Autonomic Neuropathy in Diabetes Mellitus: A Follow-up Study

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To evaluate the development of autonomic neuropathy, 23 patients with a moderate (group A) and 18 patients with a long (group B) duration of diabetes and without symptoms of autonomic neuropathy were re-investigated 6 yr after the initial studies. Autonomic nerve function was evaluated from heart reactions to deep breathing (E/I ratio) and to a rapid 90° tilt (acceleration and brake indices). Symptoms of autonomic neuropathy (SAN) developed in 18 patients (nine in each group) who showed a low mean E/I ratio and brake index in both studies. In group A, but not in group B, patients with SAN showed a decrease in the acceleration index and most SAN patients (8/9) in group A had an abnormal acceleration index in the follow-up study. We conclude that in both groups SAN developed rapidly and was preceded by decreases in E/I ratio and brake index. DIABETES CARE 1985; 8:129–33.

Prevalence and incidence of complications increase with duration of diabetes and about 50% of patients with diabetes are affected by retinopathy and peripheral neuropathy after 25 yr of the disease.[1] Prevalence and incidence of diabetic autonomic neuropathy have been difficult to assess. Recently, the evaluation of autonomic nerve function has been simplified by the introduction of noninvasive cardiovascular tests.[2] Using these methods, Ewing et al.[3] have shown that the combination of symptoms and signs of diabetic autonomic neuropathy signifies a bad prognosis. However, in cross-sectional studies, it has been shown that signs without symptoms of autonomic neuropathy frequently occur in diabetic patients,[4–9] but the importance is unclear. We have recently reported[8] that about half of the patients with diabetic peripheral neuropathy show asymptomatic autonomic neuropathy.

The present report is a prospective follow-up study of diabetic patients who were without symptoms of autonomic neuropathy during their first studies. The main object of the study was to evaluate the relationship between the development of symptoms of autonomic neuropathy (SAN) and the results of autonomic neuropathy tests.

METHODS

Patients

In the primary study 52 type I diabetic patients were investigated.[8] Group A consisted of 26 patients (14 men, 12 women) with diabetes of short to moderately long duration (5–19 yr, mean 11); the remaining 26 patients made up group B, which consisted of 14 men and 12 women with diabetes of long duration (21–49 yr, mean 35). Half of the patients in each group showed retinopathy and none reported symptoms of autonomic neuropathy (SAN). The 52 patients were invited to participate in a follow-up study 5–7 yr after the primary study and 41 accepted (23 in group A and 18 in group B), five had died (two suddenly, two of uremia, and one of myocardial infarction), and six refused to participate. Tables 1 and 2 show mean age and duration of diabetes in patients who participated in both studies. Severe impairment in renal function was absent in the subjects and only three patients in the primary study and five in the follow-up study showed a low glomerular filtration rate (<80% of expected value in ^{51}Cr-EDTA plasma clearance).[10]

Control Subjects

Group A patients were compared with 21 healthy controls (aged 28–48 yr, mean 40).[8] In primary study group B patients were compared with 24 healthy controls (aged 40–74 yr, mean 63) and in the follow-up study with 10 age-matched healthy controls (aged 55–74 yr, mean 63).[8]

Procedures

SAN. Before examination, using a questionnaire, the patients were asked for possible symptoms of autonomic neuropathy: (1) postural symptoms (feeling of imminent fainting or unsteadiness when standing); (2) gastrointestinal symp-

TABLE 1
Physical characteristics, autonomic neuropathy indices, and blood pressure in patients with a short to moderately long duration of diabetes (group A)

		Primary study		Follow-up study	
	Controls (N = 21)	Patients without SAN (N = 14)	Patients with SAN (N = 9)	Patients without SAN (N = 14)	Patients with SAN (N = 9)
Age (yr)	40 ± 2	32 ± 2	31 ± 1	38 ± 2	36 ± 1
Duration of diabetes (yr)	—	10 ± 1	12 ± 1	16 ± 1	18 ± 1
E/I ratio	1.31 ± 0.03	1.27 ± 0.04	1.15 ± 0.04	1.26 ± 0.04	1.18 ± 0.04
Acceleration index	21.0 ± 1.3	22.8 ± 1.6	17.6 ± 2.9	16.3 ± 2.1	8.7 ± 1.3
Brake index	18.7 ± 2.5	14.0 ± 2.3	6.5 ± 1.7	12.4 ± 2.0	9.9 ± 4.7
Systolic blood pressure (mm Hg)					
Before tilt	115 ± 3	118 ± 3	122 ± 4	129 ± 3	143 ± 9
1 min After tilt	114 ± 3	118 ± 5	117 ± 4	126 ± 4	136 ± 6
10 min After tilt	113 ± 3	113 ± 4	114 ± 5	125 ± 3	137 ± 6
Diastolic blood pressure (mm Hg)					
Before tilt	73 ± 3	75 ± 3	83 ± 4	85 ± 2	88 ± 3
1 min After tilt	77 ± 2	82 ± 3	84 ± 4	88 ± 2	89 ± 3
10 min After tilt	80 ± 2	80 ± 3	84 ± 5	88 ± 2	88 ± 3

