

Risk factors for Charcot foot

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ABSTRACT

Objective: *Diabetes mellitus* is the main cause of Charcot neuroarthropathy and is clinically classified as follows: Charcot foot, acute Charcot foot (ACF) when there is inflammation, and inactive Charcot foot when inflammatory signs are absent. The aim of this study was to identify the risk factors for ACF in patients with type 2 *diabetes mellitus*. **Materials and methods:** A matched case-control study was conducted to assess the factors associated with acute Charcot foot from February 2000 until September 2012. Four controls for each case were selected 47 cases of ACF and 188 controls without ACF were included. Cases and controls were matched by year of initialization of treatment. Conditional logistic regression was used to estimate matched odds ratios (ORs) and 95% confidence intervals (95% CIs). **Results:** In multivariate analysis, patients having less than 55 years of age (adjusted OR = 4.10, 95% CI = 1.69 – 9.94), literate education age (adjusted OR = 3.73, 95% CI = 1.40 – 9.92), living alone (adjusted OR = 5.84, 95% CI = 1.49 – 22.86), previous ulceration (adjusted OR = 4.84, 95% CI = 1.62 – 14.51) were at increased risk of ACF. However, peripheral arterial disease (adjusted OR = 0.16, 95% CI = 0.05 – 0.52) of 6.25 (1.92 – 20.0) was a protective factor. **Discussion:** The results suggest that PCA in type 2 diabetes primarily affects patients under 55 who live alone, are literate, and have a prior history of ulcers, and that peripheral arterial disease is a protective factor. *Arch Endocrinol Metab.* 2015;59(3):226-30

Keywords

Charcot neuroarthropathy; Charcot foot; diabetic foot; diabetic neuropathy

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INTRODUCTION

Diabetes mellitus is the main cause of Charcot neuroarthropathy (CN) (1) and is clinically classified as follows: Charcot foot (CF), acute Charcot foot (ACF) when there is inflammation, and inactive Charcot foot when inflammatory signs are absent (2).

It reduces the patients' quality of life and leads to motor disability, loss of limbs, early retirement, and death (3,4). The incidence of CF varies from 1.2 to 8.5 per 1,000 diabetic people per year (5), and its prevalence from 0.1% in the overall population of individuals with type 2 diabetes to 12.9% among the patients who seek diabetic foot care services (6-8).

ACF is characterized by local inflammation (9) associated with progressive bone and cartilage fracture and luxation resulting in the osteoarticular disorganization of a neuropathic foot (8,10). The risk factors for CF are not yet well established (7,11,12). The identification, prevention, and early manipulation of risk factors might delay the appearance and progression of CF.

The aim of the present study was to identify potential risk factors associated with ACF in patients with type 2 diabetes and foot ulcers.

MATERIALS AND METHODS

A matched case-control study was conducted with four controls selected for each case. Controls were selected randomly from medical registers and matched to cases based on year of initialization of treatment. The study took place in the diabetic foot outpatient clinic of the Alcides Carneiro University Hospital (Hospital Universitário Alcides Carneiro – HUAC), which is part of the Federal University of Campina Grande (Universidade Federal de Campina Grande – UFCG), Paraíba, Brazil, from February 2000 to September 2012.

The inclusion criteria were the following: foot ulcers in individuals diagnosed with type 2 diabetes following the criteria of the American Diabetes Association (13).

The exclusion criteria were the following: history of alcoholism according to the CAGE questionnaire

(14), varicose ulcers, hypertensive (Martorell) ulcers, leprosy, and type 1 diabetes or other types of diabetes. The study was approved by the HUAC Human Research Ethics Committee. The participants signed an informed consent form.

Cases were defined as patients with typical clinical manifestations of ACF, as follows: remarkable swelling, heat, redness, deformities, and midfoot or ankle collapse that was confirmed by simple radiography (bone destruction, subluxation, dislocation, and deformities). Controls were defined as patients with type 2 diabetes and foot ulcers without the typical clinical manifestations of ACF.

The patients who performed their first visit unescorted were referred to the HUAC social service, which contacted their families to inform them about the need for an escort. Under those circumstances, if the patients performed the second visit also unescorted, they were considered to be socially isolated. The weight and height of the participants was measured, and the body mass index (BMI) was calculated using Quetelet's equation ($\text{BMI} = \text{body weight in kg} / \text{height in square meters}$). Obesity was defined as a $\text{BMI} \geq 30 \text{ kg/m}^2$, as recommended by the World Health Organization (15).

The peripheral neuropathy was diagnosed based on the following: loss of tactile sensitivity, which was defined as a lack of perception of the monofilament contact in two out of six points using a 10-g esthesiometer (SORRI-BAURU); loss of proprioception, which was defined as an insensitivity to the vibration of a 128-Hz tuning fork applied to the back of the hallux; loss of pain sensitivity, which was defined as the inability to distinguish between the contact of blunt and sharp sticks on the hallux; and the presence of neuropathic alterations on clinical examination, including claw toes, metatarsal prominence, interosseous muscle atrophy, anhidrosis, cracks, and corns. The patients were diagnosed with peripheral neuropathy when the results of two of the abovementioned tests were positive or when neuropathic alterations were found on a clinical examination.

