AUTONOMIC NEUROPATHY PREDICTS MORTALITY IN IDDM

Naomi S Levitt, Aaron I Vinik, Kevin B Stansberry

Objective. To examine the predictive value of autonomic neuropathy (AN) for mortality.

Setting. Groote Schuur Hospital Diabetes Clinic, Cape Town.

Design. Cohort study.

Subjects. 76 IDDM patients with less than 10 years' duration of diabetes.

Methods. At baseline the patients had a clinical examination and assessment of AN using 5 cardiovascular autonomic function tests. After 9 years the patients were recalled.

Results. At follow-up 57 patients were alive, 4 could not be traced, and 15 had died. There were 13 non-accidental deaths, 7 (54%) due to renal failure, and 3 unexpected deaths at home. An abnormal response to each autonomic function test was predictive of mortality and there was a significant relationship between the severity of AN and mortality. Logistic regression analysis indicated that AN (odds ratio 2.96, $P = 0.006$) and nephropathy (odds ratio 13.15, $P = 0.018$) at baseline predicted mortality.

Conclusion. These data provide further evidence of the significant mortality associated with AN and suggest that the risk of mortality increases with increasing severity of AN.

S Afr Med J 1999; **89:** 1201-1205.

A substantial mortality of 27 - 53% at 5 years has been reported in predominantly insulin-dependent diabetic (IDDM) patients with symptomatic autoneuropathy (AN),[1-5] with nephropathy and macrovascular disease accounting for more than 50% of the identifiable causes of death. In addition, there have been reports of sudden, unexplained death in patients with features of AN.[6] It is unclear whether the association between AN and in particular nephropathy represents co-segregation of complications due to the presence of common pathogenetic mechanisms, or whether AN *per se* is the determining factor. It has been contended that only symptomatic AN increases susceptibility to premature death. It is uncertain whether asymptomatic AN diagnosed on the basis of standard criteria confers increased susceptibility to premature mortality.

Since AN seems to herald a poor prognosis, by whatever mechanism, it would be important to identify whether there are autonomic function tests predictive of premature death, so that this can be prevented or delayed. In this study of a cohort of IDDM patients followed up for a 9 - 10-year period, the predictive value of AN, its symptoms and responses to cardiovascular autonomic function tests were assessed in relation to mortality.

METHODS

Subjects

In 1981, 76 consecutive IDDM patients attending the Groote Schuur Hospital diabetes clinic over a 3-month period, aged less than 42 years, with a duration of diabetes of less than 10 years, were invited to take part in this study. All patients were dependent on insulin, had experienced diabetic keto-acidosis, or had been under 35 years of age at onset of diabetes.

Patients who were receiving drugs that interfere with autonomic nervous function and those in cardiac failure or atrial fibrillation were excluded. Seventy-six participants, 43 men and 33 women, with a mean age of 28.5 (range 16 - 41) years and a mean duration of diabetes of 4.6 (range 0.5 - 9) years, were studied using a questionnaire, a clinical examination and a battery of five cardiovascular autonomic function (CAN) tests as described previously.[7]

Procedures

CAN tests

E:I ratio. Heart rate variation during deep breathing was determined from ECG recordings during deep breathing at 6 breaths per minute for 1 minute as the ratio of the longest R-R interval during expiration divided by the shortest during inspiration. The mean of three tests at 5-minute intervals was calculated.

Valsalva. The R-R variation in response to the Valsalva manoeuvre was measured as subjects sat quietly and blew into a mouthpiece at a sustained pressure of 40 mmHg for 15 seconds. The Valsalva ratio was calculated from ECG recordings as the ratio of the shortest R-R interval during the manoeuvre to the longest R-R interval within 20 seconds of completion of the manoeuvre. The mean ratio from 3 manoeuvres repeated at 2-minute intervals was calculated.

Heart rate response to standing. This ratio was calculated as the ratio of the 30th to the 15th R-R interval on a continuously recording ECG tracing after assuming the standing from the supine position.

Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town

Naomi S Levitt, MB ChB, MD

Diabetes Institutes and Department of Internal Medicine and Anatomy/Neurobiology, Eastern Virginia Medical School, Norfolk, Virginia, USA

Aaron I Vinik, MD, PhD

Kevin B Stansberry, BS

Blood pressure response to standing. The systolic blood pressure was measured with the patient supine and at 1 minute after standing.