SAN, symptoms of autonomic neuropathy. Mean ± SEM.

toms (vomiting or other symptoms of gastro-paresis, nocturnal diarrhea, anal sphincter insufficiency); (3) bladder dysfunction (voiding disturbances unrelated to prostate hyperplasia or other obstruction); (4) gustatory sweating (profuse facial sweating when eating specific foods); (5) impotence (total impotency or declining potency for the last years) and/or ejaculatory dysfunction (retrograde or absent ejaculation).

Neuropathy Tests

All tests were performed postprandially between 10:30 and 11:30 a.m. and the patients took their usual dose of insulin before breakfast and showed no clinical evidence of hypoglycemia. The patients were told to abstain from smoking before the tests. Undue stress to the patients was avoided before and during the test procedure.

Peripheral neuropathy. Examination of the nervous system included analysis of tendon reflexes and vibration sense. Vibration sense thresholds were determined over the medial malleoli (Bio-Thesiometer, Biomedical Instruments, Newbury, Ohio). The results were expressed in volts (V) as a mean of measurement on the left and right ankles. Threshold values above the mean of the controls + 2 SD were considered abnormal (>17 V in group A and >28 V in group B). Absent ankle reflexes and abnormal vibration sense were considered signs of peripheral neuropathy.[5]

Deep breathing test. In brief, six maximal expirations and

TABLE 2
Physical characteristics, autonomic neuropathy indices, and blood pressure in patients with diabetes of long duration (group B)

	Primary study			Follow-up study		
	Controls (N = 24)	Patients without SAN (N = 9)	Patients with SAN (N = 9)	Controls (N = 10)	Patients without SAN (N = 9)	Patients with SAN (N = 9)
Age (yr)	53 ± 2	48 ± 3	61 ± 3	63 ± 2	54 ± 3	67 ± 3
Duration of diabetes (yr)	—	34 ± 1	36 ± 3	—	40 ± 1	42 ± 3
E/I ratio	1.23 ± 0.02	1.15 ± 0.04	1.13 ± 0.04	1.16 ± 0.01	1.11 ± 0.03	1.08 ± 0.01
Acceleration index	17.0 ± 1.5	14.5 ± 2.8	12.1 ± 2.1	10.7 ± 1.4	6.5 ± 2.1	10.4 ± 3.2
Brake index	14.2 ± 1.8	9.9 ± 2.9	9.0 ± 3.3	10.2 ± 0.8	9.3 ± 2.3	2.7 ± 2.0
Systolic blood pressure (mm Hg)						
Before tilt	122 ± 3	138 ± 4	132 ± 4	126 ± 5	155 ± 5	143 ± 4
1 min After tilt	120 ± 4	134 ± 4	118 ± 5	127 ± 7	158 ± 5	131 ± 6
10 min After tilt	118 ± 3	134 ± 5	120 ± 7	123 ± 5	149 ± 4	132 ± 5
Diastolic blood pressure (mm Hg)						
Before tilt	76 ± 2	81 ± 3	77 ± 3	78 ± 3	87 ± 4	81 ± 3
1 min After tilt	82 ± 2	81 ± 3	71 ± 3	84 ± 3	86 ± 3	77 ± 3
10 min After tilt	82 ± 2	80 ± 3	74 ± 5	81 ± 3	84 ± 3	76 ± 3

SAN, symptoms of autonomic neuropathy. Mean ± SEM.

