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MOVEMENT DISORDERS - SHORT COMMUNICATION

Thermal hypesthesia in patients with complex regional pain syndrome related dystonia

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Abstract The quantitative thermal test showed cold and warmth hypesthesia without increased heat pain sensitivity in the affected limbs of complex regional pain syndrome (CRPS) patients with tonic dystonia ($n = 44$) in comparison with healthy controls with a similar age and sex distribution ($n = 35$). The degrees of cold and warmth hypesthesia were strongly correlated. We conclude that dysfunction in small nerve fiber (i.e., C and Aδ) processing is present in patients with CRPS-related dystonia.

Keywords Complex regional pain syndrome · Dystonia · Quantitative thermal test · Psychophysics · TREND study

Introduction

Complex regional pain syndrome (CRPS) is characterized by various combinations of sensory, autonomic and motor disturbances and is usually preceded by a trauma. Patients with CRPS often experience spontaneous pain along with allodynia, hyperalgesia and hyperesthesia (Janig and Baron 2003; Veldman et al. 1993). In addition, negative sensory phenomena, such as hypesthesia and hypalgesia may be present, especially in chronic cases with longer disease duration (Birklein et al. 2000; Janig and Baron 2003; Rommel et al. 1999; van Hilten et al. 2001). Autonomic signs include changes in skin temperature and color, and hyperhidrosis (Janig and Baron 2003; Veldman et al. 1993). About 25% of the patients develop movement disorders, especially dystonia (Bhatia et al. 1993; Schwartzman and Kerrigan 1990; van Hilten et al. 2005). In contrast to the twisting and repetitive movements generally encountered in primary dystonia, dystonia in CRPS is typically characterized by fixed flexion postures of the distal extremities. Two types of CRPS are generally distinguished, depending on the presence (CRPS-2) or absence (CRPS-1) of major nerve damage (Merskey and Bogduk 1994).

In primary dystonia, there is compelling evidence of altered sensory processing (Tinazzi et al. 2009) which includes abnormalities in temporal and spatial discrimination and vibration-induced illusion of movements as well as higher-order sensory processing. In CRPS related dystonia, sensory integration of proprioceptive afferent input was found normal (van Rijn et al. 2009b). By definition there is no clear involvement of large nerve fibers in CRPS-1. Until now the function of the small nerve fibers (i.e., C and Aδ), as opposed to large nerve fiber function, has not been studied in this type of dystonia.

The quantitative thermal test is a non-invasive clinical test which assesses the function of small fibers and their central connections (Verdugo and Ochoa 1992; Yarnitsky 1997). The technique quantifies temperature sensation by testing minimally detectable temperature changes ('thresholds') for cold (CDT) and warmth detection (WDT), as well as for heat-induced (HPT) and cold-induced pain (CPT).

We hypothesized that small nerve fiber, in contrast to large nerve fiber, dysfunction is present in CRPS related dystonia. Though disturbances in temperature sensation were earlier shown in CRPS patients without dystonia, its presence in those with dystonia is unknown. In this study we applied the quantitative thermal test to evaluate C and Aδ fiber dysfunction in CRPS patients with dystonia. Since

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these patients may sometimes have three or even four affected extremities, and because an unaffected extremity may be involved on a subclinical level, we chose to compare results primarily with those of healthy controls. Whenever possible, comparisons were also made between affected and unaffected sides.

Patients and methods

We studied 44 consecutive CRPS-1 patients (41 women; mean age ± SD: 36 ± 13 years; mean disease duration ± SD: 10 ± 6 years) who were candidates for a study on intrathecal baclofen treatment (Table 1). This study was published in detail elsewhere (van Rijn et al. 2009a). CRPS was diagnosed according to the diagnostic criteria for CRPS-1 of the International Association for the Study of Pain (Merskey and Bogduk 1994). Patients with peripheral neuropathy were excluded. Severity of pain was evaluated with a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain). Severity of dystonia was assessed with the Burke-Fahn-Marsden (BFM) dystonia rating scale (Burke et al. 1985), which ranges from 0 to 120 with higher scores reflecting more severe dystonia.

For control purposes, 35 healthy controls (all women) with a similar age distribution (mean ± SD: 40 ± 13 years), who had no diseases of the nervous system and did not receive any neuroactive drugs were also investigated. Controls were partners, relatives or friends of patients, or were recruited among the hospital staff. We used the data from the non-dominant control limbs in the primary analyses, because we hypothesized that if there would be any differences in sensory acuity between both sides, this would be on the non-dominant side. Informed consent was obtained from all subjects according to the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Leiden University Medical Center.

