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Prospective Evaluation

Objective Sensory Evaluation of the Spread of Complex Regional Pain Syndrome

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Background: The spread of complex regional pain syndrome (CRPS) has been well documented. Many severe refractory long-standing patients have total body pain (TBP) that evolved from a single extremity injury.

Objective: The purpose of this study was to document by objective sensory threshold testing the extent of body area involvement in 20 long-standing patients with CRPS who have TBP.

Study Design: A comparison of sensory threshold testing parameters between 20 long-standing refractory patients with CRPS who have TBP versus 10 healthy participants.

Methods: Twenty patients with CRPS who stated that they suffered from total body pain were chosen from the Drexel University College of Medicine CRPS database. They were compared to 10 healthy participants that were age and gender matched to the patients with CRPS. The sensory parameters tested were: skin temperature; static and mechanical allodynia; thermal allodynia; mechanical hyperalgesia; after sensations following all sensory tests. The sites chosen for testing in the patients with CRPS were the most painful area in each of 8 body regions that comprised the total body area.

Results: Five patients with CRPS had signs of CRPS over 100% of their body (20%). One patient had pain over 87% and another had pain over 90% of their body area. The average percentage of body involvement was 62% (range 37% – 100%). All patients with CRPS had at least one sensory parameter abnormality in all body regions. All patients with CRPS had lower pain thresholds for static allodynia in all body areas, while 50% demonstrated a lower threshold for dynamic allodynia in all body regions compared to the healthy participants. Cold allodynia had a higher median pain rating on the Likert pain scale in all body areas versus healthy participants except for the chest, abdomen, and back. Eighty-five percent of the patients with CRPS had a significantly lower pain threshold for mechanical hyperalgesia in all body areas compared to the healthy participants. After sensations occurred after all sensory parameters in the extremities in patients with CRPS.

Limitations: The primary limitations of this study would be the variability of self-reported data (each subject's assessment of pain/ discomfort to a tested parameter) and the challenge to uniformly administer each parameter's assessment since simple tools and not precision instruments were used (with the exception of skin temperature).

Conclusions: TBP and objective sensory loss occur in 20% of patients with refractory long-standing CRPS.

Key words: CRPS, complex regional pain, static allodynia, dynamic allodynia, mechano-allodynia, thermal allodynia, allodynia, hyperalgesia, after sensation, total body pain, chronic pain.

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Complex regional pain syndrome (CRPS) is a well-documented chronic neuropathic disorder most often triggered by a defined peripheral nerve injury (CRPS II) or their terminal twigs in soft tissue (1-3). The diagnosis of CRPS is primarily clinical with standardized criteria derived by Harden and Bruehl (4). That the syndrome can spread from the initial site of injury is well known, however the extent of the spread to total body involvement has not been previously objectively documented (5-16).

The purpose of this study is to document the extent of body area involvement by objective sensory threshold testing in a subset of patients who stated that they suffered total body pain.

Methods

Patient Demographics

Twenty patients with CRPS were chosen from the Drexel University College of Medicine (DUCOM) CRPS database who stated that they suffered from total body CRPS pain. The control group consisted of 10 pain-free, age and gender matched participants. In the group with CRPS there were 18 women (age 21–59 years; average age, 39.9 years) and 2 men (ages 24 and 46; average age, 35 years). All patients and participants were white (Table 1). The patients had a long-standing CRPS diagnosis (from 8 months to 288 months, average duration of 109.6 months with a standard deviation (SD) of 63.4 months; the SD for the women was 9.13 years and the SD for the men was 5.28 years). The inciting trauma for 9 patients was a lower extremity (LE) injury; the other 11 had an upper extremity (UE) injury. Five of the 11 patients with UE injury suffered brachial plexus traction injuries, 2 had suffered hand crush injuries, and 4 had had carpal tunnel surgeries. Five patients with LE injury CRPS suffered radiculopathy, followed by surgery; 3 had soft tissue musculoskeletal injuries; and 2 had crush injuries of the foot with neuroma formation.

