Cardiac Autonomic Neuropathy in Diabetic Patients: Influence of Diabetes Duration, Obesity, and Microangiopathic Complications—The French Multicenter Study

P. Valensi, J. Pariès, J.R Attali, and the French Group for Research and Study of Diabetic Neuropathy

The current study sought to examine in a large series of diabetic patients the prevalence of symptoms of autonomic neuropathy and subclinical cardiac autonomic neuropathy (CAN) and their determinants, particularly the influence of diabetes duration, obesity, and microangiopathic complications. Three hundred ninety-six patients, 245 type 1 and 151 type 2, were recruited in 7 French departments of diabetology. CAN was detected by measuring heart rate variability during 3 standardized tests: deep-breathing, Valsalva, and lying-to-standing tests. At least 24.5% of the patients had one or more symptoms suggesting overt autonomic neuropathy. They were older than those free of dysautonomic symptom ($P < .001$). The deep-breathing test correlated negatively with body mass index (BMI) in type 2 diabetic patients ($P < .0001$). In the whole population, the deep-breathing and Valsalva tests correlated negatively with diabetes duration ($P = .0004$ and .019, respectively) and the log urinary albumin/creatinine ratio ($P < .002$ and .001, respectively). The prevalence of CAN (51%) was higher than the prevalence of other diabetic complications. The rate of moderate and severe CAN (defined by 2 or 3 abnormal CAN function tests) was higher in type 1 than in type 2 diabetic patients ($P = .031$). It correlated with diabetes duration ($P = .026$) and was higher in the patients with retinopathy than in those without ($P = .035$). Among type 2 diabetic patients, the prevalence of CAN was higher in the obese ones ($P = .033$); in a logistic regression taking age, diabetes duration, and obesity as independent variables, CAN was associated independently with obesity ($P = .034$). Mild or moderate CAN was found in 33.8% and 13.0% of the 80 patients with diabetes duration less than 18 months. We conclude that CAN is found early in the course of diabetes and should be considered as a prognostic marker of microangiopathic complications. Obesity could be involved in the impairment of CAN function in type 2 diabetics and body weight control could provide an approach to reducing neuropathic complications.

AUTONOMIC NEUROPATHY can affect various organs. It can be disabling. A poor prognostic value has been attributed to cardiac autonomic neuropathy (CAN) even at a subclinical stage, as the increase in mortality is mainly due to cardiovascular events.[1,2]

Ewing et al proposed assessing CAN on a battery of 5 standard bedside tests.[3] These tests are widely used because they are easily performed, are reliable provided the results are compared with an age-matched control group,[4-7] and have good reproducibility .[8] According to these tests, CAN has been found in 20% to 70% of diabetic subjects.[9-11] In a previous study we found CAN in 63% of the patients, and this complication was associated significantly with retinopathy and peripheral neuropathy. However, CAN was present in more than half of patients without retinopathy or nephropathy and in one third of patients with a normal electrophysiological investigation.[12] Some studies also suggest that CAN function is often impaired early in the course of diabetes, even within the first 2 years following diagnosis.[12,15] Peripheral autonomic function also seems to be impaired in newly diagnosed type 2 diabetic patients.[16]

The role of chronic hyperglycemia in nerve dysfunction is suggested by cross-sectional studies[12,17] and follow-up studies.[18-20] Optimized glycemic control seems to slow down the impairment in CAN function tests in type 1 diabetic patients.[21,22]

The hypothesis of the involvement of obesity in cardiac autonomic dysfunction in type 2 diabetes may be raised inasmuch as a few reports have described impairments in cardiac autonomic function tests in nondiabetic obese patients. We found that more than 50% of a series of 121 unselected nondiabetic obese subjects had at least one abnormal CAN function test.[23] Moreover, it has been shown that these tests are more impaired in obese type 2 diabetic patients than in non-obese ones.[24]

Other risk factors have been mentioned as being related to diabetic neuropathy, including serum lipids, hypertension, smoking,[25] use of alcohol,[26] and male gender.[27] CAN has also been found to be significantly associated with proliferative diabetic retinopathy during the second decade of type 1 diabetes[28] and with nephropathy.[29]

In fact, few epidemiological data are available on diabetic autonomic neuropathy.[30,31] The present work aims to examine in a large series of diabetic patients the prevalence of symptoms of autonomic neuropathy and subclinical CAN, and the determinants of these diabetic complications, particularly the influence of duration of diabetes, obesity, and microangiopathic complications.

