

The Natural Progression of Autonomic Neuropathy and Autonomic Function Tests in a Cohort of People With IDDM

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OBJECTIVE — To test the natural progression of symptoms of autonomic neuropathy (AN) and function tests in subjects with IDDM.

RESEARCH DESIGN AND METHODS — Seventy-six subjects with IDDM of <10 years duration had cardiovascular autonomic reflex tests and were evaluated for signs and symptoms of AN.

RESULTS — Fifty-seven subjects (66%) were available for restudy 9 years later (15 had died, 4 could not be located). Of the symptoms of AN, only gastroparesis increased in prevalence ($P < 0.01$). Of the five cardiovascular AN measures, only the R-R response to the Valsalva maneuver deteriorated ($F[1,44] = 10.61, P < 0.01$).

CONCLUSIONS — The progression of AN in IDDM is monitored best longitudinally by the Valsalva maneuver because of the small variance ratio in repeated measures. Prevalence rates can be monitored by expiration-to-inspiration R-R or Valsalva ratios. Most clinical signs and symptoms of AN do not progress, underscoring the need for objective and quantitative autonomic function tests to identify people at risk for premature death.

Autonomic neuropathy (AN) is a well-recognized and serious complication of diabetes. Its reported prevalence in IDDM varies depending on the method used, as well as the duration of diabetes (1–9). Reported prevalences vary from as low as 16% (10) in newly diagnosed IDDM patients to as much as 75% (11) in established diabetes. The presence of AN is typically measured by a battery of cardiovascular reflexes, developed primarily by Clarke and Ewing (12). In this study, we examined the natural progression of cardiovascular reflexes as recommended by the American Diabetes Association and the American Academy of Neurology guidelines (13,14). There have only been a few previous reports that comprehensively describe the natural history and progression of AN over time in terms of both symptoms and autonomic

function tests (15–18). This study was undertaken in a cohort of IDDM patients who were followed for 9 years to shed further light on the natural progression of clinical signs and symptoms as they relate to measurements of AN.

RESEARCH DESIGN AND METHODS

Subjects

In 1981, consecutive IDDM patients ($n = 76$) aged <40 years and with a duration of diabetes of <10 years who visited the Groote Schuur Hospital Diabetes Clinic over a 3-month period were invited to take part in this study. Patients who were being treated with drugs thought to interfere with autonomic nervous function or those with heart failure were excluded. These 76 IDDM subjects (43 men, 33

women), with a mean age of 28.5 years (range 16–41) and a mean duration of diabetes of 4.6 years (range 0.5–9.0), were originally studied using a standard questionnaire, a clinical examination, and a battery of five cardiovascular autonomic tests. Nine years later, the 57 available subjects (33 men, 24 women) were re-evaluated using the same protocol. Of the subjects from the original study, 15 had died and 4 could not be located.

Cardiovascular AN measurements

The five standard cardiovascular tests described by Clarke and Ewing (12) were measured. These measurements included R-R variation (the expiration-to-inspiration [E:I] R-R ratio), changes in heart rate with deep breathing (the E:I difference in beats per minute (Δ BPM) ratio), R-R variation with the Valsalva maneuver and with changes in posture, response of blood pressure to sustained handgrip, and resting heart rate.

Symptoms of autonomic neuropathy

The presence or absence of the following symptoms was assessed on both occasions by standard questionnaire: gastroparesis, diarrhea, impotence, loss of vaginal lubrication, hypoglycemic unawareness, and postural hypotension.

Statistical analysis

Only those 57 subjects studied on both occasions were included in the analysis. Univariate and multivariate repeated measures analysis of variance (ANOVA and MANOVA) were performed on each of the autonomic function tests to determine if the cardiovascular AN measures progressed significantly over the 9-year testing interval. The univariate model included only the constant (trials) effect. The multivariate model included the constant (trials), age, sex, and duration for each cardiovascular AN measurement. Progression of clinical signs and symptoms of AN was analyzed using the χ^2 test.

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AN, autonomic neuropathy; Δ BPM ratio, difference in beats per minute; E:I, expiration-to-inspiration.

