Cardiovascular Autonomic Neuropathy and Sensorimotor Polyneuropathy in Type 2 Diabetes Mellitus

Moțățăianu Anca[1], Bajkó Z[1], Stoian Adina[2], Bălașa Rodica[1]

[1] Department of Neurology, University of Medicine and Pharmacy, Tîrgu Mureș, Romania
[2] Department of Pathophysiology, University of Medicine and Pharmacy, Tîrgu Mureș, Romania

Background: The neuropathic complications related to diabetes may affect the somatic, sympathetic and parasympathetic nervous system, causing diabetic neuropathy. The aim of this prospective study was to investigate cardiovascular autonomic dysfunction and to determine the relationships between diabetic cardiovascular autonomic neuropathy (CAN), autonomic symptoms and diabetic sensorimotor polyneuropathy (DPN).
Methods: The prevalence of CAN among 57 patients with type 2 diabetes mellitus (DM) was assessed by the five autonomic function tests by Ewing's methodology. DPN was diagnosed on the basis of both clinical criteria and electrodiagnostic studies in upper and lower limbs.
Results: Patients with CAN had a longer duration of diabetes ($p<0.0001$), a poorer glycemic control ($p=0.02$), and a higher prevalence of DPN ($p<0.0001$). There were no significant differences in sex distribution, body mass index, lipid profile and blood pressure between patients with and without CAN.
Conclusion: Our results confirmed the associations of CAN with duration of diabetes and poorer glycemic control. The natural progression of CAN is insidious and the symptoms are miscellaneous and manifesting at a relatively late stage. With the aim of preventing CAN, diabetic patients should receive a precocious diagnosis and be instructed for having a good metabolic control.

Keywords: cardiovascular autonomic neuropathy, diabetic sensorimotor polyneuropathy, diabetes mellitus

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Introduction

Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes, which is often ignored by physicians due to its insidious onset, and not routinely tested in most diabetic clinics. A subtype of the peripheral polyneuropathies that accompany diabetes, DAN can involve the entire autonomic nervous system. Cardiovascular autonomic neuropathy (CAN) is defined as the impairment of autonomic control of the cardiovascular system [1]. CAN is one of the most clinically significant complications of diabetes mellitus (DM), associated with worsening prognosis and poorer life quality.

The reported prevalence of CAN varies greatly depending on the criteria used to identify CAN and the studied population. In a large cohort of patients with type 1 and 2 diabetes, Ziegler et al. using predefined heart rate variability tests and spectral analysis of R-R intervals, found that 25.3% of patients with type 1 diabetes and 34.3% of patients with type 2 diabetes had abnormal findings [2]. Factors that influence the prevalence of CAN include the diagnostic criteria, patient's age and the duration of diabetes [3]. Additional clinical correlates and predictors on CAN include glycemic control, presence of DPN, nephropathy, rethinopathy, blood pressure (BP) levels, obesity, smoking and cholesterol and triglycerides levels [4,5].

The autonomic nervous system plays a key role in the modulation of cardiovascular dynamics by means of interaction between the sympathetic and vagal tonus, which in physiological conditions act in a negative feedback manner. In other words, the activation of the former is followed by the inhibition of the latter. In clinical practice, this modulation is usually assessed by well-known study of heart rate variability (HRV), which means an analysis of spontaneous and induced fluctuations that occur in heart rate (or in the electrocardiographic R-R interval) as a result of sympathetic and parasympathetic activities on sinus node automaticity [6,7].

The following clinical manifestations are associated with CAN: resting tachycardia, severe orthostatic hypotension, syncope, exercise intolerance, asymptomatic myocardial ischemia and infarction, left ventricular diastolic and systolic dysfunction, increased risk of renal diseases, chronic renal failure, stroke and sudden cardiac death [3,8].

CAN may be subclinical (in which functional and reversible alterations are predominant) and clinical (when structural neuronal alteration are already present). The first one is only diagnosed by tests and may occur even at the time of the diagnosis of DM, or in the first years of the disease; the second form is a symptomatic one and occurs in more advanced stages.

Cardiovascular reflex tests are the gold standard in clinical autonomic testing. These tests have good sensitivity, specificity and reproductibility, and are non-invasive, safe, well-standardized and easily performed [9]. The most widely used tests assessing cardiac parasympathetic function are based on the heart rate response to deep breathing, Valsalva maneouver and postural change. Cardiovascular

Correspondence to Anca Moțățăianu
E-mail: motataianuanca@gmail.com

sympathetic function is assessed by measuring blood pressure response to orthostatic change and isometric contraction [10].

