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Cutaneous sensory abnormalities in children and adolescents with complex regional pain syndromes

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Abstract

Complex regional pain syndromes (CRPS) have been recognized with increasing frequency in children. These disorders appear to differ markedly from those observed in adults. The International Association for the Study of Pain diagnostic criteria for CRPS were developed based on adult studies; these criteria have not been validated for children. We performed standardized neurological examination and quantitative sensory testing (QST) in a group of pediatric patients to characterize features of sensory dysfunction. Forty-two patients, with unilateral lower extremity CRPS of a mean duration of the pain and symptoms of 12.6 months, who met IASP adult-based criteria for CRPS underwent standardized neurological examination and QST. QST parameters were compared to values previously derived from age- and sex-matched pediatric healthy controls. In most respects, QST parameters did not differ significantly between patients and the normal reference values except for cold and heat pain detection thresholds. Allodynia to cold and/or heat ($P < 0.001$) occurred in 21 patients. Cold allodynia was the most common QST abnormality in our patients. Twenty-six patients showed a combination of mechanical dynamic and static allodynia and allodynia to punctate temporal summation. There was a significant correlation between mechanical dynamic allodynia and allodynia to punctate temporal summation ($P < 0.001$). As with adult CRPS, the thermal and mechanical sensory abnormalities appear in different combinations in different patients with similar clinical presentations. In a majority of patients, the pathogenesis of pain is seemingly of central origin.

Keywords: Children; Adolescents; Complex regional pain syndrome; Quantitative sensory testing

1. Introduction

Injury to peripheral nerves and somatic tissue can result in persistent pain and neuropathic-like symptoms of aberrant cutaneous sensibility, regional autonomic dysfunction, motor impairment, and disability (Veldman et al., 1993). These constellations of symptoms were termed as reflex sympathetic dystrophy (RSD) or causalgia, respectively, in cases involving the absence or presence of an apparent peripheral nerve lesion. The pathophysiology of RSD remains incompletely understood; central neural etiologies (Sieweke et al., 1999), peripheral small fiber neuropathy (Oaklander et al., 2006) and other mechanisms such as exaggerated inflammation involving small nerve fibers (neurogenic inflammatory pain) have been implicated (Weber et al., 2001). The characteristics of the pain, sensory, motor, neurovascular and sudomotor abnormalities vary considerably from patient to patient and over time (Veldman et al., 1993; Bruehl et al., 2002). There has been no diagnostic "gold standard" for these

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disorders, and explanations of underlying mechanisms remain a challenge. The uncertainty of underlying mechanism(s) is reflected in the lack of consensus on which diagnostic criteria are important and in the variety of therapeutic approaches (Wilder et al., 1992; Stanton-Hicks et al., 1998; Sherry et al., 1999).

In response to these diagnostic difficulties, a consensus group sponsored by the International Association for the Study of Pain redefined the taxonomy of RSD and causalgia to new descriptive terms Complex Regional Pain Syndrome type 1 and type 2, respectively, using uniform diagnostic criteria (Stanton-Hicks et al., 1995). In adults, studies have attempted validation of the original (Bruehl et al., 1999) and modified (Harden et al., 1999) IASP CRPS criteria as compared to established painful neuropathic disorders and have found relatively weak inter-observer agreement or sensitivity and specificity based on clinical examination and quantitative sensory evaluation (Galer et al., 1998; Harden et al., 1999; van de Vusse et al., 2003).

RSD/CRPS has been recognized with increasing frequency in children and adolescents in the past 30 years (Sherry et al., 1999; Lee et al., 2002). Pediatric RSD/CRPS appears to have some differences in presentation compared to the adult disorder(s), including greater female to male sex ratio, greater propensity for lower extremity involvement, and more favorable prognosis using treatment programs that emphasize physical therapy and cognitive behavioral treatment (Stanton et al., 1993; Sherry et al., 1999; Lee et al., 2002). Previous pediatric case series and clinical trials have not provided detail on the patterns of sensory abnormalities or on the applicability of the IASP CRPS diagnostic criteria. We, therefore, undertook this prospective study to characterize the pain reports and patterns of aberrant cutaneous sensitivity in children and adolescents with CRPS using standardized medical history, physical and neurological examination and quantitative sensory testing (QST).