PATIENTS AND METHODS

Patients

Three hundred ninety-six patients, 226 males and 170 females, were included. They were recruited from the diabetic patients consecutively hospitalized in eight French departments of diabetology during a period of 6 months. Patients were selected after excluding those with a pathologic condition likely to disturb the CAN function tests, ie,

From the Department of Endocrinology-Diabetology-Nutrition, Paris-Nord University, Bondy, France.

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Address reprint requests to Professeur Paul Valensi, Service d'Endocrinologie-Diabétologie-Nutrition, Hôpital Jean Verdier, Avenue du 14 Juillet, 93143, Bondy Cedex, France.

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Table 1. Clinical Characteristics of the Patients Studied

	Type 1	Type 2	*P*
No. of subjects	245	151	
Males/females	144/101	82/69	.371
Age (yr)	36.1 ± 0.8	45.5 ± 0.8	.0001
Duration of diabetes (yr)	10.0 ± 0.6	6.3 ± 0.5	.0001
Height (m)	1.69 ± 0.01	1.66 ± 0.01	.002
Weight (kg)	65.8 ± 0.7	74.6 ± 1.4	.0001
BMI (kg/m^2)	23.0 ± 0.2	27.1 ± 0.4	.0001
Obesity*†	11 (4.5)	38 (25.7)	.0001
Tobacco consumption (g/d)	7.8 ± 0.8	4.5 ± 0.7	.003
Systolic blood pressure (mm Hg)	120.6 ± 1.1	126.4 ± 1.4	.001
Diastolic blood pressure (mm Hg)	76.8 ± 0.8	79.9 ± 0.9	.010
Peripheral arterial disease†	7 (2.9)	6 (4.2)	.341
Cataract†	13 (5.3)	8 (5.6)	.591
Retinopathy†	70 (28.7)	23 (16.2)	.002
Maculopathy†	18 (7.3)	10 (6.6)	.271
Albuminuria (> 20 μg/min)†‡	46 (24.3)	26 (21.5)	.078

NOTE. Results are expressed as means ± SEM.
*Defined as BMI > 30 kg/m^2.
†Number (% of patients).
‡Measured in 310 patients.

coronary heart disease, heart failure, respiratory disease, anemia, fever, or hypertension (> 160/90 mm Hg), as well as patients taking vasodilators, antihypertensives, neuroleptics. or antidepressants, and patients having other causes of neuropathy (uremia, chronic alcoholism, hypothyroidism, neoplasia). There were 245 type 1 diabetic patients and 151 type 2 diabetic patients. Among the type 2 diabetic patients, 36 were treated with insulin and 97 with oral hypoglycemic agents. Mean age (±SEM) was 39.6 (±0.6) years. Mean duration of diabetes was 8.6 (±0.4) years. Glycemic control was poor as shown by fructosamine level (309 ± 5 μmol/L ; reference value, <280 μmol/L) and by fasting and postprandial blood glucose (9.44 ± 0.21 mmol/L and 11.19 ± 0.24 mmol/L, respectively).

The assessment of diabetic complications was complete in nearly all patients and recorded on case report forms. Thirteen patients (3.3%) had clinical evidence of lower limb arterial disease. A recent ophthalmological examination, including fundus ophthalmoscopy, had been performed in 364 patients. Twenty-one (5.8%) had a cataract. Retinopathy was detected in 93 cases (25.5%) and was proliferative in 17; maculopathy was detected in 28 patients (7.7%) and was edematous in 24 cases and ischemic in the other 4. Clinical signs of peripheral polyneuropathy (abolition of ankle jerks, abnormal pin-prick sensation, or abnormal big toe position sensation) were found in 30.6% of the patients. The urinary albumin excretion rate was measured either on a night sample or on a 24-hour urine sample in 310 patients. It was increased (> 20 μg/min) in 72 patients (23.2%).

Clinical and biological features of type 1 and type 2 diabetic patients are shown separately in Tables 1 and 2. Type 1 patients were younger, had a lower body mass index (BMI), a higher rate of retinopathy, lower blood pressure, and higher tobacco consumption.

The CAN function tests were also performed in 40 healthy subjects aged 16 to 62 years.

