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Muscle hyperalgesia is widespread in patients with complex regional pain syndrome

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ABSTRACT

Patients with complex regional pain syndrome (CRPS) frequently show prominent sensory abnormalities in their affected limb, which may extend proximally and even to unaffected body regions. This study examines whether sensory dysfunction is observed in unaffected body parts of CRPS patients, and investigates whether the extent of dysfunction is similar for the various sensory modalities. Quantitative sensory testing was performed in the unaffected extremities and cheeks of 48 patients with CRPS of the arm (31 with dystonia), and the results were compared with values obtained among healthy controls. The most prominent abnormality was the pressure pain threshold, which showed a consistent pattern of higher sensitivity in unaffected contralateral arms and unaffected legs, as well as the cheek, and demonstrated the largest effect sizes. The cheeks of CRPS patients showed thermal hypoesthesia and hyperalgesia as well as a loss of vibration detection. Except for a lower vibration threshold in the contralateral leg of CRPS patients with dystonia, no differences in sensory modalities were found between CRPS patients with and without dystonia. These results point to a general disturbance in central pain processing in patients with CRPS, which may be attributed to impaired endogenous pain control. Since pressure pain is the most deviant sensory abnormality in both unaffected and affected body regions of CRPS patients, this test may serve as an important outcome parameter in future studies and may be used as a tool to monitor the course of the disease.

1. Introduction

Sensory abnormalities are a significant feature of complex regional pain syndrome (CRPS) and may include impairments related to a loss of function and a gain of function [21]. Quantitative sensory testing, a useful tool to quantify these sensory abnormalities, has highlighted increased pressure sensitivity as the most pronounced sensory impairment in CRPS, indicating a shift to more pronociceptive pain modulation in this condition [21,35]. Interestingly, changes in sensory perception levels, including thermal and mechanical hyperalgesia and hypoesthesia, have also been demonstrated in unaffected regions of CRPS patients [7,8,14,15,17,29]. The spread of hyperalgesia to unaffected body regions may be the effect of mechanisms underpinning the chronification of pain and may predispose patients to the spread of CRPS symptoms, which sometimes can occur spontaneously or be triggered by a seemingly insignificant injury [34]. However, to date is it is unknown whether sensory dysfunction is a widespread phenomenon throughout the body in CRPS patients and, if so, whether the various sensory modalities are affected to a similar extent. The aim of this study was therefore to investigate sensory function in unaffected body parts of CRPS patients and to compare their values with those of healthy controls. Based on the results of previous studies in affected limbs, we hypothesized that pressure pain thresholds (PPTs) in the patients' unaffected body regions would be different when compared with healthy controls. As pressure sensitivity (muscle hyperalgesia) was shown to be related to motor functioning in CRPS patients, as well as to the severity of dystonia [15,35], patients with and without dystonia were also compared. Other sensory modalities were tested for in an exploratory manner.

2. Methods

2.1. Participants

Forty-eight patients with CRPS of at least one upper limb (31 with dystonia and 17 without dystonia) and 42 healthy controls participated in this study, which was carried out between May

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2009 and February 2011 (Table 1). CRPS was diagnosed according to the criteria of the International Association for the Study of Pain [24], which were the recommended criteria at the time the study was conducted. Disease duration was ⩾1 year in 94% of the patients (range 0.65–35.2 yrs).

Patients were asked to rate the mean pain of their (most affected) upper limb over the last week on a numerical rating scale ranging from 0 (no pain) to 10 (worst pain imaginable). Additionally, patients used the McGill Pain Questionnaire to report which words applied to the pain of their (most affected) extremity during the week before the measurement.

Tonic dystonia was defined as a condition in which continuous muscle contractions lead to abnormal postures, from which return to a neutral position is not possible or only possible with great difficulty. The severity of the dystonia was assessed with the Burke-Fahn-Marsden scale [4]. Patients were excluded if they had lesions or diseases of the central nervous system, a genetic form of dystonia, or conditions other than CRPS that could account for the presence of dystonia. Healthy controls were not included if they had a history of lesions or diseases of the central or peripheral nervous system, or other conditions associated with pain and/or limited function of the extremities. This study was approved by the local ethics committee and written informed consent was obtained from all participants.

