathy fulfilled the criteria for autonomic neuropathy. There were no significant differences between the two groups with regard to performance on the different autonomic function tests (see Table 1). None of the reported symptoms of autonomic neuropathy was found to be associated with abnormal autonomic function tests (see Table 2).

Thirty-three (66%) of the 50 symptomatic subjects reported more than one symptom. Of these, nine had autonomic neuropathy while eight did not. There was no association between number of symptoms with the presence of autonomic neuropathy (Table 2).

There was a significant association between the presence of symptoms of autonomic neuropathy with the finding of peripheral somatic neuropathy and poor glycaemic control (Tables 3 and 4). The presence of peripheral neuropathy and poor glycaemic control were predictive of the presence of symptoms of autonomic neuropathy with odds ratios of 3.04 and 3.18, respectively.

Diabetic subjects with symptoms of autonomic neuropathy had a younger age of onset and longer duration of

diabetes than those without symptoms but these differences were not statistically significant (Table 4)

**Table 1:** Comparison of autonomic functions between symptomatic and asymptomatic diabetics

Autonomic function tests	Asymptomatic (n = 50)	Symptomatic (n = 50)	P value
<i>Heart rate (parasympathetic) responses</i>			
To deep breathing (max-min/min)	1.9 (8.6)	1.36 (7.9)	0.74
To standing (30:15 ratio)	1.02 (0.05)	1.01 (0.51)	0.66
To valsalva manoeuvre (valsalva ratio)	1.07 (0.16)	1.10 (0.21)	0.96
<i>Blood pressure (sympathetic) responses</i>			
To standing: fall in systolic BP (mmHg)	6.34 (11.8)	7.52 (13.3)	0.64
To handgrip: rise in diastolic BP (mmHg)	21.4 (11.6)	22.1 (10.8)	0.75

Standard deviation in parentheses

**Table 2:** Relationship between symptoms and abnormal autonomic function tests

Symptom	No. of subjects with AN (n = 46)	No. of subjects without AN (n = 54)	Chi square	P value
Impotence	11	12	0.04	0.84
Postural dizziness	7	8	0.35	0.82
Constipation	8	5	0.82	0.36
Sweating abnormalities	6	7	0.08	0.77
Diarrhoea	2	2	0.12	0.62*
Dysphagia	3	0	1.74	0.09
>1 symptom	9	8	0.13	0.71

\*Fisher exact p value

AN: Autonomic neuropathy

**Table 3:** Characteristics of symptomatic and asymptomatic diabetics (discrete variables).

Characteristics	Asymptomatic diabetics (n = 50)	Symptomatic diabetics (n = 50)	Chi square	P value
Peripheral neuropathy	9	20	4.86	0.027
Poor glycaemic control	27	39	5.61	0.035
Retinopathy	3	7	1.78	0.18
Leg ulcers	1	3	0.26	0.61*
Pupil abnormalities	4	2	0.12	1*
Dry legs	2	2	0.26	0.6*
Pedal oedema	1	1	0.51	0.4*
Joint deformities	1	6	2.46	0.11*

\*Fisher exact test

**Table 4:** Characteristics of symptomatic and asymptomatic diabetics: (continuous variables).

Characteristics	Asymptomatic diabetics (n = 50)	Symptomatic diabetics (n = 50)	P value
Onset age of DM (yrs)	46 (15.3)	42.2 (14.5)	0.2
Duration of DM (mths)	68.9 (106)	100.5 (121)	0.08
Systolic BP (mmHg)	143 (27.3)	141 (24.8)	0.74
Diastolic BP (mmHg)	84.1 (13.3)	85 (14.3)	0.75
FBS (mg/dL)	148 (78)	182 (105)	0.14
2HPP (mg/dL)	220 (118)	281 (114)	0.01*

\*Significant

Standard deviation in parentheses

DM: Diabetes Mellitus

BP: Blood pressure

FBG: Fasting blood Glucose

2HPP: 2-hour post-prandial blood sugar

## Discussion

One of the significant findings of this study is that autonomic function in those with and those without symptoms of autonomic neuropathy, did not differ. This confirms that the symptoms of autonomic neuropathy are generally non-specific [3]. The presence of more than one symptom did not increase the sensitivity of symptoms for autonomic neuropathy.

Constipation, and to a lesser extent, sweating abnormalities, were the only symptoms with increased frequency in those with autonomic neuropathy. Their usefulness in predicting autonomic neuropathy is however doubtful because there was no statistical significance in the difference.

Postural dizziness, which has been reported to be the most specific symptom of autonomic neuropathy [5,6], was however, found to be non-specific in this study. It is however not as rare as often reported [11], being present in 15 of the 50 symptomatic patients; only 30% of cases however had autonomic neuropathy, compared to 100% earlier reported [5]. Miscellaneous head sensations, hypoglycaemia, dehydration, cardiovascular dysfunction, presyncope and depression can all give feelings of dizziness and account for the poor specificity of the symptom for autonomic neuropathy. The specificity of postural dizziness in earlier studies is probably due to the inclusion of long-standing diabetics in whom postural hypotension reflects severe autonomic neuropathy.

Impotence was similarly found to be unreliable in this study for predicting autonomic dysfunction. Ten (66%) of the 15 diabetics reporting impotence alone in this study had normal autonomic function, and this conforms to results from other studies [5]. Vasculogenic and psychogenic impotence are frequent occurrences in diabetics and may be responsible for the poor specificity of impotence for autonomic neuropathy.

The doubts expressed as to whether diarrhoea in diabetics is a true symptom of autonomic neuropathy in diabetics [11] are emphasised by this study. Diarrhoea was found not to be specific for autonomic neuropathy. It is also a relatively infrequent symptom being present in only 8% of subjects; other studies have reported a frequency of 49% in diabetics with autonomic neuropathy [7]. Dysphagia was similarly found to be non-specific. This confirms reports that dysphagia in most

cases is reversed with treatment of hyperglycaemia [12]. The mean 2-hour post-prandial glucose levels in the 2 subjects with dysphagia in this study (416 mg/dl) were significantly higher than the mean for the diabetic group (251 mg/dl) and the mean for the symptomatic group (281 mg/dl;  $P = 0.046$ ).

The symptoms of autonomic neuropathy are therefore, unreliable in determining the presence of autonomic neuropathy. The variety of possible causes of these symptoms in the diabetic could be responsible for this. This study has however also shown an association of the symptoms with poor glycaemic control, and with peripheral neuropathy. This would suggest that the symptoms could be a reflection of these two factors on the various organ systems, dysphagia for example has been associated with poor glycaemic control in Nigerian diabetics [12].

The unreliability of the symptoms attributable to autonomic neuropathy emphasises the need to carry out autonomic function tests in all diabetics to prevent the poor prognostic outcome reported in these patients [5,7,9].

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