Inclusion and Exclusion Criteria

The inclusion criteria for the 20 patients with CRPS were: age between 18–65 years; a diagnosis fulfilling the Budapest clinical criteria (17); a history of multi-extremity or extensive pain as documented in the patient's record or examination. The patients were

Table 1. *Demographic data for all patients with CRPS enrolled. The index site is the site of first involvement by the disease. All patients enrolled were white.*

Patient ID	Age	Gender	Index Site	Disease Duration (months)	% Body with Signs on Exam
1	23	Female	Left foot	96	100%
2	26	Female	Left knee	144	90.00%
3	21	Female	Right ankle	120	87.00%
4	24	Male	Left shoulder	72	42.80%
5	33	Female	Left arm	144	100%
6	51	Female	Right shoulder/ back	168	38.30%
7	50	Female	Both feet	48	100%
8	41	Female	Right wrist	156	42.80%
9	28	Female	Right hand	144	36.70%
10	28	Female	Both thighs	60	49.40%
11	56	Female	Left foot	288	55.50%
12	56	Female	Right leg	108	42.80%
13	46	Male	Rt Forearm	24	42.80%
14	42	Female	Right foot	8	100%
15	59	Female	Right shoulder	72	52.00%
16	36	Female	Left knee	144	36.70%
17	44	Female	Diffuse	60	42.80%
18	35	Female	Left shoulder	60	100%
19	37	Female	Low back	120	39.40%
20	53	Female	Right elbow	156	52.00%

recruited from the DUCOM pain clinic. The inclusion criteria for the control participants were age and gender that matched the patients with CRPS. Exclusion criteria for control participants were any pain condition or any acute or chronic pain medication use. The control participants were recruited from the community.

Parameters Evaluated

Neurological Examination

A complete neurologic examination was performed on all patients with CRPS and control participants. The specific features pertinent to CRPS that were documented included spontaneous pain and evoked mechanical and thermal allodynia; hyperalgesia and hyperpathia; neuropathic edema; autonomic dysregulation (temperature change, mottling and livedo reticularis, hyperhidrosis); movement disorder (weakness, myoclonus, tremor, dystonia and spasm); dystrophy (thin, brittle, hypertrophic or ridged nails, increased or decreased hair growth, shiny atrophic skin, muscle and integument atrophy).

Sensory Tests

The sensory parameters tested were skin temperature; static and mechanical allodynia; thermal allodynia (18); algesic mechanical allodynia (pinprick); after sensation (following all sensory tests). The sites chosen for testing in the patients with CRPS were the most painful area they would allow to be tested in each of the 8 body regions. The sites tested in the control participants were standardized points in each of the 8 body regions. The tests were performed as briefly as possible to avoid manifestations of central sensitization that would affect consecutive tests. The examination protocol was designed to progress from the least noxious stimulus (dynamic mechanical allodynia) to the most (mechanical hyperalgesia; pinprick).

There was a 2 to 5 minute pause between each sensory test. Some patients required a longer time period between tests to return to their pain baseline, but none was longer than 10 minutes. A few patients with CRPS would not allow algesic (pinprick) mechanical hyperalgesia testing on a specific body part. There were a few patients with CRPS in whom either light touch or 20 grams of force did not reach pain threshold. Testing was terminated at this level because of a concern of increasing these patients' overall pain level or inducing a prolonged pain flare. This accounts for the difference in the number of patients with CRPS tested in each body region.

Prior to sensory testing, skin temperature was recorded in one point in each body region using an Exergen Dermatemp infrared skin thermometer (Exergen Corporation, Watertown, MA) (19). Static nonhyperalgesic allodynia was measured using a Wagner Force Dial TM algometer (Wagner Instruments, Greenwich, CT) with a one cm^2 flat rubber tip with a range of force between 0 to 5 kg (20). Prior to the start of each modality testing session the patient or participant was asked to signal to the examiner when pain was felt. The examiner placed the algometer on each specific region and gradually increased the pressure until the patient or participant experienced pain or 4 kg of pressure was reached. Static mechano-allodynia was also determined for the upper trunk of the brachial plexus in the supraclavicular fossa (C5, C6 roots) and the popliteal fossa (the bifurcation of the posterior tibial and peroneal nerves).

Dynamic mechanical allodynia measurements were obtained using a standard one-inch foam brush (21). Five strokes of the brush were made over a 3-inch sensitive area at the rate of one stroke per second. The threshold was measured as the number of strokes required to elicit pain (zero was equivalent to pain with one brush stroke and a score of 5 was no evoked pain with 5 brush strokes).

A metal tuning fork chilled in an ice water bath to 2°C was utilized to evaluate cold thermal allodynia. Patients and participants were asked to rate pain on the Likert numeric rating scale of zero to 10 (zero being no pain and 10 the worst pain imaginable) (22).