Methods

Overt autonomic neuropathy was assessed on symptomatic postural hypotension, nocturnal diarrhea, gastroparesia, sudomotor disorders, urinary symptoms, or impotence without other evident causes (arterial, hormonal, or psychogenic).[32]

Three standard tests for subclinical CAN were performed as previously described.[3,12] Briefly, they consisted of measuring heart rate variations during deep-breathing, lying-to-standing, and Valsalva tests. They were performed with the aid of AUTOCAFT , a microcomputer-based system used on a BBC Master system (ACORN Computers Ltd, Cambridge, UK).[12,33] In each center the tests were performed by the same investigator and all investigators previously trained together on this material. The result of the deep-breathing test (6 cycles per minute) was expressed as the mean value for the ratio of maximal RR interval during breathing-out and minimal RR during breathing-in. The result of the lying-to-standing test was expressed as the ratio of the longest RR interval (about the 30th beat) over the shortest RR interval (about the 15th beat). The Valsalva test was done 3 times consecutively and the mean value for the Valsalva ratio (VR) was calculated. The results of these 3 standard tests were compared with the data collected in a series of 120 healthy controls who were investigated similarly with the

Table 2. Biological Characteristics of the Patients Studied

	Type 1	Type 2	*P*
Fasting blood glucose (mmol/L)	9.45 ± 0.31	9.44 ± 0.28	.971
Post prandial blood glucose (mmol/L)	11.19 ± 0.34	11.19 ± 0.38	.999
Fructosamine (μmol/L)	323 ± 7	285 ± 9	.001
Urinary albumin excretion rate (μg/min)	22.7 ± 4.2	39.4 ± 17.0	.342
Urinary albumin/creatinine (μg/mmol)	5.15 ± 1.73	16.1 ± 9.0	.235

NOTE. Results are expressed as means ± SEM.

Table 3. Prevalence of Symptoms Potentially Due to Autonomic Dysfunction in Type 1 and Type 2 Diabetic Patients

	Type 1		Type 2	
	No.	%	No.	%
Postural dizziness	20	8.4	19	13.7
Symptoms of gastroparesia	9	3.8	5	3.6
Diarrhea	5	2.1	3	2.1
Sudomotor disorders	11	4.6	9	6.5
Symptoms of neural bladder	11	4.6	13	9.3
Weak erection*	17	12.1	18	23.1

NOTE. Autonomic symptoms were assessed in 376 patients, of whom 237 had type 1 and 139 had type 2 diabetes.

*Only 218 of the 226 men were questioned about weak erection.

AUTOCAFT device by Armstrong et al.[6] The data were log-transformed as previously done by these authors. CAN was considered to be mild, moderate, or severe when 1, 2, or all 3 tests were abnormal according to age, respectively, as previously described.[34]

Postural hypotension was determined by measuring blood pressure after 10 minutes in the recumbent position and again after 1 minute in the standing position. Postural hypotension was defined as a drop in systolic blood pressure of ≥20 mm Hg or in diastolic blood pressure ≥10 mm Hg.

All patients gave informed consent for these tests.

Statistical Methods

Results were expressed as mean ± SEM values. Comparisons between continuous variables were studied by the unpaired Student's *t* test. Correlations between 2 continuous variables were performed according to a linear regression model and correlations between 2 discrete variables were analysed by chi-square tests. Multivariate analyses were performed according to a logistic regression model with CAN as the dependent variable. Statistical analyses were carried out using the SPSS software package[35] and a Hewlett Packard computer (Palo Alto, CA).

RESULTS

Symptoms of Autonomic Neuropathy

Presence or absence of autonomic symptoms was recorded in 376 patients. Symptoms of postural dizziness were found in 39 patients (10.4%). They did not correlate with a greater postural drop in systolic or diastolic blood pressure. Symptoms of gastroparesia, nocturnal diarrhea, sudomotor disorders, and voiding difficulties suggesting neurogenic bladder were present respectively in 14 (3.7%), 8 (2.1%), 20 (5.3%), and 24 (6.3%) patients, and 35 of 218 men (16.0%) complained of impotence. The percentage of the symptoms did not differ significantly between type 1 and type 2 diabetic patients (Table 3).

Altogether at least 92 patients (24.5%) had one or more symptoms suggesting overt autonomic neuropathy. These patients were older than those free of any dysautonomic symptom (42.2 ± 0.9 *v* 37.9 ± 0.9 years, $P < .001$). The prevalence of overt dysautonomia was also significantly higher in the patients with clinical signs ($\chi^2 = 10.81$, $P = .001$) or symptoms (pain, numbness, or paresthesia) ($\chi^2 = 19.26$, $P < .0001$) of peripheral neuropathy. It was slightly higher (not significant [NS]) in type 2 than in type 1 diabetic patients. In type 2 patients, BMI was very similar in the 35 patients with and those without overt dysautonomia (27.5 ± 1.0 kg/m^2 and 27.0 ± 0.5 kg/m^2, respectively).

Cardiac Autonomic Function Tests

Deep-breathing, lying-to-standing, and Valsalva tests were performed correctly by all control subjects and by 373, 373, and 358 diabetic patients, respectively. With age taken into account, the results of the 3 tests in our control subjects were strictly within the range of values for the normal series published by Armstrong et al.[6] Compared with this series, the results of the deep-breathing, lying-to-standing, and Valsalva tests were abnormal in 79 (21.2%), 125 (33.5%), and 74 (20.7%) diabetic patients, respectively.

