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Sympathetic neuropathy in diabetes mellitus patients does not elicit Charcot osteoarthropathy

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ABSTRACT

Aim: The aim of the study was to determine the degree of neuropathy (autonomic and somatic) in patients with diabetes mellitus with or without Charcot osteoarthropathy (CA).
Methods: Forty-nine patients with diabetes mellitus type 1 or 2 were investigated. The patient population of interest was the patients with acute Charcot foot (n=17) or chronic Charcot foot (n=7). The inclusion criterion for an acute Charcot foot was a temperature difference of more than 2° between the two feet, oedema of the affected foot, typical hotspots in a bone scintigram and a typical clinical course. In addition, patients with first toe amputation (n=5), a high-risk group for development of CA, and two control groups consisting of diabetes patients with (n=9) or without somatic neuropathy (n=11) were investigated. Regional blood flow in the feet was measured by venous occlusion plethysmography. Quantitation of somatic neuropathy was done by the Neuropathy Disability Score and modified Neuropathy Symptom Score. Quantitation of autonomic neuropathy was done by measurements of local venoarteriolar sympathetic axon reflex in the feet and of heart rate variability during deep breathing and orthostatic challenge.
Results: The patients with acute Charcot foot and first toe amputation had an increased blood flow in the affected foot and weakened but not absent venoarteriolar sympathetic axon reflex. In the other patient groups, a normal venoarteriolar sympathetic axon reflex in the feet was found.
Conclusions: Peripheral sympathetic neuropathy is not likely to be the pathophysiologic mechanism behind the hyperemia in the foot during an acute attack of CA. The hyperemia is more likely secondary to local inflammatory events.

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1. Introduction

Charcot osteoarthropathy (CA) is a highly disabling disease with an incidence of 0.2%–0.3% in the general diabetic population (Fabrin et al., 2000; Giurini et al., 1991). The clinical signs of a CA is a warm, oedematous and in some cases red foot. In a recent study, we did not find any differences in bone mineral density of the calcaneus in the affected foot compared to the unaffected foot in patients with acute CA (Christensen et al., 2010). Peripheral sensory neuropathy seems to be a prerequisite to the development of CA (Jirkovska et al., 2006; Mabilleau & Edmonds, 2010; Wukich & Sung, 2009; Young et al., 1995). However, the pathogenesis of CA is at present still not well described. One theory is that sympathetic denervation in the lower limp causes increased blood flow and arteriovenous shunting that leads to increased temperature, oedema and subsequently osteopenia. Accordingly, the assessment of peripheral autonomic neuropathy in diabetic patients might be a tool for the early detection of imminent CA. Somatic peripheral neuropathy is a frequent complication in patients with diabetes mellitus. There has been focus on the somatic neuropathy and cardiac, gastrointestinal and urogenital autonomic neuropathy as these types of neuropathy cause significantly increased morbidity and mortality (Duby et al., 2004). On the contrary, the peripheral vascular autonomic neuropathy is frequently not diagnosed, partly because simple diagnostic tools are lacking and partly because there is a lack of effective treatment of the condition. However, dysfunction of peripheral sympathetic nerve fibres has been elucidated in studies of the venoarteriolar vasoconstrictor response elicited by lowering of the leg below heart level (Henriksen, 1976c; Cacciatori et al., 1997; Henriksen & Sejrsen, 1976; Henriksen & Sejrsen, 1977; Henriksen, 1976a, 1976b, 1976c; Yosipovitch et al., 1996).

Thus, the aims of the present study were to characterize the degree of central and peripheral cardiovascular autonomic neuropathy in diabetes mellitus type 1 or 2 patients with acute CA and to

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compare the findings with diabetes mellitus patients with increasing risks of CA. The lowest risk is in the patients without somatic neuropathy [incidence of 0.2% (Fabrin et al., 2000; Sinha et al., 1972)], while patients with amputation of a first toe have an frequency of CA of up to 24% (Bitsch et al., 2003).

2. Methods

Five groups of patients all having diabetes mellitus were studied. The groups comprised 17 subjects with acute CA, 7 with chronic CA, 5 with amputation of first toe, and 9 with and 11 without somatic neuropathy. The patients with acute CA, first toe amputation or chronic CA were recruited from diabetes patients who visited our foot clinic during a 2-year period. The inclusion criteria for acute CA were clinical signs of CA, namely, a warm, swollen red foot with a temperature difference from the contralateral foot by more than 2°C. The diagnosis was confirmed by scintigraphic findings since positive scans have been reported to precede radiographic changes (Sella, 2009; Shanmuga Sundaram et al., 2007). X-rays of the Charcot foot were performed in all patients. Inclusion criteria for the patients in the chronic CA group were manifest deformity of the foot that had been preceded by an acute stage describe above, but with no temperature difference between the feet (they all used orthopaedic footwear). The patients with an amputation of the first toe were defined as patients who had had surgery on a first toe. The patients were investigated just before they were allowed to walk without a weight off-loading cast, typically 6 weeks after the surgery. Furthermore, two groups of diabetes patients with neuropathy or without somatic neuropathy were studied. They were selected in an attempt to match the CA group according to age (±5 years), diabetes duration (±5 years), sex and diabetes type.

