Risk factors for Charcot foot

Marta Barreto de Medeiros Nóbrega[1], Roque Aras[1], Eduardo Martins Netto[1], Ricardo David Couto[1], Alexandre Magno da Nóbrega Marinho[2], João Luís da Silva[3], Víctor Nóbrega Quintas Colares[4], Priscilla Leite Campelo[2], Marcos André Lima Nunes[2]

[1] Federal University of Bahia (UFBA), Salvador, BA, Brazil
[2] Federal University of Campina Grande (UFCG), Campina Grande, PB, Brazil
[3] Brazilian Agricultural Research Corporation, Campina Grande, PB, Brazil
[4] School of Medical Science of Campina Grande (Cesed), Campina Grande, PB, Brazil

Correspondence to:
Marta Barreto de Medeiros Nóbrega
Universidade Federal de Campina Grande, Faculdade de Ciências Médicas de Campina Grande
Rua Silva Jardim, 111
58406-060 – Campina Grande, PB, Brazil
marta.bm09@uol.com.br

Received on May/12/2014
Accepted on Apr/8/2015

DOI: 10.1590/2359-3997000000042

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

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 potentials 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 (BMI = body weight in kg divided by the height in square meters). Obesity was defined as a BMI ≥ 30 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, BMI ≥ 30, BMI ≥ 25 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).

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 series', which did not occur in this population. The different prevalence of obesity in the population stu-

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.

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/m^2, 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.

Acknowledgments: Alcides Carneiro University Hospital, Federal University of Campina Grande, Federal University of Bahia and the Federal Brazilian Agency for Evaluation and Support of Graduate Education (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Capes) supported the study. The School of Medical Science of Campina Grande bestowed a grant. The authors thank Gustavo Adolfo Di Pace Tejo, EDSoft, Inc., for his help in editing the manuscript.

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES

1. Chantelau E, Richter A, Ghassem-Zadeh N, Poll LW. "Silent" bone stress injuries in the feet of diabetic patients with polyneuropathy: a report on 12 cases. Arch Orthop Traum Surg. 2007;127:171-7.
2. Rogers LC, Frykberg RG, Armstrong DG, Boulton AJ, Edmonds M, Van GH, et al. The Charcot foot in diabetes. J Am Podiatr Med Assoc. 2011;101:437-46.
3. Sohn MW, Lee TA, Stuck RM, Frykberg RG, Budiman-Mak E. Mortality risk of Charcot arthropathy compared with that of diabetic foot ulcer and diabetes alone. Diabetes Care. 2009;32(5):816-21.
4. Hogg FRA, Peach G, Price P, Thompson MM, Hinchliffe RJ. Measures of health-related quality of life in diabetes-related foot disease: a systematic review. Diabetologia. 2012;55:552-65.
5. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJM. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care. 2003;26:1435-8.
6. Armstrong DG, Todd WF, Lavery LA, Harkless LB, Bushman TR. The natural history of acute Charcot's arthropathy in a diabetic foot specialty clinic. Diabetic Med. 1997;14:357-63.
7. Frykberg RG, Belczyk R. Epidemiology of the Charcot foot. Clin Podiatr Med Surg. 2008;25(1):17-28.
8. Rajbhandari S, Jenkins R, Davies C, Tesfaye S. Charcot neuroarthropathy in diabetes mellitus. Diabetologia. 2002;45:1085-96.

9. Uccioli L, Sinistro A, Almerighi C, Ciaprini C, Cavazza A, Giurato L, et al. Proinflammatory modulation of the surface and cytokine phenotype of monocytes in patients with acute Charcot foot. Diabetes Care. 2010;33:350-5.
10. Jeffcoate W. The causes of the Charcot syndrome. Clin Podiatr Med Surg. 2008;25:29-42.
11. Game FL, Catlow R, Jones GR, Edmonds ME, Jude EB, Rayman G, et al. Audit of acute Charcot's disease in the UK: the CDUK study. Diabetologia. 2012;55:32-5.
12. Ross AJ, Mendicino RW, Catanzariti AR. Role of body mass index in acute charcot neuroarthropathy. J Foot Ankle Surg. 2013;52:6-8.
13. American Diabetes Association. Standards of Medical Care in Diabetes—2010. Diabetes Care. 2010;33:S11-61.
14. Sochocki MP, Verity S, Atherton PJ, Huntington JL, Sloan JA, Embil JM, et al. Health related quality of life in patients with Charcot arthropathy of the foot and ankle. Foot Ankle Surg. 2008;14:11-5.
15. WHOConsultation. Obesity: preventing and managing the global epidemic. World Health Organization technical report series 2000;894.
16. Grenon SM, Gagnon J, Hsiang Y. Ankle–brachial index for assessment of peripheral arterial disease. N Engl J Med. 2009;361:e40.
17. Schlesselman JJ. Case-control studies: design, conduct, analysis. New York: Oxford University Press; 1982.
18. Stuck RM, Sohn M-W, Budiman-Mak E, Lee TA, Weiss KB. Charcot arthropathy risk elevation in the obese diabetic population. Am J Med. 2008;121:1008-14.
19. Chantelau E, Wienemann T, Richter A. Pressure pain thresholds at the diabetic Charcot-foot: an exploratory study. J Musculoskelet Neuronal Interact. 2012;12:95-101.
20. Foltz KD, Fallat LM, Schwartz S. Usefulness of a brief assessment battery for early detection of Charcot foot deformity in patients with diabetes. J Foot Ankle Surg. 2004;43:87-92.
21. Petrova NL, Foster AVM, Edmonds ME. Difference in presentation of Charcot osteoarthropathy in type 1 compared with type 2 diabetes. Diabetes Care. 2004;27:1235-6.
22. Sinacore DR, Hastings MK, Bohnert KL, Fielder FA, Villareal DT, Blair VP, et al. Inflammatory osteolysis in diabetic neuropathic (Charcot) arthropathies of the foot. Phys Ther. 2008;88:1399-407.
23. Cavanaugh K, Wallston KA, Gebretsadik T, Shintani A, Huizinga MM, Davis D, et al. Addressing literacy and numeracy to improve diabetes care: two randomized controlled trials. Diabetes Care. 2009;32:2149-55.
24. Gerber BS, Brodsky IG, Lawless KA, Smolin LI, Arozullah AM, Smith EV, et al. Implementation and evaluation of a low-literacy diabetes education computer multimedia application. Diabetes Care. 2005;28:1574-80.
25. Rosal MC, Ockene IS, Restrepo A, White MJ, Borg A, Olendzki B, et al. Randomized trial of a literacy-sensitive, culturally tailored diabetes self-management intervention for low-income latinos: latinos en control. Diabetes Care. 2011;34:838-44.
26. Sarkar U, Fisher L, Schillinger D. Is self-efficacy associated with diabetes self-management across race/ethnicity and health literacy? Diabetes Care. 2006;29:823-9.
27. Coppini D, Masding M, Spruce M. A retrospective case study of Charcot osteoarthropathy. In The Diabetic Charcot Foot. 2007; p. 178-84.
28. Jeffcoate W. The definition of acute Charcot foot. In The Diabetic Charcot Foot. 2004, p. 178.
29. Christensen TM, Simonsen L, Holstein PE, Svendsen OL, Bülow J. Sympathetic neuropathy in diabetes mellitus patients does not elicit Charcot osteoarthropathy. J Diabetes Complications. 2011;25(5):320-4.
30. Leung HB, Ho YC, Wong WC. Charcot foot in a Hong Kong Chinese diabetic population. Hong Kong Med J. 2009;15(3):191-5.