The results of the 3 standard tests did not differ significantly according to gender or type of diabetes. They did not correlate with fasting or postprandial glycemia or serum fructosamine. However, negative correlations were found between the deep-breathing and Valsalva tests and age and duration of diabetes (Table 4). Negative correlations were also found between the deep-breathing and lying-to-standing tests and systolic blood pressure in the standing position, and between the deep-breathing test and diastolic blood pressure in the standing position. The deep-breathing test correlated negatively with BMI in the whole population and in type 2 diabetic patients, but not in type 1 diabetic patients. Negative correlations were also found between the deep-breathing and Valsalva tests and the log urinary albumin/creatinine ratio (Table 4). After adjusting for age, duration of diabetes, and BMI, the deep-breathing and Valsalva tests correlated significantly in the whole population with the log urinary albumin/creatinine ratio ($r = -0.158$, $P = .016$ and

Table 4. Correlations With the Three Standard Cardiac Autonomic Function Tests

	Deep Breathing			Lying-to-Standing			Valsalva		
	All Patients (N = 373)	Type 1 (n = 230)	Type 2 (n = 143)	All Patients (N = 373)	Type 1 (n = 228)	Type 2 (n = 145)	All Patients (N = 358)	Type 1 (n = 225)	Type 2 (n = 133)
Age	−0.489 (<.0001)	−0.483 (<.0001)	−0.430 (<.0001)				−0.210 (<.0001)	−0.248 (<.001)	−0.123 (.163)
Duration of diabetes	−0.185 (.0004)	−0.214 (<.001)	−0.261 (.003)				−0.126 (.019)	−0.161 (.017)	−0.121 (.179)
Standing systolic blood pressure	−0.202 (.010)	−0.176 (.010)	−0.216 (.014)	−0.132 (<.01)	−0.156 (.022)	−0.170 (.052)			
Standing diastolic blood pressure	−0.163 (.002)	−0.154 (.023)	−0.139 (.116)						
BMI	−0.268 (<.0001)	−0.033 (NS)	−0.324 (<.0001)						
Log urinary albumin/creatinine*	−0.201 (<.002)	−0.122(NS)	−0.220 (.038)				−0.218 (<.001)	−0.211 (0.012)	−0.192 (.082)

NOTE. *P* values are shown in parentheses.

*Log urinary albumin/creatinine was measured in 244 patients, 151 type 1 and 93 type 2.

$r = -0.186$, $P = .006$, respectively) but not with blood pressure.

When the 3 standard tests were considered together, mild, moderate, and severe CAN were detected, respectively, in 31.0%, 16.1%, and 3.9% of the patients. The total prevalence of CAN (51%) was higher than the prevalence of the other complications of diabetes. If only moderate or severe CAN was considered, the prevalence of CAN (20%) was higher than the prevalence of cataract (5.8%) or clinically evident peripheral arterial disease (3.3%) or similar to the prevalence of retinopathy (25.5%) or nephropathy (23.2%). There was no statistically significant association between CAN and cataract, peripheral neuropathy, or arterial disease. The prevalence of CAN at any stage did not differ significantly according to the department where the patients were investigated ($P = .10$), nor between smokers and nonsmokers, nor between males and females nor between type 1 and type 2 diabetic patients (54.1% and 45.4%, respectively; $P = .125$). However, the rate of moderate and severe CAN was higher in type 1 (18.2% and 4.8%) than in type 2 patients (12.3% and 2.3%) ($P = .031$). It correlated with duration of diabetes ($P = .026$), but was not statistically associated with symptoms of autonomic neuropathy. It was higher in patients with background retinopathy (59.1%) or proliferative retinopathy (80.0%) than in those without retinopathy (49.4%) ($\chi^2 = 6.68$, $P = .035$).

Among type 2 diabetic patients, the total prevalence of CAN in the obese patients (BMI $>$ 30 kg/m^2) was significantly higher than in those with BMI less than 30 kg/m^2 (60.6% *v* 40.0%, $\chi^2 = 4.127$, $P = .033$). In a logistic regression taking CAN as a dependent variable and age, duration of diabetes, and obesity as independent variables, CAN was significantly and independently associated only with obesity ($P = .044$). Such an association between CAN and BMI was not found in type 1 diabetic patients.

