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ORIGINAL ARTICLE

Cardiovascular autonomic neuropathy and charcot neuroarthropathy in type 2 diabetes: adding a new severity classification score

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Abstract

Objective This study aimed to assess the presence and characteristics of cardiovascular autonomic neuropathy (CAN) in people with type 2 diabetes with and without Charcot neuroarthropathy (CN).

Background Diabetes can affect nerves in many ways beyond sensitive neuropathy.

Methods A cross-sectional study was carried out in people with diabetes and CN who were matched for sex and age with two groups of people with diabetes without CN. All subjects underwent CAN assessment with seven tests (four Ewing tests and three bands of spectral analysis), and a severity score was constructed using these seven tests (each altered test equivalent to 1 point).

Results Of the 69 people evaluated, 49 (71%) had incipient or installed CAN. A total of 95.2% of people with Charcot neuroarthropathy had incipient or installed CAN. There was a higher prevalence of dyslipidemia among people with installed autonomic neuropathy than among those with incipient CAN or without CAN. Thirty-four (69%) people with CAN had increased urinary albumin excretion. The severity score, constructed from the seven tests used for the diagnosis of CAN, revealed a greater number of altered tests and higher scores among people with CN when compared to the other participants, indicating greater severity of the condition.

Conclusions There is a high prevalence of CAN in people with type 2 diabetes followed in a tertiary health service and the use of severity score may enable to differentiate people with or without CN. We suggest that this score could be used as a new tool in caring for people with diabetes to identify the most severe CAN.

Keywords Autonomic neuropathy · Cardiovascular neuropathy · Charcot neuroarthropathy · Type 2 diabetes · Severity score

Introduction

Autonomic neuropathy of diabetes is a complication still poorly diagnosed and investigated, in which there is damage to the autonomic, sympathetic, or parasympathetic innervation in one or more organs. This damage leads to symptoms, such as asymptomatic hypoglycemia, gastroparesis, changes in sweating, and erectile dysfunction, and strongly affects the quality of life of patients [1].

Cardiovascular autonomic neuropathy (CAN) is one of the most severe clinical forms of diabetic autonomic neuropathy, as it increases the risk of arrhythmias, silent ischemia, and sudden death in these people, who are generally at high cardiovascular risk [2]. It results from damage to the fibers of the autonomic nervous system that supply the heart and blood vessels, causing uncontrolled vascular dynamics, and a reduction in heart rate as the earliest manifestation [3, 4].

Charcot neuroarthropathy (CN) is another poorly studied complication of diabetes, characterized by progressive, often painless, osteoarticular damage, especially in the feet and ankles that can develop ulcerations and infection and culminate in the amputation of the affected limb [5].

The pathophysiology of CN appears to be multifactorial, and some risk factors are well-established including neuropathy, increased mechanical forces, and repetitive trauma. There are several theories to explain the genesis of CN, among them, the occurrence of inflammation abnormally

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protracted from neuropathy, with expression of pro-inflammatory cytokines, activation of osteoclasts by activation of receptor activator of nuclear factor kappa-B (RANK) and it's ligand RANKL [6], weakness of pedal skeleton, and progressive fracture and dislocation [7]. Another theory evolves gene variants of Wnt signaling pathway as seen in Gassel study [8].

Large studies, with more than 1000 people with CN, showed increased overall mortality by 23%, showing that this population is more likely to die than people with diabetes alone [9]. When we compare people with diabetes with or without CN, the mortality of people with CN is 2.7 times increased in a study by Chaudhary [10]. We know that the high mortality rate in these people is not only due to infections or amputations but also to the high degree of systemic inflammation, even in the chronic phase of Charcot's neuroarthropathy. [11]. In a meta-analysis by Yammine [12] with a pooled sample of 2272 Charcot feet, the mortality varies from 4 to 24.5%, depending on the number of people in each sample.