Blood pressure response to sustained handgrip. Diastolic blood pressure was recorded basally at 5-minute intervals for 10 minutes, then at 1-minute intervals for a maximum of 5 minutes during 30% of maximum voluntary contraction using a handgrip dynamometer.

Responses to the tests were classified as normal, borderline or abnormal using the criteria defined by Ewing *et al.*[7] The results of the five tests were summed: O = normal, 0.5 = borderline and 1 = abnormal. The presence of severe AN was defined by a score of > 3, definite AN a score of 2 - 3, and early AN as > 1 but < 2.

Symptoms of AN

The following were assessed as either absent or present by standard questionnaire:

Gastroparesis was identified as persistent early satiety (and frequent nausea and vomiting).

Diarrhoea was taken to be the presence of recurrent, intermittent (including nocturnal) diarrhoea, without blood, for which there was no other apparent cause.

Impotence was considered to be present if the subject reported inability to achieve or maintain an erection sufficient to obtain penetration on more than a quarter of the opportunities presented.

Loss of lubrication was identified as a diminution in vaginal lubrication on intercourse resulting in dyspareunia.

Hypoglycaemic unawareness was defined as loss of characteristic adrenergic symptoms of hypoglycaemia.

Postural hypotension was defined as a feeling of dizziness or faintness on standing.

Clinical signs of other complications

The following were also assessed as either absent or present by clinical examination. The examiner at the time of the assessment was unaware of the clinical status of the patients.

Retinopathy was defined as the presence of any degree of diabetic retinopathy on direct fundoscopy of the dilated pupil by the same experienced examiner.

Proteinuria was defined as > 1+ positive using a commercial reagent strip (= 300 mg/24 h) at the time of examination.

Peripheral neuropathy was diagnosed by the presence of: (*i*) symptoms (paraesthesiae, numbness, alteration of thermal sensation or weakness); (*ii*) abnormal findings on sensory examination (diminution or absent fine touch, pain or vibration sense using a tuning fork); (*iii*) reflex impairment (absent ankle reflexes on reinforcement); or (*iv*) overt signs of motor neuropathy.

Nine years later, the patients were recalled. Fifty-seven were alive, 4 could not be traced because they had moved from the area, and 15 had died. Information on those who had died was obtained from patient records and interviews with family members.

Statistics

The analysis excluded the 4 subjects who could not be traced and the 2 accidental deaths. Results are expressed as mean ± standard deviation (SD). Univariate analysis of variance, chi-square tests and logistic regression were used to examine the associations between autonomic symptoms, autonomic function tests, AN, other complications of diabetes and mortality.

RESULTS

At the beginning of the study, early AN was present in 33% of the patients, definite AN in 11.8% and severe AN in 8%. At that stage subjects with at least early AN were older than subjects without AN (32.4 ± 1.4 v. 26.4 ± 1.1 years; $P = 0.01$), but there were no differences in duration of diabetes or gender. In addition, nephropathy (8% v. 5%), retinopathy (26% v. 10%) and peripheral neuropathy (52% v. 42%) were not significantly different in subjects with and without AN.

There were 15 deaths over the 8 - 9-year study period, comprising 13 non-accidental and 2 'accidental' deaths (1 suicide and 1 motor vehicle accident) (Table I). Renal failure accounted for 7 of the deaths (54%); all of these 7 patients had had proliferative retinopathy at the time of death, and all had had at least early AN at baseline. One patient died in hospital from diabetic keto-acidosis. Three patients died unexpectedly at home, only 1 of whom had nephropathy. Of these 3, 1 woman died 24 hours after discharge from hospital following an uncomplicated miscarriage and another woman died 2 weeks after returning home following prolonged hospitalisation for an above-knee amputation.