2. Materials and methods

2.1. Enrollment and inclusion criteria

The Clinical Investigation Committee at Children's Hospital Boston approved the study protocol. Parents provided informed consent, and patients gave assent. Preliminary evaluation was offered to patients, ages 7–17 years, who were referred over a period of December 2001 to September 2003 with a presumptive diagnosis of CPRS. If, after completion of the preliminary evaluation, the study clinician concluded that the patient met IASP clinical criteria for diagnosis of CRPS (Stanton-Hicks et al., 1995), then they were offered enrollment, provided they did not meet exclusion criteria listed below. Exclusion criteria included: (1) ongoing chronic medical illness prior to the onset of extremity pain, (2) involvement of more than one extremity, (3) features indicative of a current or past underlying neurologic, rheumatologic or dermatologic disorder, (4) pregnancy or lactation, (5) history of ADHD or use of stimulants and depressant drugs (e.g., opioid, sedative, anxiolytic, antidepressant) that can alter alertness and pain perception within a week of testing, and (6) previous surgical and chemical sympathectomy of the affected limb. No patient was receiving opioids. If a patient was receiving non-steroidal anti-inflammatory drugs, these agents were withheld for 2 days before the testing session. (7) Presence of allodynia to brush and/or pinprick at sites on the contralateral limb opposite to the painful area. No financial compensation was offered to subjects for participating in this study.

Electrodiagnostic tests were not performed per study protocol or per prevailing pediatric clinical practice to confirm the diagnosis of nerve injury. Electromyography and nerve conduction studies had been performed previously in three adolescents and the results were normal. These studies were not performed in other patients either because they were not clinically indicated or patients and parents objected to tests that involved repeat painful needle insertions or stimulation of the painful limb without sedation. Therefore, the term CRPS in this report refers to both types of CRPS 1 and 2.

2.2. Testing procedures

On the day of testing, a single researcher (PM) documented symptoms and signs using a CRPS checklist based on IASP criteria and these measurements were used for study analyses (Stanton-Hicks et al., 1995). The same examiner performed all sensory tests in a quiet room, temperature 20–23 °C, with the patient comfortably seated or reclined, and skin sites were exposed to ambient temperature for 10–15 min before testing. Subjects were not permitted to view the test site or the QST computer screen, and were not given visual cues to indicate the start of a stimulus. Initially, each patient marked out the site of injury, maximum pain site, and the periphery of the painful zone in the affected limb. Boundaries of the painful zone of allodynia (evoked by soft brush) were defined before testing by stimulating from non-painful sites converging onto the affected area of greatest pain in four directions or more. Sensory testing was conducted on the skin area of greatest reported pain intensity. Skin temperature was also measured on the corresponding skin area of the unaffected limb. Testing was completed within approximately 80–90 min.

Thermal and vibration sensations and thermal pain detection thresholds in the affected limbs were compared to the 95th percentile normal reference values obtained from a large sample of healthy children (ages 7–17 years) previously tested via the same methodology on the same location (Meier et al., 2001). Criteria for thermal hyperesthesia, hypoesthesia, and allodynia were defined as thresholds above or below the 2.5th–97.5th percentile of normal interval values. Terms for pain and sensory abnormalities follow the definitions recommended by the IASP (Merksy and Bogduk, 1994).

Patients rated ongoing pain intensity on a chromatic analog scale using a ten-point ruler (CAS) (McGrath et al., 1996). They were asked to describe the quality of pain. If the patient had difficulty, verbal descriptors of the pain from McGill Pain Questionnaires were read to assist, but no formal effort was made to define these words.