Several studies carried out with chronic Charcot neuroarthropathy people have shown the involvement of the autonomic nervous system, when compared with people with diabetes without chronic Charcot foot [13, 14]. In this context, this study aimed to evaluate the presence and characteristics of CAN in people with type 2 diabetes with and without CN.

Materials and methods

Study design

A cross-sectional study was carried out in a diabetes reference service, selecting all people with Charcot neuroarthropathy, between the years of 2015 and 2017, diagnosed by clinical and radiological findings [15] totaling 24 people, matched by sex and age with two groups of people with diabetes without established Charcot neuroarthropathy according to the clinical diagnosis of sensorimotor peripheral neuropathy (PN) and no peripheral neuropathy. The three groups were submitted to the CAN evaluation.

All the patients studied with Charcot neuroarthropathy were in phase III according to the Eichenholtz [16] classification stage (feet without phlogistic signs, temperature difference less than two degrees in relation to the collateral foot verified by digital infrared thermometer GM-320 [17], radiography with bone remodeling or residual deformation). The temperature probe displays in increments of 0.1 °C and is accurate to within ± 1.5 °C. The diagnosis of Charcot neuroarthropathy was based on the following findings: the presence of destruction or collapse of bone structures of the foot and/or ankle in patients diagnosed with diabetes and PN [18]. All participants were assessed for clinical, demographic, and laboratory characteristics.

We excluded from the sample people with infected plantar ulcers, with a history of stroke or acute myocardial infarction, active inflammatory disease, or known malignancy.

The evaluation of peripheral sensorimotor neuropathy was performed using the tool by Moreira et al. [19] signs and symptoms score, which uses a score with symptoms and signs of peripheral neuropathy, from the neurological examination of temperature, pain, vibration sensitivity, and Achilles reflex. The diagnosis of peripheral neuropathy is made by excluding other causes and scoring 6 to 8 on the signs score with or without symptoms or scoring 3 to 5 on the signs score and 5 to 6 on the symptoms score.

Clinical assessment of CAN was performed using Ewing criteria. Heart rate variability (HRV) was evaluated using a Poly-Spectrum computer system from Neurosoft© (Russia) and applying seven parameters (four Ewing tests and three spectral analysis bands) [20]. The tests were performed according to the study by Spallone et al. [21] as follows: Ewing tests using a deep breathing test (E:I ratio) performed with the patient in supine position during deep inspiration and expiration with the duration of 5 s each; orthostatic test (ratio 30:15), when it is assessed the relationship between heart rate or RR intervals corresponding to the maximum tachycardia around the 15th beat and the maximum bradycardia around the 30th beat; evaluated hypotension orthostatic, in which blood pressure (BP) is measured at baseline time (patient still in decubitus), 1 and 3 min after orthostasis; and the test of Valsalva, in which the patient, in a sitting position, performed breathing (blowing into a mouthpiece connected to a manometer to maintain a pressure of 40 mmHg) for 15 s. The study of heart rate variability by spectral analysis was performed using a 5-min electrocardiogram. All tests were performed in the morning and in afebrile patients. They were instructed not to drink coffee or alcoholic beverages on the morning of the test and not to smoke for a minimum period of 8 h. There was also a recommendation not to use beta-blocker medication the night before and the morning of the test.

A total score was constructed in the Seven Tests Protocol, with each test change equivalent to 1 point. If it was a normal test, the score was 0, with a maximum of 7 points and a minimum of 0.

People with type 1 diabetes, infected ulcers, malignancy, active inflammatory disease (like systemic lupus erythematosus, Crohn's disease), New York Heart Association (NYHA) class III or IV heart failure, severe liver disease CHILD B or C, seropositive patients for the virus HIV or hepatitis C, psychiatric illness, or any other clinical conditions that could interfere with the clinical assessment of CAN were excluded from the study.

This study was carried out at the University of Campinas (UNICAMP), São Paulo, Brazil, in the service specialized in diabetes and diabetic foot complications, after approval by the local research ethics committee under registration number 1,332,642.

