Diabetic autonomic neuropathy

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ABSTRACT

Objective: The diabetic autonomic neuropathy is a poorly studied subject in our medical literature. This study is aimed at investigating the presence of diabetic autonomic neuropathy in a group of Sudanese diabetic patients and its relationship to factors like glycemic control, duration of diabetes and presence of peripheral neuropathy.

Methods: During one year we examined 120 diabetic patients and an age-matched control group of 42 by applying a battery of 5 cardiovascular autonomic tests, beside a full history and clinical examination. The patients were also tested for glycemic control and presence of peripheral neuropathy.

Results: Diabetic autonomic neuropathy was diagnosed in 48 patients (40%) of a mean age of 48.411 $\pm$ 12.50 years, type 1/2 diabetes was 10/38, mean duration of diabetes 16.2 $\pm$ 7.3 years, 41 with poor glycemic control (81%) and peripheral neuropathy was present in 32 patients (66%). We found a significant association between diabetic autonomic neuropathy and prolonged duration of diabetes ($P<0.001$), poor glycemic control ($0.01>P>0.001$) and presence of peripheral neuropathy ($0.02>P>0.01$).

Conclusion: Diabetic autonomic neuropathy (both asymptomatic and symptomatic) is a common problem among our diabetic patients. It is significantly associated with prolonged duration, poor control of diabetes and presence of peripheral neuropathy. We need to augment the awareness of diabetes care providers to the occurrence, and peculiar features and tests of this syndrome.

Keywords: Diabetic autonomic neuropathy, cardiovascular autonomic tests, diabetes.

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For a long time autonomic disturbances like erecticle dysfunction and sweating disturbances were reported in diabetic patients. It was, however, only in 1945 that these and other symptoms were attributed to damage in the autonomic nervous system when Rundle published the first coherent description of diabetic autonomic neuropathy (DAN).[1] Since then, especially in the 1970s, a tremendous amount of knowledge has accumulated.

The autonomic nervous system controls and integrates the unconscious regulatory functions in the body. However, cardiovascular autonomic tests (CATs) are now based on measuring cardiovascular reflex changes to standardized stimuli have become, to a large extent, reliable tests for assessing the autonomic functions.[2] Apart from DAN diagnosis, the CATs are useful for assessing the course of the disease and the effects of treatment. For example, the earlier defects such as cardiac vagal enervation can be tested in a sensitive and specific method by measuring the variability in heart rate during deep breathing.[3] The CATs are commonly abnormal in patients with longstanding and poorly controlled diabetes with absence of symptoms in the majority of these patients.[4] Peripheral somatic neuropathy, symptomatic or a symptomatic, is commonly associated with DAN.[4]

On the other hand, symptoms of DAN, affecting different body organs, are rarely encountered in patients with abnormal CATs.[3] They are usually intermittent and may persist for many years without worsening but complete remission is unusual.[3] Erectile dysfunction (ED) is the most common symptom but is difficult to assess.[5] Diabetic autonomic neuropathy affects all parts of the gastrointestinal tract producing syndromes such as gastroparesis diabeticorum and diabetic diarrhoea.[6] Bladder dysfunctions (including retention) are very

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rare. Postural hypotension is only occasionally symptomatic or disabling. Examples of other symptoms include sweating disturbances, impaired pupillary responses and unawareness to hypoglycemia.[7] Diabetic autonomic neuropathy is a common complication of diabetes mellitus. As symptoms are uncommon, and rarely life-threatening, DAN has received little attention compared to other diabetic complications especially in Sudan and other developing countries. Diabetic autonomic neuropathy is poorly studied among our patients. This study is aimed at studying the characteristics of autonomic neuropathy in a group of Sudanese diabetic patients and its relation to factors such as diabetic duration and control, and presence of sensory peripheral neuropathy.

Methods. This study was carried out in Shaab Teaching Hospital in Khartoum, Sudan, during the period September 1998 to August 1999. From a referred clinic we selected 120 diabetic patients with no history of heart disease, on no medications likely to influence the interpretation of the autonomic function tests and with normal resting electrocardiogram (ECG). All gave their consent to participate in the study. The diagnosis of DAN was based on having one or more abnormal CATs with or without autonomic symptoms.

Control group. An age and sex-matched 42 healthy subjects were studied as the control group to evaluate the sensitivity of CATs.

Cardiovascular autonomic tests. A standard battery of 5 cardiovascular function tests were performed on the patients and controls. The tests were performed and evaluated according to the procedure described by Ewing et al.[2] The diagnosis of DAN was established by presence of one or more abnormal tests.