Screening for CAN should be performed at the diagnosis of type-2 DM and 5 years after the diagnosis of type-1 DM, particularly in patients at greater risk of CAN due to history of poor glycemic control, cardiovascular risk factors, DPN, and macro- and microangiopathic diabetic complications [1,10]. Diagnostic criteria and staging of CAN are still being debated. The presence of one abnormal cardiovagal test identifies possible or early CAN; at least two abnormal HRV tests are required for definite or confirmed diagnosis of CAN, and orthostatic hypotension (asymptomatic or symptomatic), in addition to HRV test abnormalities, identify a condition of severe or advanced CAN [4,5,11].

The aim of our study was to investigate diabetic patients regarding cardiovascular autonomic dysfunction, and the relationship between DPN and CAN.

Material and method

We conducted a prospective study on 57 consecutively selected patients with type 2 DM, in the Department of Neurology of the County Emergency Clinical Hospital of Tîrgu Mureș, from September 1, 2011 to March 31, 2012. The diagnosis of diabetes was established in the clinical settings and it was confirmed using diagnostic criteria recommended by the World Health Organisation Expert Committee on Diabetes Mellitus [12]. Subjects with secondary diabetes, hypo- or hyperthyroidism, alcoholism, renal insufficiency or overt neoplasic disease were not eligible for the study. All diabetic patients were non-ketotic at the time of diagnosis. All patients signed an informed consent.

A detailed neurologic examination, including questionnaire on symptoms and clinical examination was performed. Neuropathic pain was defined as pain in the limbs in the absence of history of trauma or other evident external cause. Bilateral pain or paraesthesias of the legs or feet were considered symptoms of polyneuropathy.

All patients taking CVR tests were routinely requested to complete a questionnaire regarding autonomic-like symptoms experienced during the past year. The questions were designed to detect the following autonomic symptoms: 1. Postural dizziness; 2. Gastrointestinal symptoms; 3 Hypoglycemic unawareness; 4. Impotence (male only); 5. Dyshidrosis; 6. Urinary bladder dysfunction.

Assessment of CAN was performed by standard battery of cardiovascular reflex tests (Ewing battery) including: 1. HRV to six consecutive deep breaths; 2. HRV response to standing up; 3. HRV to Valsalva maneuver; 4. Dyastolic BP response to handgrip test and 5. Systolic BP response to standing. Global interpretation of diagnostic tests was done as follows: 1. Normal tests; 2. Subclinical CAN – if no more than one HRV test was abnormal; 3. Intermediary CAN – if at least two HRV tests were abnormal; 4. Severe CAN – if at least two HRV tests were abnormal and one BP variability test was abnormal [1]. Those who were placed in categories 1 and 2 were considered without CAN, and those from categories 3 and 4 have been considered with CAN.

All patients underwent electroneurography for the evaluation of polyneuropathy. Nerve conduction studies (NCS) were performed in four nerves (median, ulnar, peroneal and sural nerves), using surface electrodes, according to conventional techniques. Ten parameters were evaluated: median nerve (1) elbow to wrist nerve conduction velocity (NCV), (2) distal motor conduction latency, (3) elbow to wrist sensory NCV, (4) amplitude of antidromic sensory action potential (SAP) derived from the third finger; ulnar nerve (5) elbow to wrist motor NCV, (6) elbow to wrist sensory NCV; peroneal nerve: (7) motor conduction velocity between knee and ankle, (8) distal motor conduction latency; sural nerve: (9) amplitude of sensory action potential, (10) sensory NCV [13]. The reference values were obtained from our laboratory controls consisting of 20 healthy subjects aged between 20–75 years.

The subjects were classified as having definite DPN if four or more values were abnormal, both the peroneal and sural nerves were involved, and there were clinical symptoms of DPN (pain or paraesthesias in hands or legs); they were classified as having probable PNP if four or more values were abnormal and both the peroneal and sural nerves were involved, but there were no symptoms, or if either of the nerves were involved but there were symptoms. The subjects with definite or probable PNP were grouped together as subjects with polyneuropathy.

Statistical analyses

Differences between the groups in terms of outcome variables were described using standard statistics, evaluated for significance using two-sample t-tests or Wilcoxon's rank-sum tests depending on whether the distributional assumptions were satisfied judging by skewness-kurtosis tests.