The peripheral arterial circulation was assessed by measuring the systolic arterial pressure in all four limbs by means of a sphygmomanometer and DV10 vascular Doppler (Microem Produtos Eletrônicos Ltda.). The highest upper limb pressure measurement was selected for calculating the ankle-brachial index (ABI). ABI values from 0.91 to 1.30 were considered normal, and values ≤ 0.9 were considered ischemic (16).

A minimum sample size of 47 cases and 188 controls was calculated (17). We assumed the prevalence of the 50% previous ulceration amongst cases, taking a 1:4 ratio between cases and controls to increase the power of the study, with a power of 80%, at a significance level of 5% to detect an odds ratio (OR) of at least 3.

Statistical analysis was performed using SPSS software package (version 17.0, IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for each variable of interest. Normal distribution of variables was assayed with the Kolmogorov-Smirnov normality test. Paired t-test for normally distributed variables was applied to compare the cases and controls, while Wilcoxon's matched pairs test was used for not-normally distributed values. All significance tests were two-tailed and $p < 0.05$ was considered significant. Univariate and multivariate conditional logistic regression was used to compute crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). All variables considered to be significant by univariate analysis were included in multivariate logistic regression analysis. Variables were considered significant if the 95% confidence interval of the adjusted odds ratios did not include 1.

RESULTS

Over February 2000 to September 2012, 786 eligible subjects who had type 2 diabetes and foot ulcers were identified. Descriptive characteristics of total sample size selected are shown in table 1. The mean of age was 60.5 years (sd: 12.4), 106 (45%) were female, 129 (56.1%) had previous ulceration and 207 (88.5%) had Neuropathy. The prevalence of ACF in the period of study was 6%.

Continuous characteristics of the patients with type 2 diabetes and foot ulcers (controls) and ACF (cases) are compared in table 2. Between variables analyzed only the time of hypertension was significant difference.

Table 3 shows the univariate and multivariate conditional logistic analysis (matched analysis) for selected risk factors. In the univariate analysis, the OR: for males was 2.00 (95% CI 1.04 – 3.85), for less than 55 years age was 4.57 (95% CI 2.29 – 9.10), and for previous ulceration was 3.96 (95% IC 1.75 – 8.93). Peripheral arterial circulation was identified like as if it were a protective factor; the OR was 9.09 (1/0.11) times smaller (95% CI 2.56 – 33.33) for the absence of peripheral arterial circulation. Cases did not differ from controls including white ethnic origin, $\text{BMI} \geq 30$, $\text{BMI} \geq 25 \text{ kg/m}^2$. In the multivariate analysis, the variables that remained statisti-

cally significant in the model were: less than 55 years of age = 4.10 (95% CI 1.69 – 9.94), literate education = 3.73 (95% CI 1.40 – 9.92), living alone = 5.84 (95% CI 1.49 – 22.86), previous ulceration = 4.84 (95% CI 1.62 – 14.51) and peripheral arterial disease = 0.16 (95% CI 0.05 – 0.52) of 6.25 (95% CI 1.92 – 20.0) as a protective factor. After adjusting the multivariate model, a probability of 61% was estimated for Charcot foot for all characteristics in the multivariate model.

Table 1. Basic socio-demographic and clinical characteristics of cases and controls

Variables	n (%)
Sample size	235 (100)
Average age (years)	60.5 (12.4)*
Family income (minimum wages)	2.3 (2.4)*
Gender	
Male	129 (54.9)
Ethnicity	
White	114 (54.8)
Educational level	
Literate	146 (64.9)
Living alone	
Yes	29 (12.3)
Time since diagnosis of diabetes (years)	11.7 (7.3)*
Hypertension	
Yes	145 (61.7)
Previous ulceration	
Yes	129 (56.1)
Obesity	
Yes	53 (22.6)
Neuropathy	
Yes	207 (88.5)
Peripheral arterial disease	
Yes	69 (31.9)
Brachial systolic pressure (mmHg)	153.2 (30.1)*
Left leg systolic pressure (mmHg)	153.1 (59.1)*
Right leg systolic pressure (mmHg)	159.7 (66.4)*
Blood glucose (mg/dL)	237.5 (117.6)*

* Mean (Standard deviation).