Tests for parasympathetic integrity. Valsalva manoeuvre: The valsalva ratio (VR) was calculated from the ratio of the largest RR interval after the manoeuvre to the shortest RR interval during the manoeuvre. The mean of 3 VRs was taken as the final value (abnormal: 1.20 or less); Immediate heart response to standing: It is measured with an ECG recording of RR intervals at the 15th and 30th beats after standing to give a 30/15 ratio (abnormal: 1.00 or less); Heart rate variation during deep breathing (sinus arrhythmia): The maximum and minimum RR intervals during each breathing cycle were measured and converted to beats per minute. A single deep breath test was carried out and results were compared to age related normal persons (abnormal: 10 beats/ minute or less).

Test for sympathetic integrity. Blood pressure response to a sustained handgrip: Blood pressure readings were recorded three times at rest, at one minute interval during handgrip and twice immediately after release of handgrip. The change of blood pressure was taken as the difference between the mean of three testing readings and the last reading before releasing the handgrip (abnormal: 10 mm Hg or less). Blood pressure response to standing: A fall in systolic blood pressure (difference between lying and standing systolic blood pressure) of 20 mmHg or more on standing up was considered abnormal.

Autonomic symptoms. A clinical history was taken with emphasis on autonomic symptoms. All patients had a full clinical examination. Below are definitions of diabetic autonomic symptoms encountered in our study. Erectile dysfunction (ED): Persistent inability to attain or maintain an erection sufficient to permit satisfactory sexual activity, with absence of morning erections and other causes of ED.[5] Diabetic diarrhoea (DD): Watery, painless and intermittent diarrhoea with no associated evidence of malabsorption.[8] Gastroparesis diabeticorum (GD): This is a collective term for symptoms such as nausea, vomiting, persistent feeling of epigastric fullness with exclusion of the common causes of such symptoms.[6] Sweating disturbances (SD): These include gustatory sweating, and severe nocturnal sweating unrelated to hypoglycemia. Postural hypotension (PH): Postural feeling of dizziness on standing from a sitting position. The autonomic symptoms were encountered in 10 patients (of the 120) and included ED (5), PH (3), GD (2) and SD (1); one patient reported two symptoms.

Peripheral neuropathy. The sensory peripheral neuropathy was assessed according to the WHO criteria and recommendations on standardization of methods and reporting of complications of diabetes.[9] It was defined as having as a minimum an absent ankle jerk. Nerve conduction studies were done.[10] Among the 120 patients peripheral neuropathy was found in 48 patients (40%).

Glycemic control. The estimation of glycosylated hemoglobin is not available in Sudan at the present time. The glycemic control was considered satisfactory at fasting blood glucose (FBG) of less than 8mmol/L, and poor when it was above this figure. Of the 120 patients 65 (54.1%) were poorly controlled.

Statistical analysis. Data were expressed as means $\pm$ SD unless otherwise specified. Comparison of group means was calculated with two tailed t-test. Chi-square test with or without Yates correlation was used for comparison of categorical data. P-value of less an 0.05 was considered statistically significant.

Results. Of the 120 study diabetic patients, 48 patients (40%) fulfilled the diagnostic criteria of DAN (at least one abnormal CAT with or without symptoms); this was called the DAN group. The rest of the patients (72) were called the non-DAN group.

Table 1 - Results of cardiovascular autonomic function tests in both diabetic autonomic neuropathy group (DAN) (48) and controls (42) patients.

Tests	DAN group (48)	Controls (42)	Significance
Valsalva ratio	X = 1.148 ± 0.107	X = 1.32 ± 0.097	t = 6.166, P < 0.001
Immediate heart rate response to standing (15:30 ratio)	X = 0.932 ± 0.180	X = 1.15 ± 0.284	t = 4.078, P < 0.001
Heart rate variation during deep breathing (beats/minute)	X = 6.375 ± 3.547	X = 11.30 ± 3.84	t = 5.403, P < 0.001
Sustained handgrip (mmHg)	X = 11.5 ± 3.0900	X = 17.65 ± 1.191	t = 9.245, P < 0.001
Postural hypotension (mmHg)	X = 32.36 ± 19.180	X = 2.870 ± 3.307	t = 7.428, P < 0.001

The qualitative expression of the CATs in the DAN group and the control group and their statistical significance are shown in Table 1. The characteristics of both DAN and non-DAN group (mean age, sex ratio, type and mean duration of diabetes, mean FBG and distribution of peripheral neuropathy among the two group) are shown in Table 2. All the patients with DAN symptoms showed three or more abnormal CATs and all of them were of diabetic duration of more than 12 years.