The relationship between a continouos and non-continous variable was analysed by one-way ANOVA (with multiple comparisons, post test for linear trend).

Results

The age of the patients ranged from 34 to 77 years (mean age 59.1 years). Thirty-two patients (56%) showed no autonomic dysfunction, 14 patients (24.5%) showed two abnormal HVR tests (definite CAN), and 11 patients (19.5%) showed at least two abnormal HVR and at least one abnormal BP test (severe CAN). Only 10 patients (17.54%) met the diagnostic criteria of postural hypotension. Among subjects with postural hypotension, 80% had at least one abnormal HRV test suggested that postural hypotension is a late manifestation of CAN. According to our diagnostic criteria, 44% of the patients were defined as having CAN.

The diagnostic criteria and the results of HRV tests and of variability of blood pressure tests are presented in Table I.

Table I. Diagnostic criteria and the prevalence of abnormal cardiovascular reflex tests (N=57)

	Diagnostic criteria (pathological values)	Abnormal score n (%)
Heart rate variability (HRV)/ parasympathetic tests		
HRV 6 DB	Max HR-Min HR <10	13 (22.8)
HRV lying-standing (L-S)	R-R beet 30/R-R beet 15 <1.00	10 (17.5)
HRV Valsalva (V) maneuver	R-R after V/R-R during V <1.10	30 (52.6)
HRV Valsalva+HRV L-S		9 (15.7)
Variability of blood presure/ sympathetic tests		
Sitting to standing	SBP fall >30 mmHg	8 (14.0)
Isometric contraction	DBP increase <10mmHg	2 (3.5)

HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure

Table II displays the baseline characteristics of the patients with and without CAN. From the 57 patients with type 2 DM examined in this study, 32 subjects (56.2%) were without CAN (CAN–) and 25 subjects (43.8%) were with CAN (CAN+). Patients with CAN had a longer duration of diabetes (p<0.0001) and poorer glycemic control (p=0.02). There were no significant differences in age of patients, sex distribution, body mass index (BMI), lipid profile (including total cholesterol and triglyceride) and blood pressure profile between patients with and without CAN.

Table III presents the association between CAN and somatic neuropathy. From the 57 diabetic patients 28 (49.12%) were found with somatic neuropathy and 29 (51%) without somatic neuropathy. Pure cardiac autonomic neuropathy was not detected in any of the patients, and pure somatic neuropathy was detected in 5 patients (8.77%). From 28 patients with somatic neuropathy, 15 (53.5%) had parasympathetic neuropathy, 2 (7.14%) had impaired sympathetic neuropathy, and 8 (28.5%) had combined autonomic neuropathy. There was a significant correlation between CAN and somatic neuropathy (p<0.0001).

From the 57 diabetic patients who completed questionnaries, 33 (57.8%) patients had no symptoms, 11 (19.2%) patients had only one symptom, and 13 (22.8%) patients complained of 1–4 symptoms. From 25 patients with CAN, 9 (36%) were asymptomatic, 7 had one or combination of two related gastrointestinal symptoms (44%), and 9 patients (36%) combination of three symptoms. The most common symptoms of diabetic autonomic dysfunction were gastrointestinal symptoms as nausea, vomiting, constipation, diarrhea (intermittent or alternate with constipation). Table IV presents the prevalence of autonomic symptoms.

Table III. Associations between autonomic neuropathy and peripheral polyneuropathy in diabetic patients

	Polyneuropathy +	Polyneuropathy –	p-value (Fisher test)
Parasympathetic neuropathy	15/28 (53.5%)	8/29 (27.5%)	p<0.05
Sympathetic neuropathy	2/28 (7.14%)	0/29 (0%)	p<0.05
Combined autonomic neuropathy	8/28 (28.5%)	0/29 (0%)	p<0.05

Table II. Basic group characteristics

	Whole patient group	CAN +	CAN –	p value
n	57	25	32	
Age (years)	59.1±10.8	58.2±1.8	59.8±10.1	0.6
Sex (% of male)	49.1	12	16	0.7
Duration of diabetes (years)	9.89±7.9	15.6±7.9	5.4±4.3	<0.001
Fasting plasma glucose (mg%)	172±52	181±58.5	164±47	0.26
BMI (kg/m^2)	30.4±4.8	30.4±4.7	30.4±5.1	0.94
HgbA1c (%)	8.1±1.4	8.98±1.4	8.1±1.2	<0.05
Total cholesterol (mg%)	202.6±50.9	212±37.1	195±59	0.18
Triglycerides (mg%)	205±175	225±193	189±162	0.45
Systolic BP(mmHg)	145.6±22.3	147±23.4	144±21.6	0.55
Diastolic BP (mmHg)	82.2±11.6	80.6±12.6	83.4±10.8	0.38

