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Prevalence of Diabetic Autonomic Neuropathy Measured by Simple Bedside Tests

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Summary. To investigate the prevalence of diabetic autonomic neuropathy, five simple bedside tests, beat-to-beat variation during quiet respiration, beat-to-beat variation during forced respiration, heart rate and blood pressure response to standing, heart rate response to exercise, and heart rate response to Valsalva's manoeuvre were applied to 75 male insulin-dependent diabetics, mean age 40 years, (range 30–49 years). The subjects were subdivided into three groups according to duration of diabetes, which was between 0 and 40 years. Twenty-eight healthy age-matched male controls were also studied. The prevalence of diabetic autonomic neuropathy in the whole diabetic population indicated by abnormal response in beat-to-beat variation during forced respiration was 27%. Diabetic autonomic neuropathy increased in frequency with duration of disease. Patients with nephropathy or proliferative retinopathy had a significantly higher prevalence of diabetic autonomic neuropathy as indicated by abnormal beat-to-beat variation during forced respirations ($p < 0.01$) than patients without these complications.

Key words: IDDM, diabetic autonomic neuropathy, prevalence, simple bedside tests, nerve function, retinopathy, nephropathy, diabetic complications

Autonomic neuropathy is a long-term complication of insulin-dependent diabetes mellitus (IDDM) and has received considerable interest recently [1, 2]. Clinical symptoms of diabetic autonomic neuropathy, such as gustatory sweating, and those related to enteropathy, cystopathy and orthostatic hypotension are rare. On the other hand asymptomatic abnormalities are not uncommon after 10–15 years' duration of diabetes [3–6].

Recently several simple methods for quantitative estimations of autonomic nervous system abnormalities have been published, most of which are based upon measurements of variation in heart rate from beat-to-beat under different conditions [3, 7, 8]. The aim of this study was to investigate the prevalence of diabetic autonomic neuropathy as defined by simple non-invasive bedside tests in a selected population of IDDM patients and to establish whether there was a relation to duration of diabetes and to other late diabetic complications.

Patients

Consecutive male patients with IDDM attending the Steno Memorial Hospital out-patient clinic over a six month period who fulfilled the following criteria were included in the study:

1) age between 30 and 50 years,
2) no drugs taken apart from insulin,
3) normal 12 lead ECG,
4) no history of heart or lung disease.

Informed consent was obtained from each patient. A total of 75 patients was divided into three groups according to duration of diabetes: Group I, 0–9 years, (n = 20), Group II 10–19 years, (n = 21), Group III 20–40 years, (n = 34). Mean ages in the groups were: 39 years (32–49), 40 years (32–47), 40 years (30–49) (mean and range), respectively (Table 1). Careful physical examination of heart and lungs was normal in all patients. No difference was found between the diabetic groups in insulin requirements or 24-h urinary glucose excretion (Table 1).

The control group consisted of twenty-eight healthy male volunteers aged 38 years (30–48) (mean and range) with no family history of diabetes. None of the control subjects was taking any drugs. Mean age was similar in the controls and in the groups of diabetic patients (Table 1).

Methods

The examinations were carried out during a routine out-patient visit. On the day of the examination the patient had his usual breakfast and morning insulin dose.

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Table 1. Mean age, duration of diabetes, daily insulin dose and 24-hour urine glucose excretion in diabetic patients and controls

		Diabetes group I DM duration 0–9 years (n = 20)	Diabetes group II DM duration 10–19 years (n = 21)	Diabetes group III DM duration 20–40 years (n = 34)	Normal subjects (n = 28)
Age (years)	mean	39	40	40	38
	range	32–49	32–47	30–49	30–48
Duration of diabetes (years)	mean	6	15	27	–
	range	1–9	11–19	21–40	
Insulin dose, (IU/24 h)	mean	34	38	39	
	range	10–72	24–56	14–56	–
Urine glucose excretion (g/24 h)	mean	32	28	20	
	range	0–78	0–90	0–78	–

Tests for diabetic autonomic neuropathy included: beat-to-beat variation during quiet respiration [7, 10], beat-to-beat variation during forced respiration [3, 6, 11], heart rate and blood pressure response to standing [4, 7], heart rate response to exercise [8] and heart rate response to Valsalva's manoeuvre [10, 12, 13, 14]. Basal heart rate [5, 12, 15] was also recorded. Heart rates during the tests were continuously recorded on an electrocardiograph (ECG) (Mingograf 34, Elema Schönander, Sweden, paper speed 50 mm/s, mean 49.8 mm/s and range 49.0–50.0 mm/s). In all tests, variations in heart rate were measured as variations in R-R intervals.

Basal Heart Rate

After a resting period of 30 min in the supine position, basal heart rate was measured using 150 consecutive R-R intervals.

Beat-to-beat Variation during Quiet Respiration

Immediately afterwards, beat-to-beat variation during quiet respiration was obtained as the difference between maximal and minimal heart frequency during a respiratory cycle. These values were recorded as the mean values during five consecutive respiratory cycles. During the measurement of basal heart rate and the beat-to-beat variation during quiet respiration the subject was unaware of when the recording was performed.