2.2. Sensory testing

Quantitative sensory testing measures were executed according to the protocol developed by the German Network of Neuropathic Pain [27,28]. Tests were performed by a trained examiner in a quiet room where the temperature was held constant at 22–3°C. Patients were not allowed to watch the tested limb and were instructed to look away from the test site, except for the vibration threshold condition, in which patients were blindfolded. The mean of 3 measurements was used for further analysis, besides the pinprick hyperalgesia test, which was performed only once.

2.2.1. Thermal thresholds

A 3 × 3 cm Peltier element (TSA 2001-II, Medoc, Ramat Yishai, Israel) was used to test thermal sensation (warm and cold detection thresholds, heat and cold pain thresholds). All tests were performed on the dorsum of the hands and feet, and over the masseter muscle of the cheek. The method of limits was used, with temperatures increasing at a rate of 1°C/second, starting from the baseline temperature of 32°C, and with an interstimulus interval of 10 seconds. The safety cutoffs were 0°C and 50°C. Patients were instructed to press a stop-button when they felt the slightest change in temperature in the case of detection thresholds, or at the first burning or stinging sensation in the case of pain thresholds. When subjects did not perceive a detection or pain threshold, the maximum value was recorded.

2.2.2. Pressure pain thresholds

The PPT was measured over the abductor pollicis brevis, abductor hallucis, and masseter muscles with an electronic algometer (FPX50, Wagner instruments, Greenwich, CT, USA). The pressure was increased at a rate of 1 kg/second until the participant reported that the sensation was painful.

2.2.3. Pinprick hyperalgesia

The sharpness of a single application of a blunt needle to the skin was measured using a custom-made pinprick. A pinprick that exerted a force of 256 mN was used for tests over the hands and feet, whereas a lower force pinprick of 128 mN was used for tests over the cheek. Patients were asked to rate the perceived pain on a 0–100 numerical rating scale after perceiving one stimulus.

2.2.4. Vibration thresholds

A vibrameter (Type II, Somedic, Stockholm, Sweden) was used to test the vibration detection threshold on the first metacarpal and metatarsal bones, and the cheek bone. The probe was held with a constant pressure of 450 g, which was maintained with feedback displayed on the vibrameter.

2.3. Statistics

Only unaffected extremities were included in the current analysis. The values obtained from the patient's unaffected hand were compared with values obtained from the nondominant hand of the healthy controls. All analyses were performed using IBM SPSS Statistics 20.0 (SPSS Inc., Chicago, IL, USA). The normality of the parameters was tested using the Kolmogorov-Smirnov test and inspection of the normality plots. Normally distributed log-transformed values were compared between patients and healthy controls for those variables where raw data were not normally distributed. Differences between groups were assessed with unpaired *t* tests for normally distributed continuous data, whereas Mann-Whitney *U* tests were used for non-normally distributed data. Frequencies and proportions were assessed with χ^2 tests. $P < 0.05$ was considered significant. As this study was considered exploratory,

Table 1
Demographic and clinical characteristics of all participants.

	CRPS patients n = 48	Healthy controls n = 42	*P* value
Sex, male/female	13/35	9/33	0.626
Age in years, mean (SD)	46.4 (12.1)	46.7 (12.0)	0.888
Disease duration in years, mean (SD)	10.0 (7.4)		
Type of trauma or precipitating event, n			
Soft tissue trauma	17		
Fracture	11		
Surgery	10		
Spontaneous	10		
Unaffected limbs, n (right/left)			
Contralateral hands	21 (9/12)		
Ipsilateral legs	24 (16/8)		
Contralateral legs	30 (13/17)		
Patients with >1 affected extremity, n	27		
Patients with dystonia, n	31		
NRS pain score affected hand, mean (SD)	6.2 (2.1)		
McGill pain rating index	25.7 (9.8)		

CRPS, complex regional pain syndrome; NRS, numerical rating scale (range 0–10).