Autonomic Neuropathy in Recently Diagnosed Diabetes

In 80 patients, the duration of diabetes was less than 18 months (mean, 5.9 months). Forty-five had type 1 diabetes and 35 type 2 diabetes. Postural dizziness was found in 12.5% of these 80 patients (13.6% of the type 1 diabetic patients). Mild or moderate CAN was found in 33.8% and 13.0% of these 80 patients, respectively (31.8% and 13.6% of the type 1 diabetic patients). These percentages were far higher than the prevalence of cataract (5.3%), retinopathy (6.7%), or lower limb arterial disease (2.5%) in these patients.

DISCUSSION

This multicenter study included nearly 400 diabetic patients. Symptoms suggesting autonomic neuropathy were present in about 25% of these patients. This prevalence was lower than in another multicenter study by the DIACAN study group,[30] possibly because of a shorter mean duration of diabetes in the present study. CAN was assessed by 3 standard tests of heart rate variations that mainly depend on parasympathetic control and postural hypotension, which results from sympathetic neuropathy. Spectral analysis of heart rate and blood pressure variations provides a more specific assessment of vagal and sympathetic impairment but does not permit identifying clear-cut disorders when comparing patients to normal subjects. As previously done by several investigators,[28,36] CAN was here defined on the basis of at least 1 abnormal standard test. It was found in about 50% of the patients. Even if only moderate or severe CAN (defined by 2 or 3 abnormal standard tests respectively) was considered, CAN appeared as the most frequent complication of diabetes or as frequent as retinopathy or nephropathy. The 50% prevalence of CAN at any stage is very similar to that in a series of 500 patients reported by Ewing et al, where the results were not analyzed according to age,[9] but it is higher than in the DIACAN study, where CAN was defined by at least 2 out of 6 abnormal cardiac autonomic function criteria.[30] Postural dizziness, like in previous reports,[12] was far less frequent (10.3%) and did not correlate with a greater postural drop in blood pressure, which suggests that severe sympathetic dysfunction is a rare complication in comparison to parasympathetic dysfunction.

As in a previous study,[12] a significant negative correlation was found in the diabetic patients between the standard CAN function tests and age, which points out the importance of interpreting the tests according to age. Negative correlations were also found between these tests and duration of diabetes as previously reported.[12,37,38] However, CAN may occur very early in diabetes. Indeed CAN was found here in about 47% of the patients with a duration of diabetes shorter than 18 months. These results can be compared with those in previous reports of CAN dysfunction shortly after treatment of initial ketosis and in both type 1 and type 2 diabetic patients with diabetes known for less than 2 years.[15,39] The impairment in the cardiac autonomic function tests in recently diagnosed type 1 diabetes may result from autoimmune processes. Antisympathetic ganglia antibodies have been found in some type 1 diabetic patients who had a reduced increase in plasma catecholamines during the postural test.[40]

The present study failed to disclose any correlation between the CAN function tests and parameters for glycemic control. Hemoglobin A_{1c} (HbA_{1c}) was not measured in a central laboratory, and correlations between RR variations and HbA_{1c} levels had been previously reported.[12,41] The improvement in the heart rate variability after the improvement of glycemic control in recently diagnosed type 1 diabetes also pleads in favor of the metabolic hypothesis.[21]

The negative correlation between the deep-breathing test and BMI found only in type 2 diabetic patients is particularly relevant in clinical practice since most of these patients are overweight. In previous studies we found for nondiabetic obese patients impairments in the standard CAN function tests in about 50% of the cases,[23] a reduced value for the vagal spectral peak of heart rate variations,[42] and a reduction of the vasoconstrictive peripheral response to sympathetic activation.[43] Other investigators have also reported an association of impairment in autonomic nerve function with increasing overweight.[44] Obese subjects may have difficulty in expending the lungs during a deep-breathing test, leading to attenuation of chest reflexes.[45] However, we have not found any relationship between these changes and gynoid or android distribution of adiposity. The influence of obesity on CAN function tests has been reported in type 2 diabetic patients.[24,46] This factor may be particularly important in recently diagnosed type 2 diabetes as suggested

also by the peripheral autonomic impairment in such patients.[16] The high prevalence of CAN in our patients with recently diagnosed type 2 diabetes (45.4%) again supports this finding.

The significant negative correlations between the deep-breathing and lying-to-standing tests and blood pressure in this normotensive diabetic population suggests that the degradation of RR variability is accompanied by an increase in blood pressure possibly due to a vagosympathetic imbalance and an override of sympathetic tone. However, these correlations did not remain significant after adjustment for age, duration of diabetes, and BMI.