The threshold for algesic mechanical hyperalgesia was measured using a Neuropen (Owen Mumford, Oxford, United Kingdom) (23). The patients and participants were instructed to indicate when they felt pain during pen pressure applied to the body part. The Neuropen exerts force in increments of 0 g, 20 g, and 40 g. For statistical analysis purposes, a scale was constructed such that zero represented no pain evoked by 40 g of pin pressure, 1 represented pain evoked by 40g of pin pressure, 2 represented pain evoked by 20 grams of pressure, and 3 represented pain evoked by touch (no pin pressure).

After sensation, pain perception lasting longer than 30 seconds after the stimulus withdrawal was recorded following the 4 sensory tests on each limb (24).

Hand grip strength, range of motion and sustained finger tapping were assessed in each patient and participant. Hand grip strength was measured

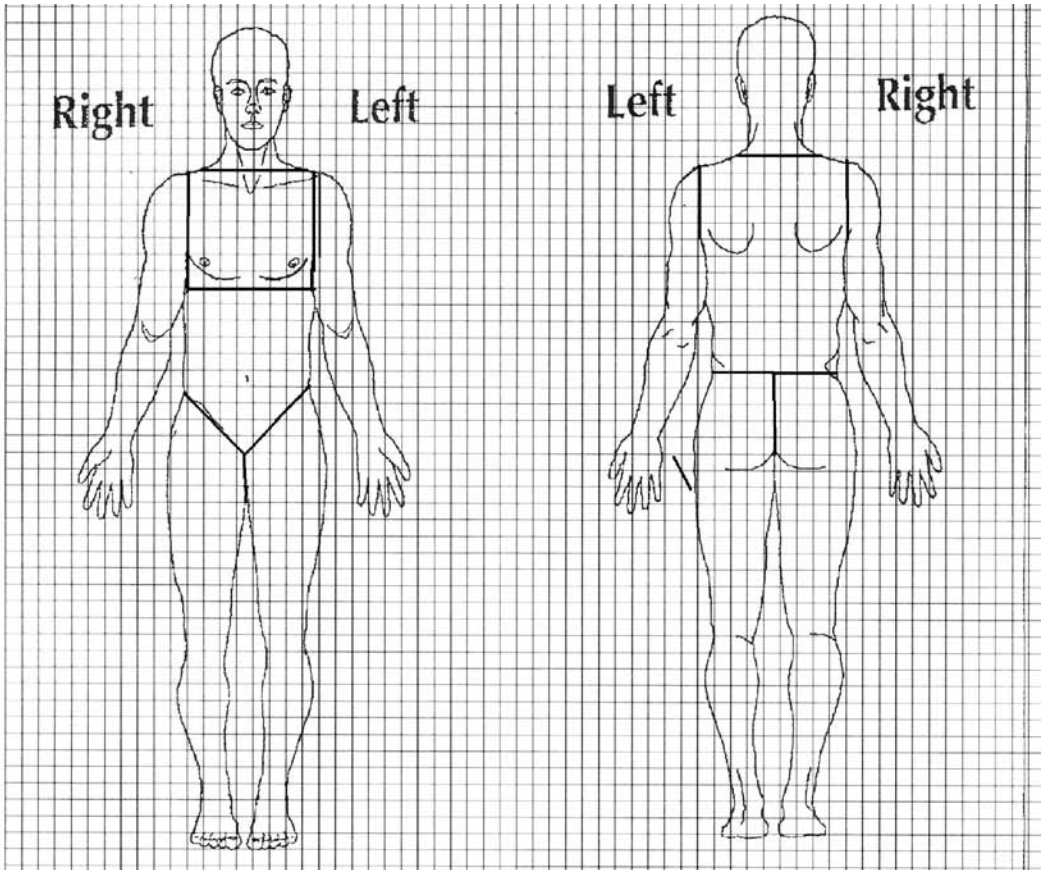

Fig. 1. Planimetry tool for estimating the extent of CRPS body involvement.

in kilograms using a Therapeutic Instruments Jamar Dynamometer (Lafayette Instrument Company; PO Box 5729; Lafayette, IN 47903).Wrists and ankles had their range of motion measured bilaterally in degrees with a Performance Associates (Performance Attainment Associates; 12805 Lake Blvd, Lindstrom, MN) universal inclinometer. Finger tapping between the thumb and second digit was measured as an assessment of fine motor control. The parameters assessed were speed, facility, and maintenance. A scale of 0–4 was utilized: zero being normal movement and 4 being severe impairment.