2.1. Assessment of somatic neuropathy

The degree of neuropathy was assessed by the Neuropathy Disability Score (NDS) (Donaghue et al., 1995), biothesiometry, examination by monofilament and a modified patient questionnaire, the Neuropathy Symptom Score (NSS) (Dyck, 1988). The NDS consist of examination of sensation and reflexes. The sensations examined were vibration threshold, pin prick, cold perception and light touch. The responses from the patient are classified according to anatomic levels, and points were given for each sense disturbance: 0, normal; 1, base of toe; 2, metatarsus; 3, ankle; 4, mid lower leg and 5, knee. The reflex examinations are of the patellar and Achilles reflex, and the outcomes were evaluated as normal (0 point), present but extra force to trick the reflex (1 point) or lacking (2 points).

The mean score from the four sensory examinations was added to the points from the reflex examinations. A score from 1 to 5 points is mild neuropathy, 6 to 16 moderate neuropathy and 17 to 28 severe neuropathy (Donaghue et al., 1995). The modified NSS elucidates the subjective symptoms and sensations from the lower legs. The questionnaire consist of seven questions about muscle cramp, cold/warm sensations, burning pain, itching pain and sleeping/dead sensations in foot and if the patient answered yes to any of the questions of whether the symptoms were present at night (Donaghue et al., 1995). Symptoms were scored with 1 point if present or 2 points if present with nocturnal exacerbation.

Semmes–Weinstein monofilaments were used to assess the cutaneous perception threshold (CCPT). The nylon monofilament was applied to the skin three times at the same spot; the subject had to register two out of three touches to be classified as sensation.

The nylon monofilament was applied to the plantar surface of the first toe, the base of the first toe, the base of the fifth toe and the heel of both feet. The monofilament applies a pressure of 10 g, and patients who are unable to feel it are considered to be at high risk of foot ulceration (Kumar et al., 1991).

2.2. Assessment of peripheral autonomic neuropathy

The activity of the local venoarterial sympathetic axon reflex was used to assess the autonomic neuropathy in the foot (Henriksen & Sejrsen, 1977). A small bolus of ^{99m}Tc was injected subcutaneously at the ankle level (above the lateral malleolus) using a 27-gauge canula about 60 min before commencement of the measurements. The washout rate was measured by a Mediscint scintillation detector system (Oakfield Instruments, Oxford, UK). The detector was strapped to the leg to avoid geometric displacement and hence a possible lower detection rate, initially with the foot placed at heart level and then with the foot placed 50 cm below heart level. The latter position results in an about 38-mmHg increase in local venous pressure, which will elicit activation of the local venoarterial sympathetic axon reflex. After this, the foot was again placed at heart level. In each position, the washout rate was recorded during 10 min. More than 40% decrease in subcutaneous blood flow with the foot below heart level was considered normal. Absolute values of subcutaneous blood flow were calculated from the washout rate of ^{99m}Tc using a tissue/blood distribution coefficient of 1 ml/g.

Total blood flow in the foot was measured after the patients had rested in a horizontal position for approximately 30 min with bare feet by venous occlusion strain gauge plethysmography (Hokanson EC6 Plethysmograph, Bellevue, WA, USA). The strain gauge was strapped around the metatarsus, and the occlusion cuff was placed at a level just proximal to the malleoli. During measurements, the cuffs were inflated to 40 mmHg. Blood flow was calculated using the NIVP software (Hokanson Ltd., Bellevue, WA, USA). The blood flow is given as an average of at least five measurements.

2.3. Assessment of central autonomic neuropathy

Heart rate variability (HRV) (PowerLab, Chart 5 v5. 5. 5; ADInstruments Pty. Ltd., Castle Hill, NSW, Australia) was assessed and analysed in the time domain during controlled respiration. After 10 min of supine rest, the subject was instructed to do six deep regular respirations per minute. Two sampling periods were performed, and the quality of the recording was verified by spectral analysis of the frequencies, where the highest amplitude of the frequencies should be at 0.1 Hz. Heart rate variability of less than 10 beats/min was considered abnormal, and that of more than 15 beats/min was considered normal (Ewing, Martyn, Young, Clarke, 1985).

2.3.1. Ethics

The ethical committee of Copenhagen approved the study [project no. (KF) 01 285758] in accordance with the Declaration of Helsinki. The Danish Data Protection Agency likewise approved the study (project no. 2005-41-4869).

The subjects were given a written and an oral description of the study and the possible risk and discomfort involved before giving their voluntary consent to participate.

2.3.2. Statistics

The data are presented as mean±S.E.M. The software SPSS version 11 was used for the statistical analysis. Values that were normally distributed were evaluated by parametric tests, differences between the feet within the groups were evaluated by paired *t* test, and differences between the groups were evaluated by analysis of variance with Bonferroni correction. $P<.05$ was considered statistically significant.

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