CAN : cardiovascular autonomic neuropathy; BMI: body mass index; DPN: diabetic sensorimotor polyneuropathy; BP: blood presure; HgbA1c: glycated hemoglobin

We found a significant linear trend toward more severe cardiac autonomic neuropathy (CAN) with increasing glycated hemoglobin level: p=0.014, R square=0.11, Slope=0.27 (one-way ANOVA with multiple comparisons, post test for linear trend) and increasing disease duration: p<0.0001, R square=0.333, Slope=2.,78 (one-way ANOVA with multiple comparisons, post test for linear trend).

Discussions

CAN in our patients involved both the parasympathetic and sympathetic nervous system, but the most frequently altered test was heart rate variability, which indicates an impairment of parasympathetic nervous system. CAN screening has been recommended in patients with type 2 DM at diagnosis and at 5 years after diagnosis of type 1 diabetes [3]. Ewing's battery of tests were suggested as the diagnostic tool for CAN [9]. Using this Ewing's methods the prevalence of CAN in this hospital-based study was 44%, which is consistent with a previous study on this type of patients, reported by Ziegler [2].

Table IV. Prevalence of autonomic symptoms (single and 2 or 3 symptoms combined)

	n	NAC –	NAC +
Asymptomatic	33/57	24	9
Single symptoms			
Dizziness	2/57	2	0
Nausea	1/57	1	0
Constipation, diarrhea	6/57	6	3
Urinary incontinence	2/57	1	1
2 symptoms combined			
Nausea + constipation	3/57	1	2
Nausea + vomiting	1/57	0	1
3 symptoms combined			
Dizziness + nausea + vomiting	1/57	0	1
Dizziness + constipation + nausea	8/57	0	8

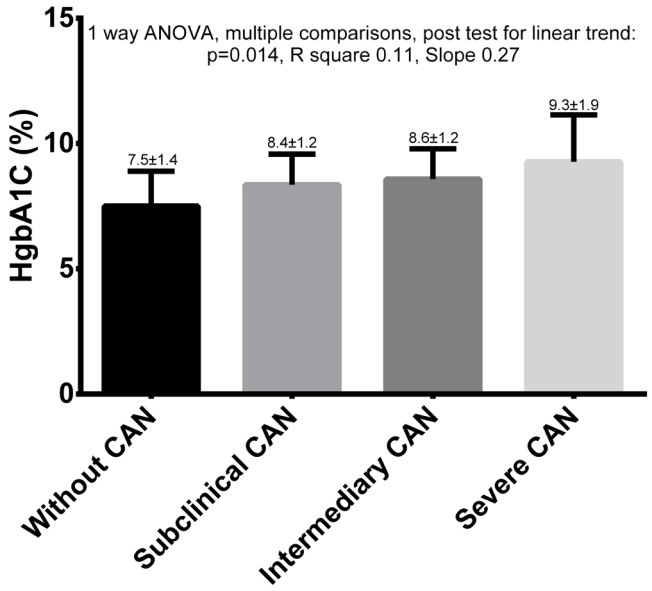

Fig. 1. Column Graph (mean with SD), one-way ANOVA (multiple comparisons, post test for linear trend) for analysing the relationship between the HgbA1C (%) level and the severity of CAN.

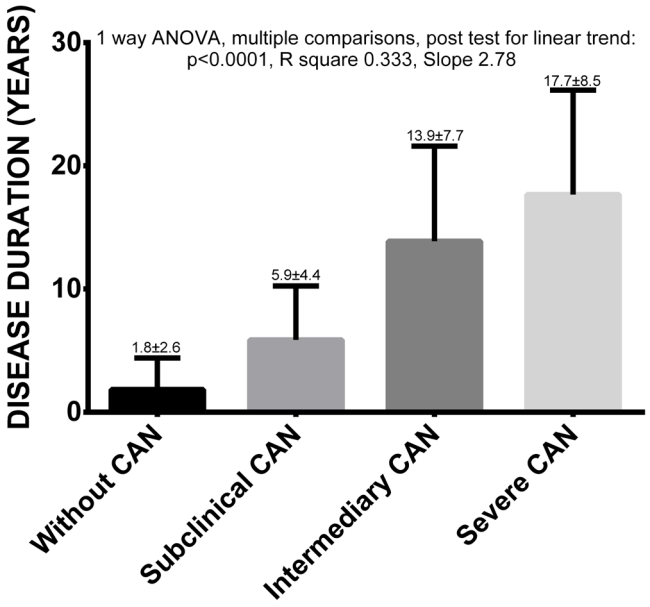

Fig. 2. Column Graph (mean with SD), one- way ANOVA (multiple comparisons, post test for linear trend.) for analysing the relationship between the duration of the disease and the severity of CAN.