Clinical assessment

At the time of assessment, demographic and clinical data were collected regarding age, sex, time since diabetes diagnosis, smoking status, presence of comorbidities such as systemic arterial hypertension, dyslipidemia, nephropathy, and previous psychiatric or cardiovascular disease. The diagnosis of dyslipidemia and systemic arterial hypertension was considered when lipid-lowering and anti-hypertensive medications were being used.

Laboratory assessment

Laboratory evaluation consisted of serum concentrations of fasting glucose, creatinine, HDL cholesterol, LDL and triglycerides, uric acid, glycated hemoglobin (HbA1c), vitamin B12, and C-reactive protein. A 24-h microalbuminuria was also assessed.

Fasting blood glucose, total cholesterol, its fractions, triglycerides, and uric acid were evaluated by the colorimetric enzymatic method. HbA1c was analyzed by high-performance liquid chromatography (HPLC). The laboratory method used for microalbuminuria and C-reactive protein was immunoturbidimetry. Creatinine was measured by the colorimetric kinetic method. From the creatinine values, we calculated the glomerular filtration rate using the KDIGO [22] CKD-EPI formula. Vitamin B12 concentrations were determined by the chemiluminometric method.

Statistical analysis

Frequency tables of categorical variables with absolute frequency (n) and percentage (%) values were prepared to describe the sample profile according to the variables under study. Descriptive statistics were made for numerical variables, with mean values, standard deviations, and minimum and maximum values. Pearson's chi-square test and, when necessary, Fisher's exact test was used to compare categorical variables. The Kruskal−Wallis test, followed by Dunn's post hoc test, the Mann−Whitney U test was used for numerical variables. The significance level adopted for the study was 5%.

For statistical analysis, the computer program SAS System for Windows (Statistical Analysis System), version 9.4, was used (SAS Institute Inc, 2002–2008, Cary, NC, USA).

Results

Demographic, disease, and peripheral neuropathy characteristics of people with diabetes with and without CAN.

A total of 72 people with type 2 diabetes participated in the study. Three people were excluded from the CN group because they had infected ulcers or had type 1 diabetes, leaving 21 people with CN, 24 with peripheral neuropathy without Charcot, and 24 without peripheral neuropathy. Of 49 (71%) people with incipient or installed CAN, 27 are men and 22 are women. Most people with CAN were non-smokers (p-value 0.0153), and there was a higher prevalence of dyslipidemia diagnosis among people with established CAN than among those with incipient CAN and without CAN (p-value 0.0247). There was no difference between people with and without CAN in relation to the other parameters (Table 1).

Assessment of Charcot neuroarthropathy, peripheral neuropathy (PN), and total CAN score

Of 49 people with CAN, 20 had Charcot neuroarthropathy, 14 had peripheral neuropathy, and 15 had no peripheral neuropathy (Table 2).

When comparing the score of the signs of peripheral neuropathy among the three groups, performed through neurological physical examination, people with CN had a higher score than those with or without peripheral neuropathy, and those with peripheral neuropathy had higher scores than those without peripheral neuropathy. The total score in the Seven Tests Protocol for the diagnosis of CAN was higher in people with CN than in those with or without peripheral neuropathy (Table 2).

Laboratory analysis

The blood glucose of people with incipient CAN was 173.32 ± 81.19 mg/dl, and 145.37 ± 53.33 mg/dl with installed CAN. The mean HbA1c was $8.64\% \pm 1.74\%$ (71 ± 14.5 mmol/mol) among those with incipient and $8.72\% \pm 2.02\%$ (72 ± 16.83 mmol/mol), with installed CAN. There was no difference in cholesterol, LDL, HDL, or triglyceride values between the three groups, also in glomerular filtration rate, uric acid, or CRP between groups with or without CAN. People without CAN had lower levels of microalbuminuria than those with installed or incipient CAN (Table 1). People with CAN had more dyslipidemia diagnosis than those without CAN (Table 3).