An association between CAN and specific microangiopathic diabetic complications has been reported many times. Likewise, significant correlations between CAN function tests and retinopathy, particularly proliferative retinopathy, and an increase in the urinary albumin excretion rate were found here. A significant association between CAN and proliferative retinopathy has been reported in type 1 diabetic patients.[28,47,48] This suggests that autonomic neuropathy may contribute to the development of retinal neovascularization all the more so as retinal vessels have receptors of the sympathoadrenal system.[49] Loss of responsiveness of the retinal vessels to metabolic and hemodynamic stimuli could lead to uncontrolled retinal hyper- or hypoperfusion. However, the association between CAN and proliferative retinopathy may not imply a causative relationship. It may only suggest that CAN is a risk indicator, a marker of processes that underlie both the development of autonomic neuropathy and proliferative retinopathy. In particular the aldose-reductase pathway is involved in the development of diabetic neuropathy[50] and may similarly be responsible for intracellular accumulation of sorbitol in retinal pericytes.[51] An increasing attenuation of 24-hour vagal activity has also been found to be associated with the severity of nephropathy,[29] and the prevalence of CAN has been shown to correlate with the urinary albumin excretion rate.[36] This association is consistent with common pathogenetic mechanisms, particularly those related to poor metabolic control. Nevertheless this may also suggest that autonomic neuropathy has a pathogenic role in the development of diabetic nephropathy. There is some evidence for a neural regulatory function of the kidney. After renal nerve stimulation in rats, vascular resistances increase with a consequent reduction in the glomerular filtration rate, and proximal water and sodium reabsorption is enhanced.[52] A 10-year prospective study has shown that the glomerular filtration rate decreased more than expected in type 1 diabetic patients with autonomic neuropathy.[53] One may therefore hypothesize that the loss of the neural control of renal hemodynamics may make the kidney more vulnerable to the hemodynamic effect of systemic blood pressure. Finally, mortality from cardiovascular events is increased by nephropathy,[54,55] and reduced cardiac vagal activity seems to be an important factor in the pathophysiology of sudden cardiac death.[1,2] The association of CAN and nephropathy may be coincidental. It may also suggest that an impairment in vagal activity is involved in the pathophysiology of increased cardiac death rates in type 1 diabetic patients with nephropathy.

In conclusion, in this series of nonhypertensive diabetic patients, the prevalence of CAN is the highest of all the chronic diabetic complications. CAN is found very early in the course of diabetes. Obesity seems to be involved in the impairments of the cardiac autonomic function found in type 2 diabetic patients. This factor must therefore be taken into account when interpreting the results for these patients. Body mass control could provide an important approach to reducing neuropathic complications. The correlation of CAN with microangiopathic complications suggests either common pathogenetic factors or the involvement of autonomic neuropathy in the onset or the aggravation of hemodynamic disorders in the retina and the glomeruli. CAN should at the very least be considered to be a marker of microangiopathic complications.

APPENDIX

Participants in the French Group for Research and Study of Diabetic Neuropathy are: Professors Jean-Raymond Attali and Paul Valensi (Jean Verdier Hospital, Bondy), Professor Gérard Cathelineau (Saint-Louis Hospital, Paris), Professor Pierre Fossati and Dr Odile Verier-Mine (Lille hospital), Professor Louis Monnier (La Peyronie Hospital, Montpellier), Professor Jean-Yves Pouget and Philippe Vague (La Timone Hospital, Marseille), Professor Marc Leutenegger (Robert Debré Hospital, Reims), Professor Jean Lubetzki and doctor Michèle Duet (Lariboisière Hospital, Paris), Professor Jean-Marie Brogard, and Dr Dominique Paris (Civil Hospitals, Strasbourg).

REFERENCES

1. Ewing DJ, Campbell IW, Clarke BF: The natural history of diabetic autonomic neuropathy. Q.J Med 49:95-108, 1980

2. Ziegler D: Diabetic cardiovascular autonomic neuropathy. Prognosis, diagnosis and treatment. Diabetes Metab Rev 10:339-383, 1994

3. Ewing DJ, Campbell JW, Clarke BF: Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. Ann Intern Med 92:308-311, 1980

4. Wieling W, Van Brederode JFM, De Rijk LG, et al: Reflex control of heart rate in normal subjects in relation to age: A data base for cardiac vagal neuropathy. Diabetologia 22:163-166, 1992

5. O'Brien IAD, O'Hare P, Corral RJM: Heart rate variability in healthy subjects: Effect of age and the derivation of normal ranges for tests of autonomic function. Br Heart J 55:348-354, 1986

6. Armstrong KM, Bradbury JE, Ellis SH, et al: A study of peripheral diabetic neuropathy. The application of age-related reference values. Diabet Med 8:S94-S99, 1991 (suppl)

7. Belmin J, Valensi P: Diabetic neuropathy in elderly patients. What can be done? Drugs Aging 6:416-429, 1996

8. Valensi P, Attali J.R, Gagant S: Reproducibility of parameters for assessment of diabetic neuropathy. Diabet Med 10:933-939, 1993