RESULTS

Cardiovascular AN measurements

According to the scoring system described by Clarke and Ewing (12), initially 36% of the subjects overall had early AN and 11% of the subjects had definite AN (4). The results of univariate and multivariate tests are summarized in Table 1. Three of the measures of cardiac variation progressed over the study interval: the Valsalva maneuver and both of the deep breathing measurements ($P < 0.01$ for each in univariate tests). However, only the Valsalva maneuver progressed significantly ($P = 0.009$) over the study interval when age, sex, and duration of disease were included in the statistical model. The E:I Δ BPM approached statistical significance in the multivariate model ($P = 0.057$). All autonomic measurements were significantly worse in the 15 patients who died, compared with those in the survivors (Table 2). Causes of death included seven renal failures, four sudden unexplained deaths at home, two accidental deaths, one diabetic ketoacidosis, and one unknown.

Clinical signs and symptoms of autonomic impairment

Of the autonomic signs and symptoms recorded here, only symptoms of gastroparesis progressed significantly over the study interval (Table 3). They were present in 1 of the 52 subjects initially and in an additional 7 (13%) at the follow-up ($\chi^2 [1, n = 52] = 7.0, P < 0.01$). There were no apparent recoveries. None of the other signs or symptoms progressed significantly.

DISCUSSION

Progression of cardiovascular AN measures

The major observation in this study of IDDM subjects with relatively short durations of diabetes was the variable rate of progression of the measures of AN over a 9-year period. Some tests progressed in only certain subgroups of age, sex, and the duration of diabetes. The only cardiovascular AN test that appeared to deteriorate consistently over time was the Valsalva ratio. Although this deterioration was distributed somewhat differently for subjects of different ages, its effect remained significant overall, and the rate of deterioration (0.015/year) was more than

Table 1—Progression of cardiovascular measures (interval variables): within-subject effects

	n	df	Trial 1	Trial 2	Univariate P	Multivariate P
E:I R-R Ratio	57	1,53	1.35	1.28	0.008	0.433
E:I Δ BPM	55	1,51	23.73	17.73	0.000	0.057
Valsalva R-R ratio	48	1,44	1.60	1.47	0.009	0.002
Postural R-R ratio	56	1,52	1.071	1.068	0.778	0.657
Postural Δ sBP	54	1,50	6.56	5.70	0.561	0.445
Handgrip Δ dB	48	1,44	23.83	27.67	0.057	0.704
Resting heart rate	52	1,48	81.00	80.44	0.777	0.196

Data for trials 1 and 2 are means. Multivariate analysis was performed with age, gender, and duration of diabetes. sBP, systolic blood pressure; dB, diastolic blood pressure.

twice that expected (0.006/year) from cross-sectional studies of aging effects in normal subjects of a similar age range (19). In contrast, small but significant declines in Valsalva ratios and blood pressure responses to handgrip and increases in postural blood pressure changes over periods of 3 months to 5 years were found in a variable number of diabetic patients (4), in whom the data was apparently not corrected for age, sex, or duration of diabetes. It is well recognized that age has an effect on autonomic function. Negative correlations between age and heart rate responses to inspiration, Valsalva maneuver, and standing and positive correlations between age and blood pressure response to standing have been found (19–22). In our study, aging had clear effects on the E:I and Valsalva ratios and on orthostatic blood pressure changes, which were distinct from the effects of AN. In addition, sex differences that have been described, in particular resting heart rate (19) and response to sustained handgrip (4), are supported by our observations that men had lower blood pressure responses to sustained handgrip and slower heart rates than women. From our data,

the first cardiac autonomic nervous reflex to show definite deterioration in IDDM was the Valsalva ratio, and standardization for the effect of age should produce an even more sensitive measurement of autonomic changes.

The deterioration in Δ BPM with respiration and the failure of the change in E:I R-R variation suggest that Δ BPM may be a more consistent measure of deterioration of the respiratory cardiac rate reflexes. There was >20% deterioration with each method of measurement, substantially more than expected from cross-sectional age differences seen in normal control subjects (19); yet the deterioration of the Δ BPM measure was nearly significant, while the E:I R-R was not. Although differences may be due to measurement error, they are likely caused by the greater effects of age and sex on the E:I ratio. These data suggest that there is a need for standardization for both of these variables. In a group of IDDM patients with normal E:I Δ BPM at baseline followed for 10–15 years, this measure declined significantly by 0.02/year, but there was no significant deterioration in those with abnormal E:I Δ BPM at com-

Table 2—Comparison of autonomic function tests in patients who died versus survivors

	Deceased	Survivors	P
n	15	57	—
E:I R-R ratio	1.16 \pm 0.04	1.35 \pm 0.03	0.001
E:I Δ BPM	11 \pm 2.03	24 \pm 1.52	0.001
Valsalva R-R ratio	1.3 \pm 0.06	1.6 \pm 0.04	0.0001
Postural R-R ratio	1.02 \pm 0.01	1.07 \pm 0.01	0.019
Postural Δ sBP	16.5 \pm 3.74	6.5 \pm 0.96	0.001
Handgrip Δ dB	14.1 \pm 2.98	23.8 \pm 1.69	0.013
Resting heart rate	90.5 \pm 2.18	81 \pm 2.12	0.034

Data are means \pm SD. Significance of numeric values was derived by one-way analysis of variance and prevalence data by χ^2 test. sBP, systolic blood pressure; dB, diastolic blood pressure.