Table 1 Characteristics of the 44 CRPS patients with dystonia

Characteristic	Value
Gender (F/M)	41/3
Age (year; mean, SD)	36 (13)
Duration of CRPS (year; mean, SD)	10 (6)
Severity of pain (NRS; mean, SD)	7.7 (1.4)
Number of affected extremities (%)	
1	0
2	8 (18)
3	7 (16)
4	29 (66)
Number of affected arms (%)	
1	9 (20)
2	33 (75)
Number of affected legs (%)	
1	9 (20)
2	34 (77)
Number of extremities with dystonia (%)	
1	2 (4)
2	11 (25)
3	9 (21)
4	22 (50)
Severity of dystonia (BFM; mean, SD)	50 (21)
Sensory abnormalities, *n* (%)	43 (98)
Mechanical hypesthesia or hypalgesia	37 (84)
Mechanical hyperesthesia, hyperalgesia or allodynia	25 (57)

BFM Burke-Fahn-Marsden dystonia rating scale (range 0–120, with 0 = no dystonia) (Burke et al. 1985), *CRPS* complex regional pain syndrome, *F* female, *IQR* interquartile range, *M* male, *NRS* numeric rating scale (range 0–10, with 0 = no pain)

Quantitative thermal test

A TSA-II NeuroSensory Analyzer (Medoc Ltd., Ramat Yishai, Israel) was used to determine CDT, WDT, and HPT of both hands (thenar eminence) and both feet (dorsal aspect of the first metatarsal bone). CPT was not tested to minimize discomfort. These tests were performed by trained technicians in a quiet room at a temperature of 20–22°C. Subjects were measured in supine position and were not allowed to watch the computer screen. The 'method of levels' algorithm was used, in which the thermode returns to its baseline temperature (32°C) after each temperature change. After each stimulus period subjects are asked whether a (painful) change was perceived. The amplitude of the next temperature change is based on the response given after a stimulus: when no change of temperature has been perceived, the temperature change for the next step is doubled. If a change was perceived, the amplitude for the next step was halved. The procedure was continued until the step size reached 0.1°C. To alert the subject that a stimulus was imminent each stimulus was preceded by an auditory cue. Lower and higher temperature limits were 15.0° and 50.0°C, respectively; rate of temperature change 1.0°C/s (CDT, WDT) and 4.0°C/s (HPT); stimulus duration 5 s; return rate 10°C/s; and interstimulus interval 5 s (CDT, WDT) and 9 s (HPT).

Statistical analysis

The data were not distributed normally (Kolmogorov–Smirnov statistics for raw and log-transformed CDT and WDT data, and raw HPT data, $P < 0.05$) and therefore non-parametric tests were used. The significance threshold was set at $P < 0.05$. For all tests, the SPSS software package version 14.0 (SPSS Inc., Chicago, IL) was used.

Results

Patients versus controls

Thermal thresholds were evaluated in 37 hands of 28 patients, and in 48 feet of 37 patients; testing on the other sites was not feasible due to dystonia or pain. The CDT and WDT were abnormal in the patients' affected limb in comparison with the controls' non-dominant limbs (Table 2). There was a strong positive correlation between CDT and WDT in patients (Spearman rho = 0.66, $P < 0.001$) and a trend towards significant association in controls (Spearman rho = 0.33, $P = 0.05$). HPT did not differ between patients and controls (HPT hand: $P = 0.50$, HPT foot: $P = 0.53$).

Compared with the non-dominant limbs of controls, CDT and WDT of patients' unaffected limbs were increased, although the difference was not significant (Table 2). There were no significant differences in thresholds between non-dominant and dominant limbs in controls (data not shown).

Within and between patients comparisons

Nine patients had one affected arm, and also nine patients had one affected leg (Table 1). The affected limbs showed elevated CDT and WDT in comparison with their unaffected counterparts, but this was only significant for WDT in the hands (Table 2).

Relations between clinical characteristics and thermal thresholds

There was no significant correlation between the severity of pain (NRS) and any threshold (data not shown), nor between dystonia (BFM) and any threshold. Although disease duration varied considerably between patients, none of the thresholds showed significant associations with this variable. There were no significant differences in thermal thresholds between patients who used analgesics versus those who did not.