Table 1 Demographic, peripheral neuropathy and laboratory characteristics of people with diabetes with and without CAN

Variables		Cardiovascular autonomic neuropathy			*p*-value
		No ($n=20$)	Incipient ($n=19$)	Installed ($n=30$)	
Age (years)		58.15 ± 8.85	61.26 ± 5.01	60.53 ± 7.94	0.4190[a]
Diabetes mellitus time (years)		13.25 ± 8.38	16.68 ± 8.27	15.53 ± 7.83	0.4631[a]
HbA1c (%, mmol/mol)		9.00 ± 1.96 75 ± 16.33	8.64 ± 1.74 71 ± 14.5	8.72 ± 2.02 72 ± 16.83	0.6495[a]
Sex	Male (*n*, %)	11 (55%)	11 (57.9%)	16 (53.3%)	0.9522[b]
	Female (*n*, %)	9 (45%)	8 (42.1%)	14 (46.7%)	
Arterial hypertension (*n*, %)		15 (75%)	15 (78.9%)	22 (73.3%)	0.9385[b]
Smoke (*n*, %)		10 (50%)	3 (15.8%)	5 (16.7%)	**0.0153[b]**
Dyslipidemia (*n*, %)		4 (20%)	6 (31.6%)	17 (56.7%)	**0.0247[b]**
Peripheral neuropathy (*n*, %)		11 (55%)	12 (63.2%)	22 (73.3%)	0.4011[a]
Fasting blood glucose (mg/dl)		162.10 ± 68.82	173.32 ± 81.19	145.37 ± 53.33	0.6028[a]
eGFR (mL/min/1.73m^2)		75.1 ± 22.89	69.16 ± 25.65	66.6 ± 26.36	0.5268[a]
Uric acid (mg/dl)		5.06 ± 1.30	5.41 ± 1.83	4.98 ± 1.34	0.7399[a]
Total cholesterol (mg/dl)		154.65 ± 47.47	164.32 ± 39.69	172.57 ± 43.68	0.2496[a]
LDL (mg/dl)		84.4 ± 37.16	92.32 ± 33.02	94.47 ± 32.20	0.9059[a]
HDL (mg/dl)		42.35 ± 9.44	43.32 ± 11.6	42.1 ± 11.24	0.8900[a]
Triglycerides (mg/dl)		165.2 ± 144.57	168.74 ± 84.85	173.97 ± 92.42	0.5421[a]
B12 vitamin (pg/mL)		410.69 ± 140.87	408.53 ± 119.8	412.14 ± 188.85	0.8837[a]
Microalbuminuria (mg/24 h)		34.18 ± 78.85	355.89 ± 827.96	303.28 ± 509.99	**0.0008[a]**

[a]Based on the Kruskal−Wallis test, followed by Dunn's test to locate differences; [b]based on the Chi-square test. Categorical variables are represented as absolute numbers and percentages (*n*, %), and continuous variables as the mean ± standard deviation. Data are represented as the mean ± standard deviation. eGFR (CKD-EPI estimated glomerular filtration rate). Smoke: current or former smokers

Table 2 Cardiovascular autonomic neuropathy (CAN) and patterns of cardiac autonomic dysfunction among people with diabetes according to the presence of CN and the presence or absence of sensory peripheral neuropathy

Variables		CN ($n=21$)	PN ($n=24$)	No PN ($n=24$)	*p*-value
Score symptoms		6 (0–9)	5 (0–7)	0 (0–4)	**< 0.0001[a]**
Score signs		10 (6–10)	6 (3–10)	0 (0–4)	**< 0.0001[a]**
CAN	No	1 (4.8%)	10 (41.7%)	9 (37.5%)	**0.0482[b]**
	Incipient	8 (38.1%)	4 (16.7%)	7 (29.2%)	
	Installed	12 (57.1%)	10 (41.7%)	8 (33.33%)	
CAN total score		4 (1–6)	2 (0–5)	2 (0–6)	**0.009[a]**
High-frequency power		10 (47.6%)	5 (20.8%)	2 (8.3%)	**0.0082[b]**
Low-frequency power		12 (57.1%)	6 (25%)	2 (8.3%)	**0.0013[b]**
Very low-frequency power		7 (33.3%)	6 (25%)	2 (8.3%)	0.1139[b]
E:I ratio		17 (81%)	14 (58.3%)	19 (79.2%)	0.1572[b]
Valsalva ratio		11 (52.4%)	5 (20.8%)	9 (37.5%)	0.0885[b]
30:15 ratio		12 (57.1%)	12 (50%)	14 (58.3%)	0.0625[b]
Orthostatic hypotension		3 (14.3%)	3 (12.5%)	3 (12.5%)	1.0[c]