Measurement of Body Area Sensory Involvement

The percentage of body involvement was calculated by planimetry. The body was divided into 8 regions. A region was counted as involved if any sign was found on physical exam or symptom elicited on sensory testing within that region. This was then mapped onto body diagrams. Transparent graph paper was then placed over the body diagrams and the percentage of body involvement was estimated by counting the number of squares in each body region. A percentage was then calculated based on the number of squares within the involved body regions and the total number of squares within the body diagram (Fig. 1).

Statistical Analysis

Statistical significance between the CRPS patients and control participants was determined by the Student's t test. Adjustment for multiple testing was performed with the Bonferroni correction. For nonparametric variables, the Kruskal Wallis one way analysis of variance was used to compare differences between groups. The data were considered significant at a $P < .05$. Statistical calculations were done with SYSTAT, version 11 (SYSTAT Software Inc., Chicago, IL) and PASW Statistics, version 18 (SPSS Inc., Chicago, IL).

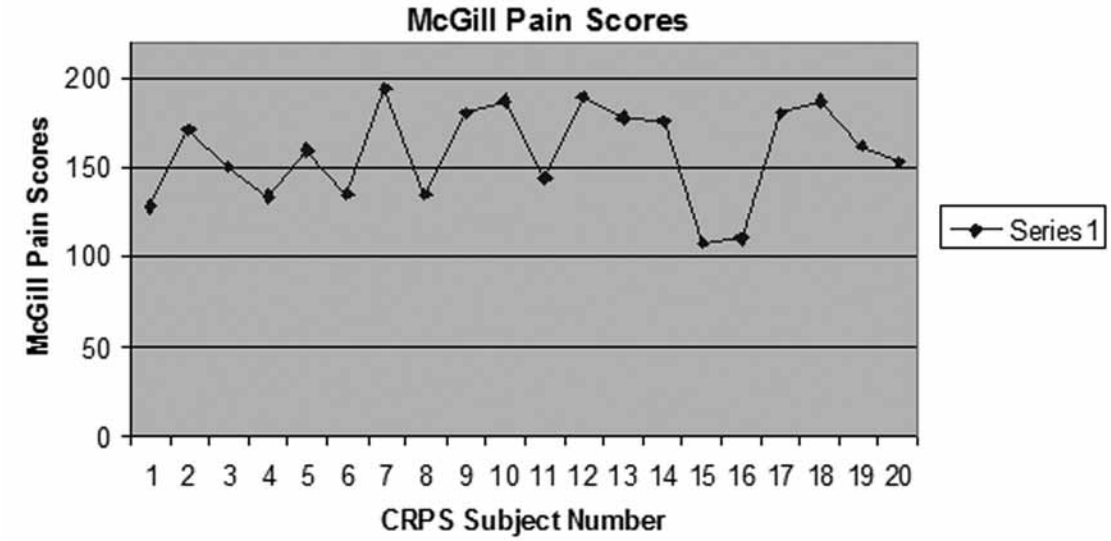

Fig. 2. *Short Form McGill Pain Questionnaire 2 (SF-MPQ-2): The McGill Pain Questionnaire asks subjects to rate 22 qualifiers that describe non-neuropathic pain, neuropathic pain and the affective aspects of pain. Each qualifier is rated from 0 (no pain) to 10 (worst possible), for a total highest score 220.*