TABLE 3
Prevalence of symptoms of autonomic neuropathy (SAN) in diabetic patients

	Group A		Group B	
	One symptom (N = 7)	Two symptoms (N = 2)	One symptom (N = 8)	Two symptoms (N = 1)
Impotence and/or ejaculatory dysfunction	4	0	3	1
Gustatory sweating	3	2	0	0
Gastrointestinal symptoms	0	1	0	0
Postural symptoms	0	1	5	1

Group A, patients with a short to moderately long duration of diabetes; group B, patients with a long duration of diabetes.

inspirations were performed in the supine position during the recording of a continuous electrocardiogram (EKG). The E/I ratio, measuring parasympathetic vagal nerve activity, was calculated from the mean value of the longest R-R interval during expiration (E) and the shortest during inspiration (I).[5] A ratio below the lower range of controls was considered abnormal (group A < 1.1 and group B < 1.09).[8] Repeated measurements of the E/I ratio in healthy subjects showed a coefficient of variation of 8.7% and, in type I patients, 3.6%.

Orthostatic test. In brief, the subject was tilted rapidly (2 s) to the upright position (90°) and remained so for 10 min.[11] The EKG was recorded continuously during the test starting 1 min before tilting. Systolic and diastolic blood pressures were recorded in the right arm with a sphygmomanometer 4 min before tilt and every min thereafter. To clarify the immediate heart rate changes (an immediate acceleration followed by a transient deceleration), the acceleration and the brake indices were estimated.[11] Accordingly, the R-R intervals were measured during the first 15 s of the last minute before tilt and the mean value was taken as the R-R interval at rest (A). Then, during the first minute after tilt the shortest R-R interval (B) before the transient deceleration was selected as well as the longest R-R interval (C) after B.

The acceleration index, A − B/A × 100, and the brake index, C − B/A × 100, measure mainly vagal parasympathetic nerve function, although the acceleration index is influenced also by sympathetic nerve activity.[8] An index below the lower range of controls was considered abnormal, i.e., in group A an acceleration index <11.5 and a brake index <3.8 and in group B, <5.2 and <3.8.[8] Repeated measurements in healthy subjects showed a coefficient of variation of 17.8% for the acceleration index and 12.0% for the brake index and, in type I patients, 21.5% for the acceleration index and 38.1% for the brake index.

Statistical analysis. Two-tailed Mann-Whitney U-test, Wilcoxon's signed rank test, and Fisher's exact probability test were used. $P < 0.05$ was considered significant. Results are given as mean ± SEM.

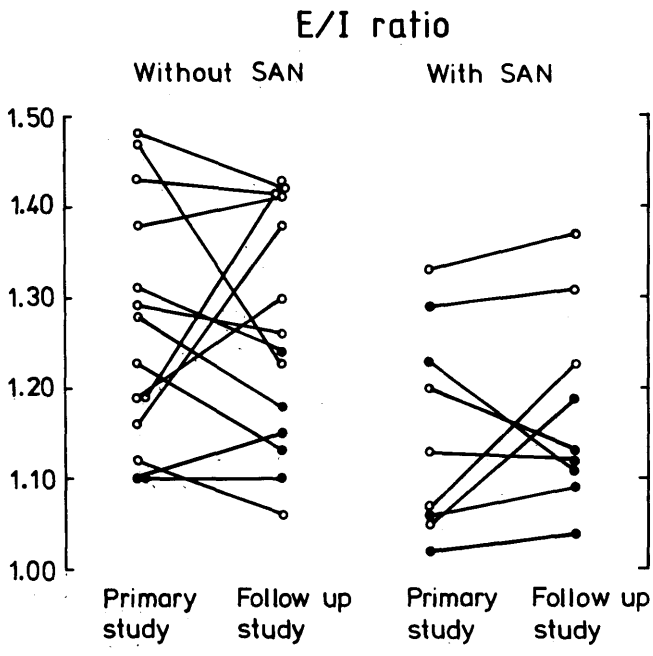

FIG. 1. Changes in E/I ratio during observation period in patients with a short to moderately long duration of diabetes mellitus (group A). SAN, symptoms of autonomic neuropathy. ○, Without signs of peripheral neuropathy; ●, with signs of peripheral neuropathy.

RESULTS

Group A

Among the participating 23 patients, nine had developed SAN and their main complaints were sexual dysfunction and gustatory sweating (Table 3). In the follow-up study, there was an increase in the prevalence of peripheral neuropathy (6/23 versus 11/23). Of the nine patients who developed SAN, four showed peripheral neuropathy in the primary study and six showed peripheral neuropathy in the follow-up study.