[a]Based on the Kruskal−Wallis test, followed by Dunn's test to locate differences; [b]based on the Chi-square test; [c]based on Fisher's exact test. Categorical variables are represented as absolute numbers and percentages of altered tests (*n*, %), and continuous variables as the median (min–max)

Discussion

Most patients (71%) in this study had a diagnosis of CAN, even in people without a previous diagnosis of peripheral neuropathy and/or Charcot neuroarthropathy. It is estimated that among people with long-term diabetes, more than 65% present CAN. CAN is still a poorly evaluated and diagnosed complication in most services that assist people with diabetes, although it is interesting to investigate in type 2 at diagnosis and 5 years after type

Table 3 Simple and multiple logistic regression analyzes to study factors associated with CAN in the total group

Variables		OR	IC95%	*p*-value
Age (years)		1.033	0.973; 1.096	0.2865
Diabetes mellitus time (years)		1.023	0.968; 1.080	0.4200
HbA1c (%, mmol/mol)		0.949	0.753; 1.196	0.6559
Sex	Female × male	1.076	0.446; 2.594	0.8706
Arterial hypertension		0.898	0.324; 2.487	0.8363
Dyslipidemia		3.714	1.420; 9.713	**0.0075**
Peripheral neuropathy		1.886	0.749; 4.749	0.1781
Fasting blood glucose (mg/dl)		0.997	0.990; 1.003	0.3376
eGFR (mL/min/1.73m^2)		0.990	0.972; 1.008	0.2601
Uric acid (mg/dl)		0.954	0.707; 1.287	0.7557
Total cholesterol (mg/dl)		1.008	0.997; 1.019	0.1404
LDL (mg/dl)		1.004	0.990; 1.017	0.5958
HDL (mg/dl)		0.997	0.957; 1.039	0.8888
Triglycerides (mg/dl)		1.001	0.997; 1.005	0.7401
B12 vitamin (pg/mL)		1.000	0.997; 1.003	0.9623
Microalbuminuria (mg/24 h)		1.001	1.000; 1.002	0.2486

eGFR (CKD-EPI estimated glomerular filtration rate).

1 diabetes diagnosis [23], since CAN increase the risk of silent myocardial ischemia, perioperative and exercise instability, and worsens people's quality of life [24].

In our study, the most altered CAN tests were deep breathing (E:I ratio) and the orthostatic test (30:15 ratio), tests that only assess the parasympathetic component of the autonomic nervous system. This data reflects the literature, which is clear when it states that the initial alterations of the autonomic nervous system are of the parasympathetic system [25]. In the population with Charcot neuroarthropathy, we found impairment of the sympathetic (low-frequency power) and parasympathetic (high-frequency power) autonomic nervous system when compared to the population without CN, findings like those in the literature [14].

Another analysis performed and not found in the literature was the use of scores for the seven CAN assessment tests and a comparison between patients with and without Charcot neuroarthropathy. We verified higher scores in people with CN, that is, a greater number of altered tests, suggesting a more severe type of CAN. This score could be used to stratify severity among people with installed CAN. Jirkovská [26–28] studied a population with diabetes using insulin and CN in the acute phase, and compared the use of spectral analysis versus the four Ewing tests in the diagnosis of CAN. In that study, spectral analysis normality values were obtained from a group of healthy people with normal Ewing tests in a linear regression model. They found that spectral analysis assessment was as sensitive as Ewing's tests in the diagnosis of CAN. Unlike our study, we grouped the Ewing and spectral analysis tests into the same score, which could be more specific in the diagnosis of CAN.