Beat-to-beat Variation during Forced Respiration

These values were subsequently recorded, still in the supine position, as the mean difference between maximal and minimal heart rate during five respiratory cycles. Maximal inspiration was immediately followed by a maximal expiration, each lasting five seconds.

Heart Rate Response to Standing

Following a supine resting period of 15 min, heart rate and blood pressure response to standing was assessed. Blood pressure was measured by the standard auscultatory method. Heart rate and blood pressure were measured with the patient in the supine position and at the end of 2 min standing. The heart rate response to standing was defined as the ratio between heart frequency at beat 15 after rising to the vertical position and heart frequency at beat 30.

Heart Rate Response to Exercise

The subjects then mounted an ergometer cycle (Monark, Sweden). Following a 15 min resting period, exercise with a load of 50 W at a pedalling frequency of 100/min was performed. The difference between the heart rate after 20 seconds exercise and the resting heart rate was recorded as the heart rate response to exercise.

Heart Rate Response to Valsalva's Manoeuvre

After 15 min of rest in the sitting position, Valsalva's manoeuvre was carried out by the patient expiring against a resistance of 40 mm Hg in a modified mercury sphygmomanometer. A nose clip was used. After 15 sec, the pressure was abruptly relieved by removing the mouthpiece and nose clip, and the ECG recorded for a further 30 seconds. The Valsalva ratio was calculated as the maximal divided by the minimal heart rate obtained during the test.

Threshold for vibration sense (Volts) was determined on the pulp of the first toe on each foot with a Biothesiometer (Bio-Medical Instruments Company, Ohio) [16]. Decreased sense of vibration was considered to be present if the threshold was above the range in the control group (2–20 Volts). From the medical records, ophthalmoscopic examination (dilated pupils), serum creatinine and proteinuria were noted. Patients were regarded as having nephropathy if persistent proteinuria (Albustix® positive 24-h urine specimen at three consecutive visits to the out patient clinic with an interval of at least 1 month) was present.

Among the diabetics with nephropathy only one had a slightly elevated serum creatinine value (161 μmol/l). These parameters were all measured within 12 months prior to this investigation.

Diabetic autonomic neuropathy was considered present, if a test value was below the range in the control group (beat-to-beat variation during quiet respiration, beat-to-beat variation during forced respiration, heart-rate response to standing, heart-rate response to exercise and heart-rate response to Valsalva's manouvre) or above the range in the control group (basal heart rate).

Mean values were compared by means of Wilcoxon non-parametric rank sum test and frequency by means of chi-square test with Yates' correction. The level of type I error (2α) was chosen at 0.05.

Table 2. Outcome of tests for diabetic autonomic neuropathy and prevalence of diabetic autonomic neuropathy in relation to duration of diabetes

			Diabetes group I DM duration 0–9 years (n = 20)	Diabetes group II DM duration 10–19 years (n = 21)	Diabetes group III DM duration 20–40 years (n = 34)	Total diabetic population (n = 75)	Controls (n = 28)
Beat-to-beat variation during quiet respiration (beats/min)	Test value	mean	5	3	3	–	4
		range	(0–18)	(0–12)	(0–12)	–	(0–11)
	Frequency of abnormal results	n	0	0	0	0	–
		%	0	0	0	0	–
Beat-to-beat variation during forced respiration (beats/min)	Test value	mean	18	16	13	–	19
		range	(7–45)	(4–36)	(0–47)	–	(9–34)
	Frequency of abnormal results	n	2	5	13	20	–
		%	10	24	38	27	–
Heart rate response to standing (ratio)	Test value	mean	1.14	1.15	1.10	–	1.14
		range	(0.97–1.39)	(1.00–1.61)	(0.95–1.44)	–	(0.93–1.38)
	Frequency of abnormal results	n	0	0	0	0	–
		%	0	0	0	0	–
Heart rate response to exercise (beats/min)	Test value	mean	17	10	11	–	18
		range	(3–34)	(0–36)	(0–37)	–	(6–23)
	Frequency of abnormal results	n	3	6	7	16	–
		%	15	29	21	21	–
Heart rate response to Valsalva's maneouvre (ratio)	Test value	mean	1.92	1.73	1.52	–	1.76
		range	(1.19–3.57)	(1.16–2. 31)	(1.01–2.17)	–	(1.29–2.45)
	Frequency of abnormal results	n	3	3	7	13	–
		%	15	14	21	17	–

Results

Table 2 shows the number of abnormal test values found in the total diabetic group as well as the distribution within the different groups for each of the tests performed, together with the mean value and ranges for the tests.

No patient had reduced beat-to-beat variation during quiet respiration. Twenty diabetics (27%) had reduced beat-to-beat variation during forced respiration. No diabetics had an abnormal heart-rate response to standing. Sixteen patients (21%) had abnormal heart-rate responses to exercise. An abnormal heart-rate response to Valsalva's manoeuvre was found in 13 diabetics (17%). For basal heart rate the number of abnormal test values in the whole diabetic group was 26 (35%). The numbers of patients with elevated basal heart rate was three, seven and sixteen in diabetics group I, II and III, respectively.