Discussion. Although it is difficult to draw a significant conclusion about the prevalence of DAN in this study, but a 40% 'incidence' in our sample indicates a high occurrence of this syndrome in our diabetic population. As the majority of the DAN cases are asymptomatic, we should encourage the workers in diabetes care to test the autonomic functions as they find a chance especially before surgery or even in an annual routine check up. There is evidence that early intervention by meticulous glycemic control may influence the course of the early phases of DAN.

Autonomic dysfunction can conveniently be detected by testing the cardiovascular responses to various stimuli.[7] Most of our patients with one or two abnormal CATs had only parasympathetic involvement. It seems that the progression of DAN in our patients is similar to other works (from normal function, then parasympathetic damage and eventually sympathetic involvement).[11] Some authors may argue that the parasympathetic damage is more common. However, we should remember that the majority of the conventional tests (CATs) assess the parasympathetic rather than the sympathetic involvement which can be reported in higher incidences by modern tests.[12] On the other hand, most of the symptomatic patients had more than three abnormal CATs and prolonged duration of diabetes (more than 12 years) indicating that presence of autonomic symptoms indicate necessarily a severe form of DAN. This is in accordance with the findings of Smith.[13] We think that the rigid division of DAN into sympathetic and parasympathetic is not appropriate as both nerves are involved to differing degrees in most patients. Being rarely life threatening (as many doctors believe), the symptoms of DAN received little attention by researchers compared to other diabetic complications. We think that the autonomic symptoms follow a rather

Table 2 - A profile of diabetic patients with and without diabetic autonomic neuropathy (DAN).

Variables	Diabetic patients		Significance
	DAN	Without DAN	
Number	48	72	
Mean age (SD) years	48.411 ± 12.50	50.240 ± 14.03	t = 0.2873, P > 0.5
Sex ratio (male/female)	34/14	46/26	x^2 = 0.251 (NS)
Type 1/2 diabetes	10/38	14/58	x^2 = 0.010 (NS)
Mean duration of diabetes (SD) years	16.2 ± 7.3	8.895 ± 6.22	t = 4.751, P < 0.001
Fasting blood glucose Mean + (SD) (mmol/L)	13.32 ± 1.90	9.60 ± 1.88	t = 9.059, P < 0.001
Peripheral neuropathy Present Absent	- 32 16	- 16 56	x^2 = 6.107 with Yates correlation 0.02 > P > 0.01

prolonged asymptomatic phase of progressive impairment of the autonomic system (three quarters of our patients were asymptomatic). On the other hand, Ewing and co-workers refuted that the DAN symptoms are not life-threatening. He reported in a 5 year prospective study of 73 diabetic patients that DAN symptoms combined with abnormal CATs suggest a poor prognosis.[14]

Erectile dysfunction is common among diabetic patients and often the only symptom of DAN.[4] In our society it seems that ED is far more common than the reported figures; this is due to embarrassment of patients and reluctance of doctors to discuss sexual matters with them. Diabetic diarrhoea although troublesome, is not associated with evidence of malabsorption and can be self-limiting.[8] Before considering DD as a diagnosis, we should exclude the more common parasitic causes of diarrhoea like giardiasis. Gastroparesis diabeticorum when symptomatic, is distressing, difficult to treat and may even impairs the glycemic control when the delayed gastric emptying causes alterations of meal absorption.[15] A problem appears when GD is treated mistakenly as giardiasis or peptic ulcer.[6] Postural hypotension as in other studies is a disabling symptom and sometimes there is a need to differentiate it from hypoglycemic dizziness.

In Sudan poor glycemic control is a common feature among our diabetic patients. This is due to poor diabetic care, shortage of anti-diabetic drugs, diet and treatment non-compliance.[6] The diabetes mellitus among our sample is typically longstanding, and poorly controlled. Thus from our view, there is an association between these two factors and the development of DAN. In contrast some workers reported early DAN in childhood.[16] Another argument is that the reluctance of doctors in testing the autonomic functions in asymptomatic patients may lead to delay of diagnosis in a proportion of them. A third factor significantly associated with DAN in our patients was peripheral neuropathy (peripheral neuropathy were detected in two thirds of our DAN patients), this is in accordance with the other works.[17] The high prevalence of DAN among patients with sensory peripheral neuropathy has lead some authors to recommend screening such patients with bedside tests to pick early signs of DAN and then might benefit from improving their glycemic control.[18]

We hope that this study can augment the awareness of diabetes care providers to the occurrence of DAN among their patients, and provide a clear idea of the symptoms and tests of this syndrome. Evidence of DAN can be found by using simple means, even in asymptomatic, or recently diagnosed patients. We need to encourage an annual screening for autonomic functions in our diabetic people; intervention by meticulous glycemic control at early asymptomatic neuropathy may alter its course. Further studies of the pathological basis of DAN are also highly needed.

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