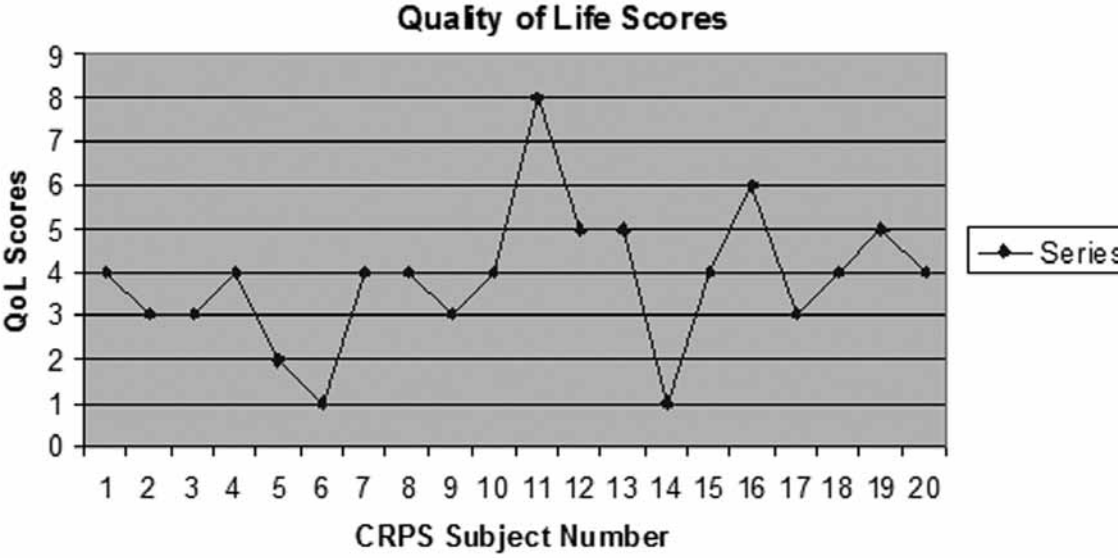

Fig. 3. *American Chronic Pain Association Quality of Life Scale, rates quality of life from a scale of 0 (Stay in bed all day, feel hopeless and helpless about life) to 10 (Go to work/volunteer each day, normal daily activities each day, have a social life outside of work and takes an active part in family life).*

Results

The median overall pain level reported by patients with CRPS on the discriminative McGill Pain Questionnaire was 161 out of a possible 220 (range 111–194). The median quality of life score was 4 (range 1–8), interpreted as capable of simple chores around the house and minimal activities outside the house 2 days a week (Figs. 2 and 3). The average length of illness among the patients was 109.6 months (range 8–288 months) (Table

1). The treatments and therapies utilized by patients during the course of their illness are described in Table 2.

Five patients had signs of the syndrome over 100% of their body (in all 8 regions). Two patients had signs over 87% and 90% of their bodies. Nine patients had signs over 40% of their body. Four patients had 36.7% to 39.4% involvement. The average percentage of body involvement, documented by neurologic examination, was 62.2% (range 36.7% – 100%) (Table 1).

Edema was evident in some area of the body in all patients with CRPS. Livido reticularis and erythema were found in 19 (95%) of them and dystonia of an extremity in 18 (90%). Three patients had hand tremors, one had a foot tremor, and one had tremors in both hands and feet. One patient had full body myoclonic jerks. Both hyperhidrosis and thin, brittle nails were found in the extremities of 16 (80%) of the patients. Other nail changes included ridged nails in 10 (50%) and hypertrophic nails in 7 (35%). Muscle atrophy of the extremities was also found in 10 patients (50%) (Table 3). The results of this study indicate that all patients with CRPS had at least one sensory abnormality, either a decreased sensory threshold, or increased level of cold allodynia on the Likert pain scale in all regions of the body.

All patients with CRPS showed a significantly lower pain threshold for static allodynia in all body regions tested compared to the control participants (face, $P = 0.045$; chest, $P = 0.004$; abdomen, $P = 0.012$; right arm, $P = 0.001$; left arm, $P < 0.0001$; right leg, $P < 0.0001$; left leg, $P < 0.0001$; back, $P < 0.0001$). There were also significantly lower pain thresholds for pressure in the 4 brachial plexus trunks and tibial nerve points tested (right supraclavicular, $P < 0.005$; left supraclavicular, $P = 0.008$; right posterior popiteal fossa, $P < 0.0001$; left posterior popiteal fossa, $P < 0.0001$).

More than half of the patients with CPRS showed a significantly lower pain threshold for dynamic allodynia in all body regions tested compared to control participants (face, n = 12, $P = 0.0225$; chest, n = 15, $P < 0.0001$; abdomen, n = 13, $P < 0.0001$; right arm, n = 15, $P < 0.0001$; left arm, n = 16, $P = 0.001$; right leg, n = 18, $P = 0.0001$; left leg, n = 17, $P = 0.00064$; back, n = 13, $P < 0.0001$). The mean thresholds for static allodynia (kg of pressure) and the mean thresholds for mechanical allodynia (number of brush strokes) are summarized in Table 4. Not all patients with CRPS would allow complete sensory testing in all painful areas.