Deep breathing test. The mean E/I ratio was significantly lower ($P < 0.05$) in patients with SAN than in controls in both studies and did not deteriorate significantly between the studies (Table 1, Figure 1). In the primary study, four of nine patients, who later developed SAN, showed an abnormal E/I ratio. However, the E/I ratio increased in two of them and only two patients with SAN and one without showed an

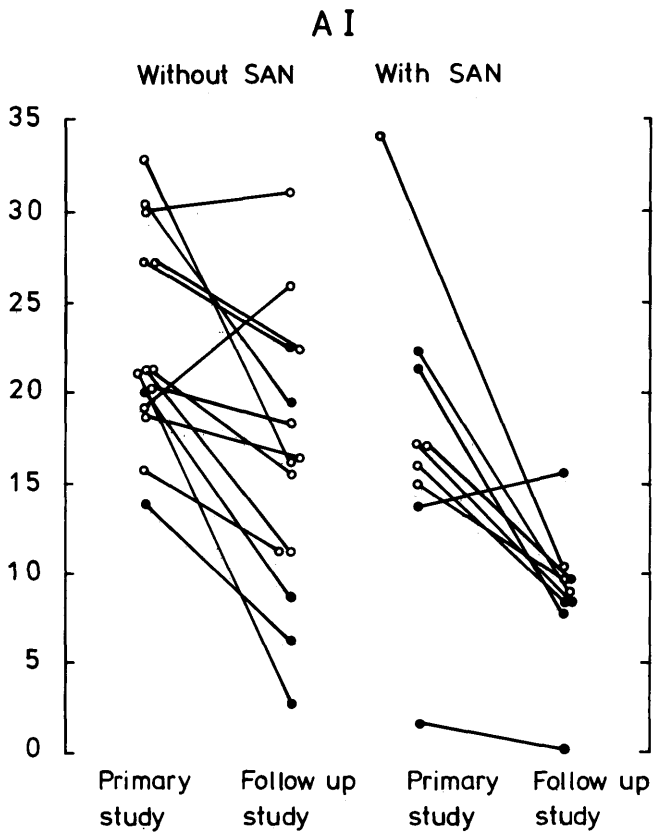

FIG. 2. Changes in acceleration index (AI) during the observation period in patients with a short to moderately long duration of diabetes mellitus (group A). SAN, symptoms of autonomic neuropathy. ○, Without signs of peripheral neuropathy; ●, with signs of peripheral neuropathy.

abnormal E/I ratio in the follow-up study (Figure 1). On the other hand, most patients (5/6) who developed peripheral neuropathy showed a decrease in their E/I ratio (Figure 1).

Orthostatic test. The mean brake index was significantly lower ($P < 0.05$) in patients with SAN than in controls in both studies and did not deteriorate significantly between the studies (Table 1). An abnormal brake index was shown in three SAN patients in both studies. In contrast, the mean acceleration index fell between the studies in patients with SAN and was significantly lower than in controls ($P < 0.001$) and patients without SAN ($P < 0.05$) in the follow-up study (Table 1, Figure 2). In the primary study, the acceleration index was normal in most SAN patients (8/9), while in the follow-up study the acceleration index was abnormal in most SAN patients (8/9). The prevalence of an abnormal acceleration index was also significantly higher in patients with SAN than in those without in the follow-up study ($P < 0.02$). The only patient with SAN and with a normal acceleration index showed an abnormal E/I ratio.

All patients with SAN showed at least one abnormal autonomic neuropathy test in the follow-up study as compared with 34% of patients without SAN (9/9 versus 5/14; $P < 0.01$).

Blood pressure. There were no important differences in blood pressures before and after tilt between patients with and without SAN (Table 1).

Group B

Among the participating 18 patients, nine reported SAN and their main complaints were postural symptoms and sexual disturbances (Table 3). The prevalence of peripheral neuropathy was high in both studies (13/18 versus 15/18). Of the nine patients who developed SAN, seven showed peripheral neuropathy in the primary and all nine showed peripheral neuropathy in the follow-up study.

Deep breathing test. In both studies, the mean E/I ratio was significantly lower ($P < 0.05$) in patients with SAN than in controls (Table 2). In the follow-up study, however, the mean E/I ratio was significantly lower ($P < 0.05$) in patients without SAN than in controls. An abnormal E/I ratio was found in nine patients in both studies (five with SAN in the primary and six with SAN in the follow-up study).