Another fact that caught our attention in our study was that only one person with CN did not have a diagnosis of CAN, leading to questions about the influence of autonomic neuropathy on the pathophysiology of Charcot neuroarthropathy. In the pathophysiology of Charcot neuroarthropathy, the neurotraumatic, neurovascular theories, and the genetic susceptibility [29, 30] stand out. In the neurovascular theory [8], autonomic dysfunction, with loss of peripheral vasomotor control, would lead to increased blood flow and greater bone demineralization in neuropathic feet. Some authors agree with the statement that the change in the autonomic nervous system contributes to the genesis of Charcot neuroarthropathy but consider that it would not be the main cause because sympathetic denervation and increased blood flow occur bilaterally and not asymmetrically, as in most cases of Charcot neuroarthropathy [31].

Like other microvascular complications of diabetes, dyslipidemia and the presence of albuminuria seem to be related to CAN, as we found in our study. Fleischer [32] evaluated CAN in 382 people with type 1 diabetes and 272 with type 2 diabetes and found that the presence of macroalbuminuria was associated with CAN in people with type 1 diabetes and that BMI and smoking were related to CAN in people with type 2 diabetes. Andersen's longitudinal study [33], carried out with 299 people with type 2 diabetes followed between 6 and 13 years, showed an association between the presence of CAN and hyperglycemia, obesity, and hypertriglyceridemia. Our population consisted of people with type 2 diabetes being monitored in a tertiary hospital with microvascular complications, and LDL targets were pursued with great commitment. Due to this, we noticed the high prevalence of dyslipidemia in our population.

The strength of the present study is the evaluation of people with CN using the seven tests for the diagnosis of CAN (four Ewing tests and three spectral analyses). In addition, the use of a total score is indicative of severity in a population with diabetes and different degrees of peripheral neuropathy (CN × peripheral neuropathy × no peripheral neuropathy). People did not differ in the type of diabetes, duration of illness, glycemic control, age, or gender, which can be confounding factors. We assessed laboratory parameters in search of new markers that would make the diagnosis of CAN more evident to the attending physician, such as the presence of macroalbuminuria. On the other hand, a limitation was the small number of patients, mainly because Charcot neuroarthropathy represents a rare complication of diabetes and, in addition, because of the difficulty in assessing peripheral neuropathy using other techniques, such as electroneuromyography or skin biopsy for evaluation of fine fiber neuropathy. Furthermore, other limitation is that symptoms of autonomic neuropathy were not objectively captured, as symptom scores COMPASS 31 [34] or SAS [35] uses.

Conclusion

We conclude that the prevalence of CAN in people with type 2 diabetes followed in a tertiary health service was high, even in those without peripheral neuropathy, indicating the need to investigate this complication as soon as a diagnosis of diabetes is made, despite being asymptomatic. The diagnosis of dyslipidemia in patients with CN was associated with the presence of CAN.

Through the scoring seven tests protocol, it was possible to differentiate people with CAN and CN from people with CAN without CN. Furthermore, this score would be able to identify the most severe CAN indicated by the highest number of altered tests. However, to confirm this finding, further studies with a larger number of participants are needed.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Jessica Castro de Vasconcelos, Yeelen Ballesteros Atala, Denise Engelbrecht Zantut-Wittmann, and Maria Cândida Ribeiro Parisi. The first draft of the manuscript was written by Jessica Castro de Vasconcelos, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The entire data supporting the results of this study was published in the article itself.

Declarations

Ethical clearance and consent of patient This study was approved by the ethical and research committee of University of Campinas, São Paulo, Brazil. All patients filled out a consent form stating that they agreed to participate in the study.

Competing interests The authors declare no competing interests.

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