The patients with CRPS reported a significantly higher median pain rating on the verbal Likert pain

Table 2. *Prior treatments and therapies. This information was reported by the patient or supplied with the patient's medical records.*

Treatment/Therapy	# Reporting Use	% Reporting Use
Nonsteroidal Anti-inflammatory Drugs	20	100%
Antidepressants/ Serotonin–Norepinephrine Reuptake Inhibitors	19	95%
Corticosteroids	9	45%
Anesthetics	18	90%
Anticonvulsants	19	95%
Topical Analgesics	10	50%
Opioids	20	100%
Nerve Blocks	18	90%
Muscle Relaxants	17	85%
Physical Therapy	14	70%
Spinal Cord Stimulation/ Nerve Stimulator	9	45%
Triptans	4	20%

Table 3. *The number of incidences of select CRPS physical examination findings organized by distribution on the body.*

Body Area	Edema	Livedo Reticularis	Discoloration	Dystonia	Hyperhidrosis	Muscle Atrophy
Face	14	0	13	0	1	1
Chest	14	2	12	0	2	0
Abdomen	1	4	6	0	2	0
Right Arm	16	18	19	4	11	7
Left Arm	16	17	17	1	12	7
Right Leg	14	18	17	18	5	5
Left Leg	15	18	18	18	3	3
Back	5	5	4	0	0	0

Table 4. *For static allodynia, all patients with CRPS indicated significantly lower pain thresholds than control participants in all areas of the body. For dynamic allodynia, more than half of the patients with CRPS indicated significantly lower pain thresholds than control participants.*

Area	Static			Dynamic			
	Allodynia Control	Allodynia CRPS	*P* values	Allodynia Control Brush-strokes	Allodynia CRPS Brush-strokes	*P* values	# of patients with CRPS
	(kg mean ± SD)	(kg mean ± SD)		(mean ± SD)	(mean ±SD)		
Face	1.20 ± 0.684	0.328 ± 0.646	< 0.045	5	3.00 ± 1.54	0.0225	n = 12
Chest	1.66 ± 0.662	0.528 ± 0.671	< 0.004	5	2.93 ±1.53	0.0032	n = 15
Abdomen	2.09 ± 0.854	0.795 ± 0.829	< 0.012	5	2.38 ±1.26	0.0122	n = 13
Right Arm	2.39 ± 0.981	0.428 ± 0.463	< 0.001	5	3.20 ±1.66	0.0032	n = 15
Left Arm	2.19 ± 0.665	0.715 ± 0.964	< 0.0006	5	3.44 ±1.46	0.0015	n = 16
Right Leg	3.25 ± 1.09	0.593 ± 0.904	< 0.0001	5	3.44 ±1.46	0.0003	n = 18
Left Leg	3.26± 0.969	0.560 ± 0.898	<10-6	5	3.65 ±1.62	0.0006	n = 17
Back	2.74 ± 0.964	0.520 ± 0.640	< 0.0002	5	3.69 ±1.18	0.0083	n = 13

scale on all areas of the body tested for cold allodynia compared to control participants except for the chest, abdomen, and back. The median pain rating in all areas for the control participants was 0. For the patients with CRPS, the median pain rating for the face, chest, right upper extremity, and back was 5. For the left upper extremity and right lower extremity the median pain rating was 6. For the abdomen the median pain rating was 3 and for the left lower extremity it was 7 (face, $P < 0.01$; chest, $P < 0.15$; abdomen, $P = 0.40$; right arm, $P < 0.0001$; left arm, $P < 0.0001$; right leg, $P = 0.013$; left leg, $P = .001$; back, $P = 0.14$).

At least 85% of the patients with CRPS had a significantly lower pain threshold for mechanical hyperalgesia in all body areas compared to control participants (face, n = 17, $P = 0.001$; chest, n = 19, $P = 0.0001$; abdomen, n = 18, $P = 0.0001$; right arm, n = 20, $P < 0.0001$; left arm, n = 18, $P < 0.0001$; right leg, n = 20, $P < 0.0001$; left leg, n = 19, $P < 0.0001$; back, n = 19, $P < 0.0001$).

There were significantly more reports of after sensation in all 4 limbs of the patients with CRPS compared to control participants following static touch (right arm, $P = 0.004$; left arm, $P = 0.079$; right leg, $P = 0.0004$; left leg, $P = 0.003$) These findings were also observed during an earlier study by Wolanin et al (24). In all four limbs, following dynamic touch or cold stimulus, there was a significantly greater ($P < 0.01$) number of CRPS subjects reporting after sensation as compared to the control participants. There were also significantly more reports of after sensation following pin prick (right arm, n = 20, $P = 0.001$; left arm, n = 18, $P < 0.0001$; right leg, n = 20, $P < 0.0001$; left leg, n = 19, $P < 0.0001$).