Table I. Causes of death

	No.	%
Renal failure	7	46.7
Diabetic keto-acidosis	1	6.7
Sudden death at home	3	13.3
Accidental	2	13.3
Unknown	2	13.3
Total	15	100

There were no baseline differences in age, duration of diabetes, gender, or incidence of retinopathy between those who survived and those who died (Table II). There were, however, significant differences between the two groups with

Table II. Clinical characteristics of subjects who died non-accidental deaths compared with the survivors at commencement of the study

	Deceased ($N = 13$)	Alive ($N = 57$)	P
Age (yrs)	28.5 ± 1.1	29.1 ± 1.8	NS
Duration of diabetes mellitus	4.4 ± 0.4	5.8 ± 0.6	NS
Gender	8 F 5 M	24 F 33 M	NS
Valsalva ratio	1.3 ± 0.06	1.6 ± 0.04	0.0001
E:I (bpm)	11 ± 2.03	24 ± 1 ± 52	0.001
E:I R-R ratio	1.16 ± 0.04	1.35 ± 0.03	0.001
Postural R-R ratio	1.02 ± 0.01	1.07 ± 0.01	0.019
Handgrip systolic BP (mmHg)	14.1 ± 2.98	23.8 ± 1.69	0.013
Postural BP (mmHg)	16.5 ± 3.74	6.5 ± 0.96	0.001
Resting heart rate (bpm)	90.5 ± 2.18	81 ± 2.12	0.034
Gastroparesis	8%	2%	0.030
Postural hypotension symptoms	31%	2%	0.002
Impotence	31%	1%	0.030
Diarrhoea	23%	0%	0.001
Hypoglycaemic unawareness	31%	4%	0.006
Loss of lubrication	15%	0%	0.008
Retinopathy	30%	13%	NS
Nephropathy	30%	2%	0.003
Peripheral neuropathy	58%	44%	NS

Significance of numeric values was derived by one-way ANOVA and prevalence data by chi-square statistic.

Table III. Predictive levels for mortality of each CAN measure

		Deceased		Surviving			
Test	Diagnostic cut-off level	No. abnormal	Total	No. abnormal	Total	Risk ratio*	P (χ^2)
E:I ratio	< 1.21	11	13	12	57	4.02 (2.3 - 7.0)	0.0001
E:I (bpm)	< 15	10	13	12	57	3.65 (1.1 - 6.0)	0.0001
Valsalva ratio	< 1.20	6	13	3	56	8.62 (2.1 - 19.7)	0.001
Postural R-R ratio	< 1.04	9	13	21	56	1.85 (1.1 - 3.0)	0.037
Postural BP	> 10	8	13	14	57	2.51 (1.3 - 4.7)	0.012
Handgrip BP	< 16	8	11	13	48	2.69 (1.5 - 4.8)	0.005

* 95% confidence intervals.

regard to frequency of the symptoms of AN, the responses to each autonomic function test, and the frequency of proteinuria.

Each of the CAN tests was significantly predictive of mortality (Table III). In addition, there was a significant relationship between the severity of AN and mortality. The mortality rate was 100% in patients with severe AN, 43% in those with definite AN, 15% in those with early AN, and 7% in those without AN. Furthermore, higher AN scores (summed abnormalities of CAN tests) conferred a significant increase in mortality risk (Fig. 1).

Logistic regression indicated that both AN and nephropathy predicted mortality. Mortality rates in the presence and absence of both AN and nephropathy are illustrated in Fig. 2. The odds ratio for mortality in the presence of AN was 2.96 ($P = 0.006$) and in the presence of nephropathy 13.15 ($P = 0.018$). The risk ratio for nephropathy is somewhat extreme owing to the low incidence of nephropathy overall.

Discussion

In addition to confirming that AN is associated with an increased mortality rate, this study identified a 'dose-dependent effect' of AN on mortality and found that abnormal responses to each individual cardiovascular autonomic test and each symptom of AN were predictive of poor outcome.

Previous reports have described mortality rates of 27 - 56% at

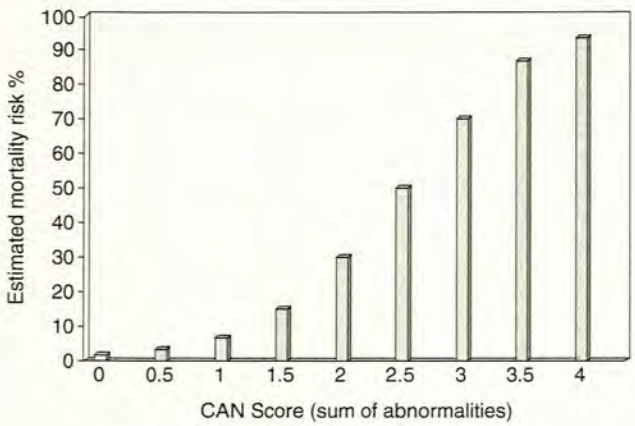

Fig. 1. Estimated 10-year mortality risk conferred by cardiac autonomic neuropathy score (summed CAN test abnormalities). Estimates are derived from univariate logistic regression modelling.