3. Results

3.1. Patient characteristics and enrollment

Sixty-three patients presenting at the Children's Hospital Chronic Pain Clinic and fulfilling the criteria of CRPS underwent preliminary evaluation. Eight patients were excluded: 5 declined participation prior to the formal examination and 3 declined to enroll because of severe touch allodynia and intolerance to pain-eliciting tests on screening examination. Thirteen patients were enrolled and evaluated, but are excluded from the current report because QST was performed on sites different than the sites examined in the reference control study of healthy children (Meier et al., 2001). Forty-two patients (40 females, 2 males; ages 13.2 ± 2.6 years), all Caucasian, assented/consented to participate, completed the studies, and were included in the analyses reported here. CRPS affected one leg and foot involving the right limb in 16 patients and left limb in 26 patients. The onset of pain followed a specific noxious event in all patients: 13 experienced a sports-related injury, 19 incurred an incidental sprain/strain, 3 had fractures, 3 developed pain after surgery, one after recovery from spontaneous deep vein thrombosis, and 3 patients sustained minor soft tissue injury. All patients in this study reported spontaneous pain at rest (4 intermittent and 38 constant, median CAS 6.2; IQR 25–75, 4.6–8.2) that increased with movement of the affected limb. The mean duration of the pain and symptoms was 12.6 months (range 0.5–72 months). Patients reported pain of cutaneous and deep tissue that was associated with autonomic dysfunction and difficulty weight bearing. Most patients self-reported pain using sensory pain descriptors rather than affective and other pain dimensions on modified McGill pain scale; sensory ($n = 32$), affective ($n = 18$), evaluative ($n = 2$), and miscellaneous ($n = 4$). The following autonomic symptoms and signs were present; purple or red color change ($n = 28$), excessive sweating ($n = 12$), dry skin ($n = 15$), swelling ($n = 25$), hair increase/decrease ($n = 28$), and nail growth ($n = 7$). Skin temperature was colder ($n = 20$) or warmer ($n = 5$) than the unaffected foot. Paired t-test showed significant difference in skin temperature between the affected (28.0 ± 2.3) and unaffected (29.1 ± 1) feet, $P < 0.001$. Twenty-three patients presented with mild-to-moderate atrophy and weakness of gastrocnemii muscles and 8 presented with mild atrophy of quadriceps muscles and only one patient exhibited tremor. At the time of testing, thirty patients were unable/unwilling to bear weight due to pain. None of our patients gave a history of, or exhibited clinical evidence of, local or systemic inflammatory disease or infection. No patient had a history or physical examination suggestive of central nervous system injury or stroke as an initiating factor in his or her CRPS.

There were no differences in the median CS, WS and VS detection thresholds between the patients' affected site and control normal values (Table 1). The median cold detection pain threshold was significantly greater (cold allodynia) than the median threshold value of the normal reference values (26.3 °C vs. 21.5 °C, $P < 0.001$). The median heat pain detection threshold was significantly lower (heat allodynia) than the median threshold value of the normal reference values (39.1 °C vs. 42.3 °C, $P < 0.001$) (Table 1). Allodynia to cold was present in 14 patients, to heat in 7 patients and to both cold and heat in 3 patients. No patients displayed hypoesthesia to HP or CP detection thresholds (Fig. 1). Cold hypoesthesia and hyperesthesia (thresholds for cold sensations below the 2.5th or above 97.5th percentile threshold of normal reference values) were observed in 5 and 3 patients, respectively. Warm hypoesthesia or hyperesthesia (warm sensation thresholds above 97.5th or below 2.5th percentile threshold of normal reference values) was observed in 4 and 2 patients, respectively.

On the unaffected contralateral limb, median values of thresholds for CS, WS, VS and CP detection thresholds were not significantly different from those of normal controls (Table 1). Although all of these patients reported no spontaneous or mechanically evoked pain in their contralateral limbs, the median values for thresholds for HP detection thresholds in the contralat-

Table 1
Comparison of thermal and vibration thresholds between the study group and normal controls

Sensation	CRPS study group ($n = 42$)		Normal controls[a] ($n = 101$)	P value	
	Affected foot	Unaffected foot	Foot	Affected vs. controls	Unaffected vs. controls
Cold (°C)	29.4 (27.9–30.5)	30.4 (29.5–30.9)	30.1 (29.1–30.7)	0.08	0.07
Warm (°C)	35.2 (34.5–36.6)	34.9 (34.2–35.9)	35.1 (34.6–36.2)	0.93	0.16
Cold pain (°C)	26.3 (21.1–29.2)	20.5 (11.0–23.0)	21.5 (12.1–24.5)	<0.001[b]	0.71
Heat pain (°C)	39.1 (37.5–41.6)	40.7 (38.8–43.1)	42.3 (40.6–44.8)	<0.001[b]	<0.01[b]
Vibration (μm)	0.45 (0.20–1.30)	0.65 (0.38–1.00)	0.48 (0.40–0.68)	0.62	0.13

CRPS, complex regional pain syndrome. Data represent median values with interquartile range (25th–75th percentile) shown in parentheses. μm, micrometers.