Skin temperature showed no significant difference in terms of regional differences in patients with CRPS compared to control participants. Patients with CRPS demonstrated significantly less hand grip strength, slower finger tapping speeds, and range of motion compared to control participants.

Discussion

This study is the first to document the phenomena of total body CRPS through sensory testing, neurologic examination, and patient reports. On examination, 5 of the 20 patients with CRPS had signs or symptoms elicited by physical exam of the syndrome over 100% of their body area; 2 patients had signs or symptoms over an estimated 87% and 90% of their skin surface. All patients with CRPS demonstrated a lower total body threshold for static mechano-allodynia, while 50% demonstrated decreased dynamic allodynia over their entire body surface. Seventeen of the 20 (85%) patients with CRPS had lower static mechano-hyperalgesia than control participants in all body areas. All patients with CRPS demonstrated after sensations following static and dynamic touch and cold and mechanical hyperalgesia (pin prick) in all extremities compared to control participants (24,25).

Previous studies have shown that the spread of CRPS is a common phenomenon over time in refractory patients (9,16,26-31). Mirror spread (9), contiguous spread (16), followed by ipsilateral contiguous extremity spread, seems to be most common. Rapid noncontiguous spread has also been described (32,33). A recent study of the natural history of CRPS found that 92% of 656 patients reported the spread of pain in some pattern over the course of their illness (1).

Many surrogate animal models of neuropathic pain demonstrate signs and symptoms resembling human CRPS after unilateral peripheral nerve injury (34-36). The clinical symptoms in these models occur simultaneously while they evolve over time in patients with CRPS. Animal models demonstrate bilateral histologic changes in the spinal lamina of pain transmission neurons (PTNs). Bilateral simultaneous spread of pain following unilateral peripheral injury was not encountered in this series or that reported by Veldman and Gorisin their 1,183 patients (15). The mechanism of contralateral mirror spread is not known. The changes that occur at the same contralateral segment in surrogate animal models following nerve injury include:contralateral sprouting of sympathetic postganglionic efferent axons onto dorsal root ganglion cells (from sympathetic innervation of blood vessels) (37,38); trans-synaptic changes in the contralateral spinal cord dorsal horn (39-42); a contralateral activation of microglia and astrocytes (31,43); alterations of neurotransmitter binding (38,40); and aberrant pain processing through commissural interneurons (33).

Central sensitization of PTNs is likely to play a pivotal role in contiguous spread, ipsilateral involvement of the other extremity, and the generalized spread of CRPS (25,44). It is manifested by spontaneous pain at the site of injury and beyond its spatial extent; mechanical pain hypersensitivity – most importantly shown by A-β fiber dynamic mechano-allodynia but also secondary punctate and pressure hyperalgesia; temporal summation ("wind-up"); and after sensation. The enhanced membrane excitability, synaptic efficacy, and disinhibition of PTNs decreases previously subthreshold synaptic afferent input to nociceptors above and below affected segments (carried by Lissaur's tract) which amplifies their function and increases receptive field size (45-48). PTNs also receive small amplitude low threshold mechano-afferent and nociceptive inputs outside of their receptive field which become functional during central sensitization (44) that further decrease receptive field threshold, increase receptive field size, and amplify temporal summation. Van Rijn (33) reported 47% of patients in a cohort of 187 had CRPS in multiple extremities. The study demonstrated an ipsilateral pattern of spread in 30% of patients and a diagonal pattern in 14% (33). Rommel (30) documented decreased light touch, pinprick, and temperature thresholds beyond the affected area in 67% of his CRPS cohort. Eight of these patients had hemisensory deficits (30). The maintenance of central sensitization often requires a low level of peripheral nociceptive input from neuropractic injuries, neuromas, poorly healed fractures, or muscle sensitization (49).

Burstein (50) has recently demonstrated the transformation of headache into generalized whole body allodynia and hyperalgesia during a migraine attack. In rats, trigeminal vascular neurons in the thalamus, which process converging mechanical and thermal input, were activated and exhibited long-lasting hyperexcitability to cephalic and extracephalic skin stimulation following meningeal inflammation. Similarly functional magnetic resonance imaging in migraine patients with generalized mechanical allodynia demonstrated acute thalamic activation to dynamic mechano-allodynia and heat stimuli. The authors postulated that central sensitization of these thalamic neurons occurs with whole body receptive fields or pain-facilitation from "on" cells of the rostral medullary nucleus that project to the thalamus or descend to the spinal cord and induce hyperexcitability of PTNs at all spinal levels. During a migraine attack, blood oxygenation level-dependent signals are induced in the rostral pulvinar by extracephalic heat from wide body areas. The intralaminar nuclei (central lateral and central medial-parafascicular complex) have nociceptive neurons with whole body-body receptive fields and are activated by extracephalic heat stimuli during migraine attacks (51,52).