9. Ewing DJ, Martyn CN, Young RJ, et al: The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 8:491-498, 1985

10. Pfeifer MA, Weinberg CR, Cook DL, et al: Correlations among autonomic, sensory, and motor neural function tests in untreated non-insulin dependent diabetic individuals. Diabetes Care 8:576-584, 1985

11. Valensi P, Attali JR, Sachs RN, et al: Intérêt comparé de l'enregistrement ECG des 24 h et des manoeuvres standardisées dans la détection et l'exploration de la neuropathie autonome cardiaque chez le diabétique. Diabetes Metab 13:205-209, 1987

12. Valensi P, Huard JP, Giroux C, et al: Factors involved in cardiac autonomic neuropathy in diabetic patients. J Diabetes Complications 11:180-187, 1997

13. Fraser DM, Campbell JW, Ewing DJ, et al: Peripheral and autonomic nerve function in newly diagnosed diabetes mellitus. Diabetes 26:546-550, 1977

14. Pfeifer MA, Weinberg CR, Cook DL, et al: Autonomic neural dysfunction in recently diagnosed diabetic subjects. Diabetes Care 7:447-453, 1984

15. Ziegler D, Cicmir I, Mayer P, et al: Peripheral and autonomic nerve dysfunction in newly diagnosed insulin-dependent diabetes. Transplant Proc 18:1593-1594, 1986

16. McDaid EA, Hayes JR, Monaghan B, et al: Peripheral autonomic impairment in patients newly diagnosed with type II diabetes. Diabetes Care 17:1422-1427, 1994

17. The Diabetes Control and Complications Trial (DCCT): Design and methodologic considerations for the feasibility phase. Diabetes 35:530-545, 1986

18. Hillson RM, Hockaday TDR, Newton DJ: Hyperglycaemia is one correlate of deterioration in vibration sense during the 5 years after diagnosis of type 2 (non-insulin-dependent) diabetes. Diabetologia 26:122-126, 1984

19. Young RJ, McIntyre CCA, Martyn CN, et al: Progression of subclinical polyneuropathy in young patients with type 1 (insulin-dependent) diabetes: Associations with glycaemic control and microangiopathy (microvascular complications). Diabetologia 29:156-161, 1986

20. Graf RJ, Halter JB, Pfeifer MA, et al: Glycemic control and nerve conduction abnormalities in non-insulin-dependent diabetic subjects. Ann Intern Med 94:307-311, 1981

21. Jakobsen J, Christiansen JS, Kristoffensen I, et al: Autonomic and somatosensory nerve function after 2 years of continuous subcutaneous insulin infusion in type 1 diabetes. Diabetes 37:452-455, 1988

22. The Diabetes Control and Complications Trial Research Group: The effect of intensive diabetes therapy on the development and progression of neuropathy. Ann Intern Med 122:561-568, 1995

23. Valensi P, Ngoc PTB, Lormeau B, et al: Cardiac autonomic function in the obese patients. Int J Obes 19:113-118, 1995

24. Bergstrom B, Lilja B, Osterlin S, et al: Autonomic neuropathy in non-insulin-dependent (type II) diabetes mellitus: Possible influence of obesity. J Intern Med 227:57-63, 1990

25. Maser RE, Steenkiste AR, Dorman JS, et al: Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh Epidemiology of Diabetic Complications Study. Diabetes 38:1456-1461, 1989

26. McCulloch DK, Campbell IW, Prescott RJ, et al: Effect of alcohol intake on symptomatic peripheral neuropathy in diabetic men. Diabetes Care 3:245-247, 1980

27. The DCCT Research Group: Factors in development of diabetic neuropathy. Baseline analysis of neuropathy in feasibility phase of Diabetes Control and Complications. Trial (DCCT). Diabetes 37:476-481, 1988

28. Krolewski AS, Berzilay J, Warram JH, et al: Risk of early-onset proliferative retinopathy in IDDM is closerly related to cardiovascular autonomic neuropathy. Diabetes 41:430-437, 1992

29. Molgaard H, Christensen PD, Sorensen KE, et al: Association of 24-h cardiac parasympathetic activity and degree of nephropathy in IDDM patients. Diabetes 41:812-817, 1992

30. Ziegler D, Gries FA, Mühlen H, et al: Prevalence and clinical correlates of cardiovascular autonomic and peripheral diabetic neuropathy in patients attending diabetes centers. Diabetes Metab 19:143-151, 1993