A difference in prevalence of abnormal test values was found in basal heart rate between group I and III ($p < 0.05$). Mean values differed significantly between group I and group III ($p < 0.05$) for beat-to-beat variation during forced respiration and the heart rate response to Valsalva's manoeuvre. Differences in mean values between group III and controls were found for beat-to-beat variation during quiet respiration, beat-to-beat variation during forced respiration and the heart rate response to exercise ($p < 0.05$).

Seven patients had two abnormal test values. In all cases decreased beat-to-beat variation during forced respiration was present. The second abnormal test was either an abnormal heart rate response to Valsalva's manoeuvre or an abnormal heart rate response to exercise. In only three patients were all these three tests simultaneously abnormal.

The number of diabetics with proliferative retinopathy, nephropathy and elevated threshold for vibration sense or without any of these complications and their relationship to autonomic neuropathy is shown in Table 3.

The prevalence of abnormal results for beat-to-beat variation during forced respiration was significantly increased in patients with proliferative retinopathy or nephropathy, compared to patients without these complications ($p < 0.01$). As the pre-

Table 3. The prevalence of diabetic autonomic neuropathy in relation to other diabetic complications

Number of patients with other complications: / Number of patients with normal results		Beat-to-beat variation during forced respiration (n = 20)	Heart rate response to exercise (n = 16)	Heart rate response to Valsalva manoeuvre (n = 13)
Proliferative retinopathy (n = 11)	n	7[a]	3	4
	%	64	27	36
Nephropathy (n = 9)	n	6[a]	1	3
	%	67	11	33
Elevated threshold for vibration sense (n = 9)	n	1	3	2
	%	11	33	22
No complications (n = 52)	n	9	10	7
	%	17	19	13

[a] Prevalence of abnormal beat-to-beat variation during forced respiration is significantly increased in patients with proliferative retinopathy or nephropathy compared to patients without these complications ($p < 0.01$)

valence of abnormal subjects with respect to beat-to-beat variation during quiet respiration and heart rate response to standing is zero in all diabetic groups, these tests are not shown in Table 3.

Discussion

Many reports dealing with diabetic autonomic neuropathy measured by simple bedside tests have recently been published [3, 4, 6, 7, 9, 10, 11, 12, 14]. The patients in these publications were not totally matched for duration of diabetes, age, sex and type of diabetes. In addition no account was taken of drugs administered apart from insulin, other somatic diseases than IDDM or advanced age. The aim of this study was to estimate the prevalence of diabetic autonomic neuropathy in a clinic population matched for these variables. Patients all had IDDM and were divided into groups according to duration of diabetes, which was then the only variable.

Depending on the test used, the prevalence of diabetic autonomic neuropathy in this study ranged from 17% (heart rate response to Valsalva manoeuvre) to 27% (beat-to-beat variation during forced respiration). An intermediate prevalence of 21% was obtained if the heart rate response to exercise was the discriminatory test.

In this study the normal range for beat-to-beat variation during quiet respiration and heart rate response to standing had a lower limit which made it impossible to separate any patients with abnormal responses. This finding in contrast to other reports [8, 9]. This difference may be due to differences in recording techniques.

Diabetic autonomic neuropathy has previously been reported [5, 12, 15] to be associated with an increased basal heart rate. In the present study, basal heart rate was increased particularly in long-standing diabetics, although some subjects with diabetes of short duration also had elevated values. Outside factors, such as excitement, smoking, etc. may however influence basal heart rate, making this an unreliable test of autonomic nervous function.

It is impossible to isolate from this study the best single test for assessment of diabetic autonomic neuropathy. However beat-to-beat variation during forced respiration is easily performed and has been thoroughly investigated [3, 4, 10, 11, 12]. In the present study only beat-to-beat variation during forced respiration was related ($p < 0.01$) to other diabetic complications (nephropathy and proliferative retinopathy, Table 3).

Of particular note is the decreased beat-to-beat variation during forced respiration and decreased heart rate response to Valsalva's manoeuvre in long-standing compared with short-term diabetics. Previous reports of increased prevalence of autonomic neuropathy in long-term diabetics may have been influenced by the greater age of patients with diabetes of long duration compared with the short-term diabetics studied. In the present study the mean age of patients was similar irrespective of the duration of diabetes and our results suggest that long-standing diabetes per se is important in the development of autonomic neuropathy, independent of the influence of advancing age.

Finally autonomic neuropathy was associated with the other diabetic complications, proliferative retinopathy and nephropathy. Mortality rate is

increased in patients with nephropathy [17] and two recent reports [18, 19] suggest an increased mortality rate in patients with autonomic neuropathy. This excess mortality in patients with autonomic neuropathy may thus be related to other diabetic complications rather than neuropathy itself. Further studies are necessary to separate these influences.

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