Pain facilitation by central sensitization from neuro-immune interactions is well supported in both the experimental and clinical literature. These interactions result in the activation of glial cells (28,31,53-57) and support the role of microglial activation in the initiation of neuropathic pain and astrocytes in its maintenance. Nerve injury has been implicated in the disruption of the blood-spinal cord barrier (BSCB) that results in an influx of inflammatory mediators and the segmental spinal recruitment of T cells and monocytes (58,59). The chemokines CCL2 and CCL20 are pivotal in this process, which is integral in the development of neuropathic pain (58,59). Nerve injury results in a persistent increase in the spinal cord expression of CCL2 (60). Increased spinal signaling of CCL2 through CCR2, its receptor, contributes to microglial activation, BSCB permeability and enhanced pain (58,60-62). CCR2 activation triggers spinal cord infiltration of macrophages (61) and mechanical hyperalgesia, which is abolished in CCR2 knockout mice (60).

Following nerve injury, T-lymphocyte deficient mice have less mechanical allodynia than wild-type animals (63). The ability of autoreactive T cells to cross

the BSCB is enhanced by an interleukin-6 dependent up-regulation of CCL20 (59). Activated spinal cord astrocytes (reported in an autopsied case of CRPS) (28) will increase spinal cord expression of CCL2. At the moment, these neuroimmune interactions important to the spread of CRPS pain have been best characterized in the spinal cord. They initiate leukocyte, monocyte, macrophage, and auto-antibodies invasion of the spinal parenchyma. There is support for the possiblilty that neuro auto-antibodies initiate a spreading inflammatory response through the neuroaxis (31). Banati (64,65) utilized radiolabelled PK11195 as a biomarker of microglial activation and demonstrated activation at the first dorsal horn synapse, and in a minority of patients, transynaptic activation in the thalamus. The only autopsied patient with long-standing generalized CRPS demonstrated significant posterior horn cell loss and activation of both microglia and astrocytes most prominently at the index site (L5) but extending throughout the spinal cord (28). A possible mechanism for both symptom spread and neuronal loss is activated glial secretion of pro-inflammatory cytokines, nitric oxide, excitatory amino acids, prostaglandins, and adenosine triphosphate (53,66,67). Patients with CRPS demonstrate elevated levels of proinflammatory cytokines, glutamate, and nitric oxide in the cerbrospinal fluid (54,55,68).

The reorganization of the somatosensory cortex after peripheral nerve lesions has been demonstrated with functional magnetic resonance imaging (69) and may be important for generalized pain. The pain matrix which encompasses discriminative, affective, motivational, and inhibitory components is modulated in CRPS (70-76) which may also have major effects on the development and maintenance of widespread pain.

In summary, CRPS spreads and may encompass the entire body surface in a significant portion of long-standing refractory patients. There are specific patterns of spread but none that would predict its extent. The parallel processes of central sensitization and consequent neuroimmune interaction are the most likely mechanisms.

Conclusions

Complex regional pain syndrome, as shown by this study, may not be truly "regional" in a significant subset of patients as experimentally demonstrated by this study. In terms of future studies, a comparison of patients with advanced CRPS who report total body symptoms can be compared to those who have CRPS confined to one limb. It may be the case that signs and symptoms of CRPS in patients with limited disease may be present in other areas of their body even though they do not perceive these areas as being involved because of a lack of spontaneous pain in those areas. Additional analysis of factors such as medication use, types of injury, treatments undertaken, and comorbidities could identify the risk factors for progression to full body involvement.

Disclaimers

This manuscript documents the first study of the phenomena of total body CRPS through sensory testing, neurologic examination and subject reports. It employed several parameters to quantify the sensory tests information to form the most objective picture possible. All patients have been documented and reviewed by the same physicians throughout the study, Dr. Schwartzman and Dr. Edinger.

This work has not been published or submitted for publication in any other journals. All authors declare that there are no financial or other relationships that may lead to a conflict of interest. Drs. Schwartzman and Edinger had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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