Our data demonstrated strong correlations between CAN and HbA1c, as well as the duration of diabetes. Prolonged exposure to hyperglycemia is known to be a metabolic insult, which plays an important role in the pathogenesis of diabetic neuropathy. In addition, the impact of hyperglycemia on development and progression of chronic diabetic complications has been documented in large trials, as the DCCT and UKPDS studies [14,15,17,18].

Obesity is a metabolic risk factor of many diseases, particularly diabetes and cardiovascular disease. Association of obesity with CAN has been observed by some authors [16]. However, lack of association of BMI with CAN was found in our study. The relatively small group of patients investigated in our study could explain this discrepancy.

Hypertension and hyperlipidemia are other cardiovascular risk factors shown to be associated with CAN in previous studies [17,18]. In our study we did not find any significant association between systolic, diastolic BP, plasma lipid levels and CAN, however there was a trend toward higher values of cholesterol (p=0.18) and diastolic bood pressure (p=0.38). We considered that our group of patients was too small, and there is a need for further investigation on a greater number of diabetic patients.

A strong correlation was observed between changes in cardiac autonomic neuropathy and alterations in distal somatic neuropathy (assessed by measurement of different electroneurographic parameters in four peripheral nerves) in our prospective study.

Our study results showed strong associations between parasympathetic neuropathy, sympatethic neuropathy and DPN. DPN represents a diabetic microangiopathy, and autonomic neuropathy and other diabetic microangiopathy often occur concurrently. The concurrent occurrence of these diabetic complications and CAN suggest that they may share some common pathogenic pathways. Poor glycemic control has been recognized as a common denominator in the development of various diabetic complications, particularly microangiopathy. The strong connections between CAN and DPN suggest that the impairment of microcirculation may play an important role in development of CAN, and diabetic microangiopathy could be a strong predictor for CAN [19]. But this aspect must be the subject of future research, to examine the relationship between CAN and other microangiopathic complication related to DM (nephropathy, retinopathy).

Our results support a significant coexistence of somatic and autonomic neuropathies in type 2 DM, and support the existence of a parallel involvement of peripheral somatic and autonomic cardiovascular nerve fibers in this patients. These data are not in accordance with a recent study performed in diabetes, which demonstrates a divergent development of autonomic and peripheral somatic neuropathy in diabetic patients [20]. In this mentioned study, evaluation criteria for polyneuropathy included just clinical neurological examination and history of the patients. In our study the evaluation criteria for these patients was done on the base of neurophysiological data obtained from electroneurography, which probably detected the cases that would otherwise be considered asymptomatic.

The basic mechanism underlying the damage of hyperglycemia on somatic and autonomic nerves is not dissimilar, and there is not a different susceptibility of autonomic (small and mostly unmyelinated) and peripheral somatic (large and myelinated) nerve fibers to hyperglicemia.

In our study we observed that many patients with mild CAN (parasympathetic dysfunction) are asymptomatic, and the clinical manifestations of autonomic symptoms usually occur in more advanced stage of CAN. Symptoms-

free patients cannot be excluded from having CAN, particularly in patients at an early stage of disease. The fact that the most common symptoms were gastrointestinal, suggests that in diabetic autonomic neuropathy, gastrointestinal autonomic dysfunction appears before cardiovascular autonomic dysfunction.

Conclusions

Our results confirmed the association of CAN with the duration of diabetes, poorer glycemic control, but not with obesity, lipidic profile and blood pressure. Simultaneous appearance of CAN and DPN suggest that they may share some common pathogenic pathways. Prolonged exposure to hyperglycemia plays an important role in the pathogenesis of diabetic neuropathy. The patient's history and physical examination are ineffective for early indication of autonomic nerve dysfunction and thus recommendations for the use of non-invasive tests that have demonstrated efficacy are warranted.

With the aim of preventing these complications, the diabetic patients should receive a precocious diagnosis and be instructed for having a good metabolic control.

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