Autonomic neuropathy in African diabetic patients

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Summary: To determine the prevalence and extent of autonomic neuropathy amongst Africans with insulin-dependent diabetes mellitus (IDDM), we investigated 50 such patients at our clinic. Mean age (± 1 s.d.) was 26 ± 6 years, male:female ratio was equal (25M:25F) and duration of diabetes was 4.0 ± 3.0 years. A battery of six validated tests of autonomic function was performed, testing both sympathetic and parasympathetic systems. Overall 16 (32%) had evidence of autonomic damage, affecting parasympathetic only in 14, and both sympathetic and parasympathetic in two. Those with autonomic neuropathy had a significantly longer diabetes duration than those without (6.0 ± 2.8 years versus 3.1 ± 2.7 years, $P < 0.005$), but there was no difference in glycosylated haemoglobin (HbA_{1c}) between the two groups. Autonomic neuropathy was also not significantly associated with peripheral neuropathy or other diabetic complications. Autonomic neuropathy carries a poor prognosis in IDDM and this high prevalence in a group of patients with relatively short diabetes duration gives cause for concern.

Introduction

Autonomic neuropathy is an unusual but important manifestation of diabetic complications. Its importance has only been appreciated since effective clinical tests of cardiovascular responses to autonomic stimuli have been described.¹ Using such criteria it has been demonstrated that autonomic neuropathy affects some 20–40% of the diabetic population,^{2,3} the parasympathetic system being involved first and the sympathetic later.⁴ Classical symptoms of autonomic neuropathy such as diarrhoea, vomiting, bladder dysfunction, postural dizziness and impotence, are clearly important, but they are relatively rare, and are also non-specific and poor indicators of overall autonomic neuropathy prevalence.^{3,4} One exception appears to be gustatory sweating, which seems quite specific to diabetes.⁵ Of great importance is the observation that the presence of autonomic neuropathy greatly worsens the prognosis of diabetes: the follow-up study by Ewing and colleagues⁶ suggested a 50% mortality risk at 5 years from diagnosis.

There is little information in the literature on autonomic neuropathy in Black African diabetes, apart from single reports on South African⁷ and Zambian⁸ patients. The latter study tested patients by electrocardiogram (ECG) R-R changes during

deep breathing but only those with a postural drop of blood pressure on standing were investigated. This is likely to account for the small number (11/600 or 1.8%) of positive cases. This study is of interest, however, in that 44% of patients were impotent, compared with 22% of controls, though 26% of the impotent diabetics were on anti-hypertensive drug treatment.

The South African study⁷ was of 70 diabetic patients at our own hospital, reported in 1977. The patients were of mixed type, though most (84%) were 'maturity onset'. Five tests of autonomic function were performed including postural blood pressure drop, blood pressure response to handgrip and pulse rate response to the Valsalva manoeuvre. Resting heart rate and sinus arrhythmia were also tested. Some tests were not standardized in the way of more recent studies. Diagnostic criteria were also low (for example, a 10 mm drop of blood pressure on standing was taken as positive), and this together with the older onset of diabetes may explain the very high prevalence of 72% with supposed autonomic neuropathy.

Our study was therefore defined to look at a group of young insulin-dependent diabetes mellitus (IDDM) patients only, using modern validated tests of autonomic function.⁹

Patients and methods

Fifty patients were chosen from the Diabetic Clinic of Baragwanath Hospital in Soweto, South Africa.

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Health care in South Africa is no longer segregated, but the township of Soweto, served by the clinic, remains exclusively Black. The patients were thus indigenous Black South Africans, of varying tribal origin, but predominantly Zulu. Effective diabetes care and supply of insulin is available only from Baragwanath Hospital; the clinic therefore treats all local diabetics and there is no selection or referral bias in studies such as this. The 50 patients fulfilled World Health Organisation criteria for the diagnosis of diabetes mellitus¹⁰ and had typical insulin-dependent (IDDM, Type 1) diabetes. Age of onset was below 30 years, all had presented abruptly or in ketosis, and had required insulin treatment from diagnosis. The patients for study were chosen simply as consecutive attenders fulfilling these criteria for true IDDM. Patients with medical conditions potentially interfering with cardiac or autonomic function were excluded (for example, angina, heart failure, hypertension, other cardiac disease, malnutrition, alcoholism, renal failure or significant neurological disease), as well as those on drugs which might interfere with autonomic function tests. Patients were investigated and assessed as follows:

- A questionnaire was filled in with the patient to determine the presence of symptoms of autonomic neuropathy. These were postural dizziness, vomiting, diarrhoea, bladder disturbance, abnormal sweating and impotence.
- A full neurological examination was carried out.
- Blood was taken for glycosylated haemoglobin (HbA_{1c}; local non-diabetic reference range 5.0–8.0%).
- A battery of five autonomic functions tests were performed, as described by Ewing and Clarke^{1,4} and summarized in Table I.

The final assessment as to whether autonomic neuropathy was present and to what degree, was made according to the criteria in Table II. Patients were considered 'normal', 'borderline' or 'abnormal' according to their autonomic test results. Those in the abnormal group could be further subdivided into 'early parasympathetic damage' (Grade I), 'definite parasympathetic damage' (Grade II) and 'combined sympathetic and parasympathetic damage' (Grade III). In this young age group, we defined 'peripheral neuropathy' as any definite deficit in sensation (touch, pain, vibration

Table I Autonomic function tests performed and interpretation of results (after Ewing and Clarke, 1982)

Test no.	Test	Normal	Borderline	Abnormal
Parasympathetic function				
1	Heart rate response to Valsalva manoeuvre (ratio)	> 1.21	1.11–1.20	<1.10
2	Heart rate variation (R-R) during deep breathing (difference between maximum and minimum)	>15/minute	11–14/minute	<10/minute
3	Immediate heart rate response to standing (30:15 R-R ratio)	>1.04	1.01–1.03	<1.00
Sympathetic function				
4	BP response to standing (fall in systolic BP)	<10 mmHg	11–29 mmHg	>30 mmHg
5	BP response to sustained hand grip (increase in diastolic BP)	>16 mmHg	11–15 mmHg	<10 mmHg

Table II Category of patients according to autonomic function tests

Parasympathetic test results	Sympathetic test results	Autonomic status	Grade
Normal	Normal	Normal	
One or more borderline	Normal	Borderline	
One abnormal	Normal	Early parasympathetic damage	I
Two or more abnormal	Normal	Definite parasympathetic damage	II
Two or more abnormal	One or more abnormal	Combined sympathetic and parasympathetic damage	III

or joint position sense), motor function or tendon reflex (knee or ankle).

Results were expressed as means $\pm$ standard deviation (s.d.) and significance was assessed by Student's *t*-test and the chi-squared test with Yates' correction.

Results

(a) Clinical features

Sex distribution, age, duration of diabetes and HbA_{1c} levels are shown in Table III. Four had retinopathy (8%) and 38 (76%) had peripheral neuropathy. This consisted of a peripheral sensory deficit alone in 25 patients and a sensory deficit plus absent ankle reflexes in 13. No patients had significant painful neuropathy,¹¹ amyotrophy¹² or neuropathic cachexia.¹³

(b) Autonomic function tests

These were considered positive in 16 patients (32%) (see Table III). Four (8%) had borderline tests and in 30 (60%) the tests were normal.

Table III Clinical features, complications and results of autonomic neuropathy tests (mean $\pm$ s.d.)

Number	50
Sex	25M:25F
Age (years)	26 $\pm$ 6 (range 14–39)
Duration of diabetes (years)	4.0 $\pm$ 3.0 (range 0.1–11.0)
HbA _{1c} (%)	9.4 $\pm$ 1.8
Complications	4 (8%) retinopathy
	38 (76%) neuropathy
Autonomic tests*	
Grade I	12
Grade II	2
Grade III	2
Total	16 (32%)

*Grade I = early parasympathetic damage; Grade II = definite parasympathetic damage; Grade III = combined sympathetic and parasympathetic damage.

(c) Characteristics of group with autonomic neuropathy

Table IV compares those with and without positive tests of autonomic function. Sex distribution, age and mean HbA_{1c} were not significantly different between the two groups. The duration of diabetes was, however, significantly longer in those with autonomic neuropathy (6.0 $\pm$ 2.8 years versus 3.1 $\pm$ 2.7 years, $P < 0.0005$). Only two patients with diabetes of duration less than 4.0 years had autonomic neuropathy.