Table 2. Comparative clinical characteristics of cases and controls

Characteristics	Cases	Controls	P-value
Age (years) [†]	53.6 (10.2)	62.2 (12.3)	0.231
Time since diagnosis (years) [†]	12.1 (6.8)	11.6 (7.4)	0.742
Age at diagnosis (years) [†]	41.4 (11.3)	50.5 (13.5)	0.400
Length of hypertension (years) [§]	0.8 (0 – 3)	5 (2 – 10)	0.028
BMI (kg/m ²) [†]	28.5 (6.1)	26.9 (4.4)	0.766
Blood glucose (mg/dL) [†]	268 (119.6)	228.1 (115.8)	0.673
Creatinine (mg/dL) [§]	1 (0.8 – 1.3)	1 (0.8 – 1.3)	0.419
Brachial systolic pressure (mmHg) [§]	150 (130 – 160)	150 (130 – 180)	0.736
Left leg systolic pressure (mmHg) [†]	185.8 (66.4)	149.1 (63.9)	0.722
Right leg systolic pressure (mmHg) [§]	160 (140 – 190)	140 (110 – 160)	0.634

[†]Mean (SD) and paired t-test; [§]Median (IQR: 25th–95th percentile) and Wilcoxon matched-pairs test.

DISCUSSION

The risk factor most strongly associated with the PC was social isolation. Stuck and cols., in a prospective study found that single men were at higher risk (18).

It was hypothesized that for those patients with diabetes and foot ulcers that live alone, the unrestrained weight bearing on an insensitive foot (19) renews the trauma and activates the inflammatory cascade that is typical of ACF.

The past history of ulcers was the second most associated with ACF and is described in the literature as a risk factor (20).

The average age of those with cases of CF in the present study was 53.7 years old, thus agreeing with the reports of other authors that showed it affects individuals in the fifth and sixth decades of life (21,22). The age of the cases with less than 55 years of age was significantly associated with ACF; however, the time since diagnosis of diabetes was similar, thus suggesting that the severity of the neuropathic complications of type 2 diabetes was a predominant factor mainly among the youngest patients (20).

Although illiteracy directly impacts health outcomes, particularly in those with diabetes (23-26), being literate was not able to protect patients from ACF.

Peripheral ischemia was identified as a protective factor for ACF, with this being consistent with the results of other authors (12,27). The loss of sympathetic innervations leads to increased blood flow and decreased vascular resistance in the feet of patients with peripheral neuropathy (3,28) and, in the patients with PC, this increase in blood flow is even greater when compared to those with neuropathy alone (3,29).

Obesity was reported as a risk factor for CF in other case series⁷, which did not occur in this population. The different prevalence of obesity in the population stu-

Table 3. Results of univariate and multivariate conditional logistic regression of socio-demographic and clinical risk factors for Charcot foot

Risk factors	Cases n (%)	Controls n (%)	Univariate analysis Odds ratio (95% CI) [†]	Multivariate analysis Odds ratio (95% CI) [†]
Socio-demographics				
Masculine gender	32 (68.1)	97 (51.6)	2.00 (1.04 – 3.85)	–
White ethnic origin	18 (48.6)	96 (56.1)	0.74 (0.37 – 1.50)	1.47 (0.77 – 3.05)
Literate education	40 (85.1)	106 (59.6)	3.88 (1.71 – 8.81)	4.39 (1.74 – 9.53)
Living alone	9 (19.1)	20 (10.6)	5.33 (1.93 – 14.75)	4.50 (1.38 – 14.67)
Clinicals				
Hypertension	22 (46.8)	123 (65.4)	0.47 (0.24 – 0.91)	–
Previous ulceration	36 (80.0)	93 (50.3)	3.96 (1.75 – 8.93)	4.38 (1.72 – 11.18)
BMI ≥ 30 (kg/m ²)	13 (27.7)	40 (21.3)	1.41 (0.68 – 2.95)	–
BMI ≥ 25 (kg/m ²)	34 (72.3)	121 (64.4)	1.44 (0.72 – 2.92)	–
Peripheral arterial disease	3 (6.7)	66 (38.6)	0.11 (0.03 – 0.39)	0.14 (0.04 – 0.51)
Peripheral neuropathy [‡]	38 (100.0)	161 (85.6)	–	–

[†] 95% Confidence Interval; [‡] OR could not be included because of the absence of values in cells of cases.

died by Stuck, which was 50%, and in this, which was 21%, might account for this divergence (18). An association was also not found when the OR was calculated for ACF with BMI ≥ 25 kg/m², which agrees with the results of other case control studies (12,20,27).

The prevalence of ACF was 6% in the investigated population; whereas, in other published series, it varied from 0.1 to 12.9% as a function of the type of regional healthcare service sought, namely, general or specialized in diabetic foot care (6,7).

The present study employed a sample of outpatients who spontaneously sought assistance at a public service, and some of the results might be attributed to the inclusion criteria (for example, the acute cases) or even to the lower frequency of CF among non-white European populations (5,18,30).

One of the possible limitations is the criteria for the selection of cases and controls. As the cases were selected from clinical suspicion, milder cases of PCA, in which there were no deformities, may have been included in the control group. Also, between cases, some patients may have developed ACF after admission into the diabetic foot clinic, but had lost the follow up.

It can be concluded that ACF is a significant complication of type 2 diabetes, affecting socially isolated patients. With previous history of foot ulcers and being less than 55 years of age being possible risk factors for ACF in patients with type 2 diabetes and foot ulcers.

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