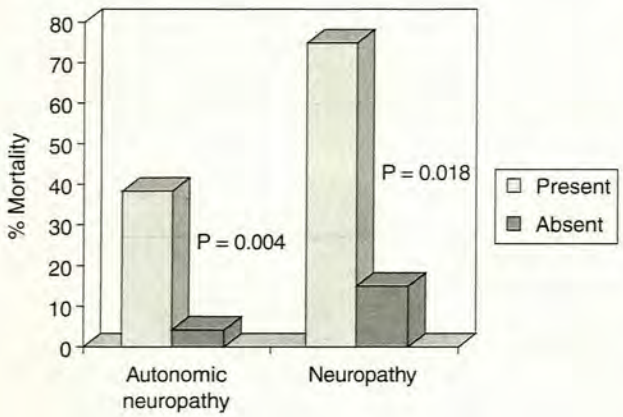

Fig. 2. Mortality rates in the presence and absence of autonomic neuropathy and nephropathy.

5 years in diabetics with AN.[1-4] The highest rate, 56%, was reported in a heterogeneous group of IDDM and NIDDM patients with symptomatic AN who were up to 69 years of age, had a relatively long duration of diabetes (mean 16.6 years) and included 36% of subjects with impaired renal function.[1] In IDDM patients with asymptomatic abnormal autonomic function tests lower 5-year mortality rates, 27 - 33%, have been reported,[3,4] although the 7-year mortality rate was 40% in the latter study. The reason for these discrepancies may relate to choice of subject, access to health care and transplantation, entrance criteria, duration of diabetes, and duration and degree of severity of AN.

At the outset of this study, subjects with the symptoms of AN were rare, probably because of the selection of subjects with less than 10 years' duration of diabetes. Nonetheless, symptoms of postural hypotension, gastroparesis, hypoglycaemic unawareness, impotence and loss of lubrication were present significantly more often in those who later died than in the survivors. The ominous presence of the first three of these symptoms has been noted previously[1] and suggests that they may be late manifestations of AN. The symptom of loss of vaginal lubrication was not sought in previous studies. The observation of impotence as a predictor of poor outcome was surprising in view of its multifactorial pathogenesis and further contrasts with its reported association with increased mortality only in the presence of other symptoms of AN.[1] The finding that symptomatic but not asymptomatic AN,[2] and therefore more severe AN, was associated with increased mortality was consistent with our observation.

An abnormal response to each cardiovascular autonomic function test in this study was associated with significantly increased risk of death, with the odds ratio being highest for the Valsalva and E:I ratios. In order routinely to identify patients at risk of premature death, it may therefore be adequate to perform either or both of these two tests, at least one of which was included in previous such studies.[2-4] In these, AN was deemed as present or absent, based on the responses to one, two, or in one report, four autonomic function tests, and no attempt was made to stratify the degree of autonomic dysfunction. This is particularly pertinent in view of the observation that greater degrees of AN, i.e. early, severe and definite, resulted in a stepwise increase in mortality rates in this study. The use of a battery of tests to stratify those patients at greater risk of premature mortality, and who would possibly benefit most from close observation, in particular in the peri-operative period, should therefore be considered.

This study confirms previous reports of renal failure as the major cause of death in patients with AN. Sudden unexplained deaths also occurred, in agreement with earlier reports.[3,7] The precise nature of unexplained deaths is conjectural. A failure of the initiation of respiratory drive under conditions of hypoxia in patients with AN has been described[8,9] and may cause sudden death. Further, a relationship between Q-Tc interval prolongation and sudden death in patients with AN has been established,[10,11] but even among these patients it was not apparent that dysrhythmias were the cause of death. Alternative explanations may include macrovascular events such as massive strokes or myocardial infarctions. The fact that 2 of the 4 patients in this study who died suddenly had had amputations may support the coexistence of macrovascular disease.