(d) Symptoms of autonomic neuropathy

Symptoms compatible with autonomic neuropathy were present in 22 patients (44%), but only nine of these (41%) had abnormal autonomic tests. Conversely, of the 16 with abnormal tests only nine (50%) had symptoms. Analysis by the chi-squared test showed no significant association between symptoms and test results.

(e) Relationship between autonomic and peripheral neuropathy

Of the 16 patients with definite autonomic neuropathy, 14 (87%) had evidence of peripheral neuropathy. Of the 34 patients without autonomic neuropathy, however, 24 (71%) also had peripheral neuropathy. Again, analysis by the chi-squared test failed to show a significant association between peripheral and autonomic neuropathy.

Discussion

The findings of a 32% prevalence of confirmed autonomic neuropathy amongst our IDDM population, are in accord with other estimates as previously mentioned.^{2,3} Most of our patients had early parasympathetic damage (12 out of 16), but two had more advanced damage and two also had sympathetic dysfunction. The patients with autonomic neuropathy had a significantly longer duration of diabetes than those without. This is in

Table IV Comparison of patients with and without autonomic neuropathy

	Number	Sex	Age (years)	Duration of diabetes (years)	HbA _{1c} (%)
Autonomic neuropathy	16 (32%)	M7:F9	28 $\pm$ 5	6.0 $\pm$ 2.8 (range 1.4–11.0)*	9.4 $\pm$ 1.8
No autonomic neuropathy	34 (68%)	M18:F16	25 $\pm$ 7	3.1 $\pm$ 2.6 (range 0.1–11.0)	9.5 $\pm$ 1.9
Significance		NS	NS	$P < 0.005$	NS

*Only two of the autonomic neuropathy group had a duration of diabetes below 4.0 years. NS, not significant.

agreement with other studies.^{3,14} However, the duration of diabetes in our patients was relatively short (overall mean 4.0 ± 3.0 years), though it is known that autonomic neuropathy can occur in diabetic patients of less than 2 years duration.¹⁵

There is a known relationship between peripheral and autonomic neuropathy,^{16,17} some suggesting that peripheral nerve dysfunction is present in all cases of autonomic neuropathy.¹⁸ Overall 87% of our group with autonomic neuropathy had associated peripheral neuropathy, but the figure for those without autonomic neuropathy was also high at 71% and the difference was not significant. Because of the higher overall prevalence of peripheral neuropathy (76%), we would presumably require larger numbers to demonstrate an association. Similarly our prevalence of retinopathy was too small to allow us to attempt correlation with autonomic neuropathy.

As has been mentioned, symptoms of autonomic neuropathy are non-specific,^{3,4} and our results confirm this with suggestive symptoms present in only 41% of patients with autonomic neuropathy and also in 38% of those without.

The actual cause of diabetic neuropathy is still unknown, but it is widely thought to be related to prolonged poor glycaemic control and frequently ameliorates with improved control.^{19,20} Such

studies, however, are concerned with *peripheral* rather than *autonomic* neuropathy. The latter does not often improve or resolve in the same way as peripheral neuropathy⁶ and may possibly be due to different underlying processes. In this context it is of interest that overall glycaemic control, as measured by current HbA_{1c} levels, was similar in those with and without autonomic neuropathy in our series. A recent Swedish study,²¹ and particularly the American DCCT study²² have confirmed the strong association of glycaemic control with complication risk in IDDM. In the latter study,²² autonomic function tests were performed and the risk of development of autonomic neuropathy was reduced in the cohort with intensified glycaemic control.

The autonomic function tests we used are not technically difficult to perform, though the full battery of five tests is relatively time-consuming. Nevertheless, there is no doubt that to properly assess the prevalence of autonomic neuropathy, this type of screening has to be performed. Our prevalence of 32% in young Sowetan IDDM patients, at an average duration of only 6 years, is of considerable concern, particularly in view of the gloomy prognosis of autonomic neuropathy, with over half dying at 5 years from diagnosis.⁶

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