Table 3—Progression of prevalence of clinical signs and symptoms of autonomic impairment

	Final negative	Final positive	n	χ^2	P
Gastroparesis			52	7.00	<0.01
Initially negative	44 (85)	7 (13)			
Initially positive	0 (0)	1 (2)			
Diarrhea			52	Undefined	
Initially negative	51 (98)	1 (2)	$t = -1.0$		NS
Initially positive	0 (0)	0 (0)			
Impotence			29	0.20	NS
Initially negative	22 (76)	2 (7)			
Initially positive	3 (10)	2 (7)			
Loss of vaginal lubrication			23	Undefined	
Initially negative	21 (91)	2 (9)	$t = -0.09$		NS
Initially positive	0 (0)	0 (0)			
Hypoglycemia unawareness			52	0.67	NS
Initially negative	46 (88)	4 (8)			
Initially positive	2 (4)	0 (0)			
Symptomatic postural hypotension			52	0.20	NS
Initially negative	50 (96)	1 (2)			
Initially positive	1 (2)	0 (0)			

Data are frequency (% of n) unless otherwise indicated. The test applied to these repeated measures contingency tables was McNemar's symmetry χ^2 . In one-way tables (those in which both cells in a row are empty), the dependent t test was used to indicate significance of progression.

mencement (15). We cannot make this distinction, since all measures of autonomic function were significantly worse in the patients who died. Similarly, Sundkvist and Lilja (17) found no deterioration in the E:I ratio in patients with AN investigated after 6 years and a variable response in those without AN originally.

None of the other autonomic tests showed significant changes over the study period. The postural R-R showed very little mean change within subjects and a very strong effect of age between subjects, suggesting that this measure must be carefully standardized for age effects before being analyzed. The two blood pressure responses, postural and handgrip-stimulated, actually showed slight improvement over time. Interestingly, the only effect of duration of diabetes, which had been actively range-restricted in this subject pool (duration <10 years), was a within-subject effect on the postural blood pressure response. Subjects with longer durations of IDDM deteriorated somewhat in the postural blood pressure response, while those with shorter durations improved dramatically, accounting for the overall slight (but nonsignificant) improvement noted. The blood pressure response to handgrip was strongly affected by sex both between and within

subjects, suggesting that large-scale normative studies should be used to standardize this measure by sex before the effects of AN can be properly analyzed. Resting heart rate remained essentially unchanged throughout this study period, and the strong between-subject effect of sex suggests that, unless standardized by sex, only gross abnormalities should be considered evidence of autonomic involvement.

Progression of symptoms

The symptoms of gastroparesis, diarrhea, impotence, loss of vaginal lubrication, and hypoglycemic unawareness and symptoms of postural hypotension occurred in 13, 2, 7, 9, 8, and 2% of subjects, respectively, by the end of the study period (Table 2). The small number of symptomatic subjects, as well as the tendency for certain of the symptoms, for example hypoglycemic unawareness, to recover mitigated against a significant increase in the frequency of these symptoms, with the exception of gastroparesis. There was no correlation of the onset of gastroparesis with any of the tests of autonomic function, and its clinical significance is unclear. Some degree of reversibility of diarrhea has been reported

previously in 2 of 11 patients (15), as has improvement of erectile dysfunction (16).

CONCLUSIONS— Our data suggest that the Valsalva-stimulated R-R response is highly susceptible to changes in autonomic function over time and is evidently robust against longitudinal measurement effects. The other measure of respiratory cardiovascular responsiveness, the E:I ratio, should be scrutinized in much greater detail because the two methods used for calculation in this study were different in their sensitivities to apparent changes in autonomic function over time. The clear effects of age and sex on certain tests suggest that broad-based normative and longitudinal studies, such as this study and that of O'Brien et al. (19), are needed to establish further standardization for the effects of age and sex.

Gastroparesis is the only clinical sign or symptom of AN that appeared to increase in frequency, underscoring the need to perform objective quantitative tests of autonomic function in identifying patients with autonomic dysfunction.

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