Discussion

Although thermal thresholds have previously been examined in CRPS patients without dystonia (Birklein et al. 2000; Huge et al. 2008; Kemler et al. 2000; Rommel et al. 2001), this issue has not been addressed in CRPS patients with dystonia. These earlier studies have yielded variable findings that most likely are explained by differences in applied methods and population characteristics. The general picture that arises from these studies is that CDT and WDT are elevated (i.e. reflecting thermal hypesthesia) in patients with disease durations up to 4 years, with the possible exception of CDT in patients with short disease duration (6 months); findings on CPT and HPT are contradictory. In the present study we found cold and warmth hypesthesia together with normal HPT in the affected arms and legs of CRPS patients with dystonia.

Thermal hypesthesia may be caused by disturbances at multiple levels of the nervous system. First, small fiber pathology has been demonstrated in CRPS (Albrecht et al. 2006; Oaklander et al. 2006; van der Laan et al. 1998) and may explain our findings. In addition, it is known that impairment of C and Aδ fibers typically leads to thermal hypesthesia while sparing heat-induced pain, due to

Table 2 Comparison of thermal thresholds between CRPS patients' affected and controls' non-dominant extremities and between patients' affected and unaffected side

	Hand			Foot		
	CDT (ΔT)	WDT (ΔT)	HPT	CDT (ΔT)	WDT (ΔT)	HPT
Patients versus controls						
Patients, $n = 44$	−1.0 (−2.4 to −0.5)	1.7 (0.7–5.6)	43.0 (35.0–48.8)	−5.1 (−8.9 to −1.9)	10.2 (3.7–13.2)	44.0 (36.5–49.0)
Controls, $n = 35$	−0.2 (−0.5 to −0.1)	0.5 (0.3–0.7)	44.0 (43.0–46.8)	−0.5 (−1.5 to −0.4)	2.6 (1.8–5.6)	45.8 (42.8–47.0)
P value	<0.0005	<0.0005	0.50	<0.0005	<0.0005	0.53
Patients[a]						
Affected limb, $n = 7$	−0.5 (−1.4 to −0.4)	2.0 (0.8–5.4)	41.5 (35.0–48.5)	−3.3 (−8.4 to −0.1)	10.4 (3.1–11.7)	46.5 (45.5–47.0)
Unaffected limb, $n = 7$	−0.4 (−0.6 to −0.1)	0.7 (0.3–1.5)	47.0 (42.8–47.3)	−1.3 (−2.3 to −0.6)	4.4 (2.3–11.8)	46.0 (43.5–47.8)
P value	0.24	0.01	0.46	0.25	0.18	0.46

Data represent median values (°C) with interquartile ranges shown in parentheses

CDT cold detection threshold (difference from baseline temperature), *CRPS* complex regional pain syndrome, *HPT* heat-induced pain threshold, *WDT* warmth detection threshold (difference from baseline temperature), ΔT difference with baseline temperature

[a] Note that most patients were excluded because they had two affected hands or two affected feet; number of patients is slightly different from Table 1 because testing was impossible in two patients due to dystonia or pain (both for hands and feet)

differences in spatial summation requirement (Verdugo and Ochoa 1992). Second, C fiber activation by capsaicin injection elicited reversible tactile hyperalgesia and hypesthesia not only at the site of injection, but also in the adjacent tissue (Magerl and Treede 2004). This was attributed to rerouting of somatosensory input from non-nociceptive into nociceptive pathways in the spinal dorsal horn. Therefore, plasticity-related changes of sensory processing at the spinal level may also be an explanation for our findings. Third, in a population of 40 CRPS patients with one affected extremity, neurological examination showed hemisensory deficits including the face in 15 (38%) (Rommel et al. 2001). The authors suggested that functional changes in the thalamus may play an important role in the pathogenesis of sensory abnormalities. Fourth, a shrunk representation area of the affected hand was found in the primary somatosensory cortex of CRPS patients (Juottonen et al. 2002; Maihofner et al. 2003; Pleger et al. 2004). Reduced activation of the contralateral primary and secondary somatosensory cortex after tactile stimulation has also been reported in CRPS (Pleger et al. 2004) and similar cortical changes may underlie thermal hypesthesia.

In conclusion, we found thermal hypesthesia in CRPS patients with dystonia. Apparently, dysfunction in small nerve fiber (i.e., C and Aδ) processing is present in these patients. Whether this sensory abnormality is a secondary phenomenon or is in fact involved in the causal pathway to dystonia is uncertain.

For a further understanding, clinical studies on the efficacy of sensory rehabilitation in CRPS-related dystonia are warranted.

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Conflict of interest The authors state that they have no conflict of interest.

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