31. O'Brien IAD, O'Hare JP, Lewin IG, et al: The prevalence of autonomic neuropathy in insulin-dependent diabetes mellitus: A controlled study based on heart rate variability. Q J Med 61:957-967, 1986

32. Valensi P: La dysautonomie diabétique. Gravité, méthodes de détection, tentatives thérapeutiques. Ann Med Int (Paris) 142:31-41, 1991

33. Smith SE: AUTOCAFT. Lancet 2:772, 1988

34. Valensi P, Attali JR: Pourquoi et comment faut-il rechercher une neuropathie autonome cardiovasculaire chez les diabétiques? Diabetes Metab 23:351-356, 1997

35. SPSS: SPSS/PC + Advanced Statistics. V4.0 1. Chicago, IL, SPSS, 1992

36. Spallone V, Barini A, Gambardella S, et al: Relationship between autonomic neuropathy, 24-h blood pressure profile, and nephropathy in normotensive IDDM patients. Diabetes Care 17:578-584, 1994

37. Bergström B, Lilja B, Osterlin S, et al: Autonomic neuropathy in type 1 diabetes: Influence of duration and other diabetic complications. Acta Med Scand 222:147-154, 1987

38. Masaoka S, Lev-ran A, Hill LR, et al: Heart rate variability in diabetes: Relationship to age and duration of the disease. Diabetes Care 8:64-68, 1985

39. Lehtinen JM, Niskanen L, Hyvönen K, et al: Nerve function and its determinants in patients with newly-diagnosed type 2 (non-insulin-dependent) diabetes mellitus and in control subjects. A 5-year follow-up. Diabetologia 36:68-72, 1993

40. Brown FM, Brink SJ, Freeman R, et al: Anti-sympathetic nervous system antibodies. Diminished catecholamines with orthostasis. Diabetes 38:938-941, 1989

41. Dyrberg T, Benn J, Sandahl Christiansen J, et al: Prevalence of diabetic autonomic neuropathy measured by simple bedside tests. Diabetologia 20:190-194, 1981

42. Sibony-Prat J, Pariès J, Chabert M, et al: Altération du contrôle vagosympathique cardiovasculaire évalué par l'analyse spectrale des variations de fréquence cardiaque et de pression artérielle chez les obèses. Arch Mal Coeur Vaisseaux 8:1155-1158, 1997

43. Valensi P, Smagghue O, Pariès J, et al: Impairment of skin vasoconstrictive response to sympathetic activation in obese patients: Influence of rheological disorders. Metabolism 49:600-606, 2000

44. Peterson HR, Rothschild M, Weinberg CR, et al: Body fat and the activity of the autonomic nervous system. N Engl J Med 318:1077-1083, 1988

45. Hirsch JA, Bishop B: Respiratory sinus arrhythmia in humans: How breathing pattern modulates heart rate. Am J Physiol 241:H620-H629, 1981

46. Straub RH, Palitzsch KD, Thum M, et al: Impact of obesity on neuropathic late complications in NIDDM. Diabetes Care 17:1290-1294, 1994

47. Smith SE, Smith SA, Brown PM: Cardiac autonomic dysfunction in patients with diabetic retinopathy. Diabetologia 21:525-528, 1981

48. Clark CV: Autonomic neuropathy in proliferative diabetic retinopathy. Eye 1:496-499, 1987

49. Ferrari-Dileo G, Davis EB, Anderson DR: Angiotensin binding sites in bovine and human retinal blood vessels. Invest. Ophthalmol Vis Sci 28:1747-1751, 1987

50. Greene DA, Lattimer SA, Sima AAF: Sorbitol, phosphoinositides, and sodium-potassium-ATPase in the pathogenesis of diabetic complications. N Engl J Med 316:599-606, 1987

51. Vinores SA, Campochiaro PA, Williams EH, et al: Aldose reductase expression in human diabetic retina and retinal pigment epithelium. Diabetes 37:1658-1664, 1988

52. Pelayo JC, Quan AH: Neurogenic control of renal function, in Massry SG, Glassock RJ (eds): Textbook of Nephrology (ed 2). Baltimore, MD, Williams & Wilkins, 1989, pp 65-69

53. Sundkvist G, Lilja B: Autonomic neuropathy predicts deterioration in glomerular filtration rate in patients with IDDM. Diabetes Care 16:773-779, 1993

54. Borch-Johnsen K, Andersen P, Deckert T: The effect of proteinuria on relative mortality in type 1 (insulin dependent) diabetes mellitus. Diabetologia 28:590-595, 1985

55. Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A, et al: Coronary heart disease in young type 1 (insulin dependent) diabetic patients with and without diabetic nephropathy: Incidence and risk factors. Diabetologia 30:144-148, 1987