Orthostatic test. The mean brake index but not the mean acceleration index was significantly lower ($P < 0.05$) in patients with SAN than in controls in both studies (Table 2). An abnormal acceleration index was found in four patients in the primary (one with SAN) and in seven (two with SAN) in the follow-up study. An abnormal brake index was found in three patients (one with SAN) in the primary and in seven (five with SAN) in the follow-up study.

Most patients (15/18) showed at least one abnormal autonomic neuropathy test in the follow-up study (8/9 with SAN) compared with 10/18 in the primary study (6/9 with SAN).

Blood pressure. In both studies, systolic blood pressure fell significantly ($P < 0.05$) 1 min after the tilt in patients with SAN but not in those without (Table 2). Furthermore, in the primary study, the diastolic blood pressure fell significantly ($P < 0.05$) in patients with SAN, was unchanged in those without, and rose ($P < 0.001$) in controls during the first minute after the tilt (Table 2).

DISCUSSION

It has previously been found that abnormal autonomic neuropathy tests frequently occur in patients with diabetes mellitus, although SAN is not reported.[4–9] This may imply that autonomic test deviations are loosely related to SAN. However, the present report shows that autonomic nerve test abnormalities are connected to SAN. Furthermore, autonomic test deviations precede the development of SAN. The prognostic capacity differs between the tests. In the primary study, patients with a short to moderately long duration of diabetes (group A), and who later developed SAN, generally showed abnormal E/I ratios and brake indices. In the follow-up study, however, most of these patients showed an abnormal acceleration index. Thus, vagal neuropathy, as measured by the E/I ratio and the brake index, occurs early in the development of autonomic neuropathy. This confirms that the deep breathing test is a sensitive test of autonomic neuropathy.[7]

The nervous mechanism behind the immediate heart rate

acceleration of the orthostatic test is complicated. Most likely, a combination of withdrawal of vagal nerve tone and an increase of sympathetic nerve activity is responsible.[12] The present report shows that a disturbed immediate acceleration, measured here by the acceleration index, is closely correlated with SAN. In addition, an abnormal brake index often precedes the development of an abnormal acceleration index. However, when the acceleration is evaluated, the influence of age has to be considered, as shown from the findings in group B. The acceleration index decreases with age and the fall is rapid after the age of 50–55 yr. A disturbed immediate acceleration is a characteristic of autonomic neuropathy in patients below the age of 50–55 yr. The E/I ratio is also influenced by age,[13,14] although not as profoundly as the acceleration index. In contrast to the acceleration index, the brake index does not deteriorate to the same extent in higher age groups.

The features of SAN differed between groups A and B. Symptoms of sympathetic denervation and drops in blood pressure after tilt occurred mainly in group B. Sympathetic neuropathy is a complication in diabetes of long duration. This is in agreement with earlier observations.[15]

An important finding was the observation that vagal neuropathy as measured by the deep breathing test may improve in diabetic patients. In group A, two of four patients with SAN, who exhibited an abnormal E/I ratio in the primary study, showed a normal E/I ratio in the follow-up study. This finding is in contrast to that of others.[6] Conversely, the E/I ratio fell in most group A patients who developed peripheral neuropathy. It is not likely that differences in methodology are responsible for these changes in E/I ratio. The deep breathing test is a very reproducible test of autonomic neuropathy.[16] It appears that patients with a short to moderately long duration of diabetes may have reversible vagal neuropathy. In contrast, the E/I ratio fell during the observation period in 50% of patients with a long duration of diabetes (group B). Most likely, the deterioration in these patients represented an irreversible vagal neuropathy.

The impact of autonomic neuropathy on the prognosis of diabetes is difficult to evaluate. To date, five patients of the original cohort have died and four of them showed autonomic neuropathy in the primary study. Thus, autonomic neuropathy might influence the prognosis. Sudden death was noted in two patients, both of whom showed autonomic neuropathy in the primary study. This is in agreement with others who have found sudden death to be a feature of autonomic neuropathy.[17] The high mortality in autonomic neuropathy reported by Ewing et al. was not confirmed.[3] However, they found a high mortality in patients with a combination of signs and symptoms of autonomic neuropathy. Most likely, the disease in our patients was less advanced, since the symptoms had just emerged. Future studies of our patients might disclose the natural history of autonomic neuropathy.

ACKNOWLEDGMENTS: We thank Anita Eriksson and Ann-Christin Jönsson for their skillful assistance in the performance of the tests.

This work was supported by grants from research funds of the University of Lund and Malmö General Hospital.

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