The 7 patients who died from renal failure in this study, 3 with early and 4 with definite AN, all had proliferative retinopathy. The common coexistence of proliferative retinopathy and autonomic neuropathy has been described,[12,13] and so has an association between AN and nephropathy.[13,14] This may suggest common pathogenic or risk factors, such as poor glycaemic control or a related condition for these complications. Alternatively, as has been suggested, AN may play a role in the development or progression of retinal neovascularisation[12] and nephropathy.[15]

We attempted to identify whether AN or nephropathy was more predictive of mortality. Although both were independently predictive of poor outcome, the high odds ratio for the latter suggested that nephropathy was more predictive. This should, however, be viewed with caution in view of the small number of subjects with nephropathy at the outset and the large confidence intervals.

Despite the small sample size in this study, each autonomic function test and symptom was predictive of death. Further, the data suggesting that increasing severity of AN was associated with increasing risk of mortality were striking. These observations are particularly important in the context of improved survival of patients with AN and a functioning pancreas transplant[4] and the improvement in measures of autonomic dysfunction with intensive insulin therapy,[16] dictating the need to focus energy and efforts on improved diabetes control if the high mortality of AN is to be mitigated. The recent observations that nerve growth factor may restore function of small unmyelinated C fibres of the somatic and autonomic nervous system[17] also heralds hope for the future.

References

1. Ewing D, Campbell I, Clarke B. The natural history of diabetic autonomic neuropathy. *Q J Med* 1980; **49:** 95-108.
2. Sampson MJ, Wilson S, Karagiannis P, Edmonds M, Watkins PJ. Progression of diabetic autonomic neuropathy over a decade in insulin independent diabetics. *Q J Med* 1990; **75:** 635-646.
3. O'Brien IA, McFadden JP, Corrall RJ. The influence of autonomic neuropathy on mortality in insulin-dependent diabetes. *Q J Med* 1991; **79:** 495-502.
4. Navarro X, Kennedy WR, Sutherland DE. Autonomic neuropathy and survival in diabetes mellitus: effects of pancreas transplantation. *Diabetologia* 1991; **34:** suppl 1, S108-S112.
5. Kahn JK, Sisson JC, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. *J Clin Endocrinol Metab* 1987; **64:** 751-754.
6. Page M, Watkins PJ. Cardiorespiratory arrest and diabetic autonomic neuropathy. *Lancet* 1978; **1:** 14-16.
7. Ewing D, Martyn C, Young R. The value of cardiovascular function tests: 10 years experience in diabetes. *Diabetes Care* 1985; **8:** 491-498.
8. Sobotka P, Liss H, Vinik A. Impaired hypoxic ventilatory drives in diabetics with autonomic neuropathy. *J Clin Endocrinol Metab* 1992; **C2:** 658-663.
9. Vinik AI, Holland MT, LeBeau JM, Linzzi FJ, Stansberry KB, Colen LB. Diabetic neuropathies. *Diabetes Care* 1992; **15:** 1926-1975.
10. Kahn J, Sisson J, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. *J Clin Endocrinol Metab* 1987; **64:** 751-754.
11. Ewing DJ, Boland O, Neilson JM, Cho CG, Clarke BF. Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. *Diabetologia* 1991; **34:** 182-185.
12. Krolewski AS, Barzilay J, Warram JH, Martin BC, Pfeifer M, Rand LI. Risk of early-onset proliferative retinopathy in IDDM is closely related to cardiovascular autonomic neuropathy. *Diabetes* 1992; **41:** 430-437.
13. Dryberg T, Benn J, Christiansen JS, Hilsted J, Nerup J. Prevalence of diabetic autonomic neuropathy measured by simple bedside tests. *Diabetologia* 1981; **20:** 190-194.
14. Molgaard H, Christensen PD, Sorensen KE, Christensen CK, Mogensen CE. Association of 24 hour cardiac parasympathetic activity and degree of nephropathy in IDDM patients. *Diabetes* 1992; **41:** 812-817.
15. Spallone V, Gambardella S, Maiello MR, Barini A, Frontoni S, Menzinger G. Relationship between autonomic neuropathy, 24 hr blood pressure profile and nephropathy in normotensive IDDM patients. *Diabetes Care* 1994; **17:** 578-584.
16. Diabetes Control and Complications Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998; **41:** 416-423.
17. Apfel SC, Arezzo JC, Brownlee M, Federoff H, Kessler JA. Nerve growth factor administration protects against experimental diabetic sensory neuropathy. *Brain Res* 1994; **634:** 7-12.

Accepted 19 Sep 1999.