[a] Meier et al. (2001).

[b] Statistically significant compared with controls (non-parametric Mann–Whitney U-test).

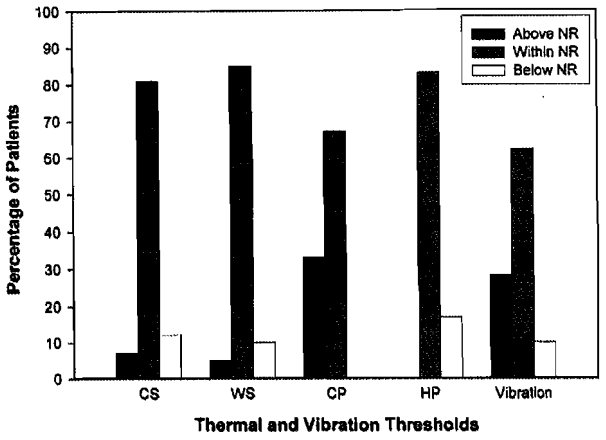

Fig. 1. Proportions of patients who had thermal (°C) and vibration (micrometers) detection thresholds above, within and below the 2.5th–97.5th percentile of normal reference intervals (NR). CS, cold sensation; WS, warm sensation; CP, cold pain; HP, heat pain.

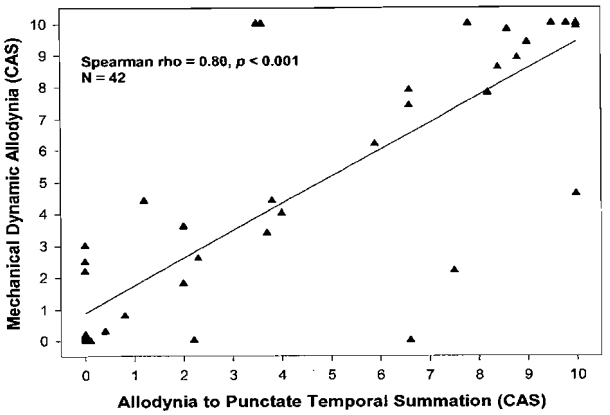

Fig. 2. Chromatic analog scale (CAS) measurements of the relationship between mechanical dynamic allodynia and allodynia to punctate temporal summation; in most patients the mechanical dynamic allodynia rating progressively increased with repetitive punctate stimulation ($P < 0.001$).

eral limbs were significantly different from (lower than) those of normal controls (Table 1). Allodynia to cold and to heat in the contralateral limb was present in 3 (7%) and 5 (12%) patients, respectively.

Vibration sensation thresholds in the affected limbs in CRPS patients were lower (hyperesthesia) than the 2.5th percentile or greater (hypoesthesia) than the 97.5th percentile threshold of control normal values in 4 and 12 patients, respectively. On the contralateral limbs, vibration hyperesthesia was present in one patient and hypoesthesia was not present in any patient.

Evoked pain was observed from mechanical dynamic allodynia in 28 patients (median CAS = 6.6), to mechanical static allodynia in 29 patients (median CAS = 5.4), and to both mechanical types of allodynia in 26 patients. Allodynia to punctate temporal summation was observed in 30 patients (median CAS = 7.5). Twenty-six patients exhibited all these three evoked painful sensations of mechanical dynamic and static allodynia and allodynia to punctate temporal summation, and 6 patients exhibited two of these three evoked painful sensations. Of the 26 patients who exhibited all three types of evoked pain, 21 patients exhibited abnormal thermal and/or vibration sensation testing, but there was no consistent pattern among these abnormalities; for example, some had combined heat and cold allodynia, and some had isolated cold or heat allodynia, and some had vibration hypoesthesia with or without thermal allodynia. In the remaining 10 patients, no evoked painful sensations could be detected. None of the patients showed mechanical dynamic and static allodynia or allodynia to punctate temporal summation in the contralateral limb. There was a significant correlation between mechanical dynamic allodynia and allodynia to punctate temporal summation ($P < 0.001$, Fig. 2).

By physical examination, 14 patients (33%) showed various combinations of increased and decreased detection thresholds in thermal, vibratory and mechanical stimuli primarily in the distribution of nameable peripheral nerves: superficial peroneal nerve ($n = 7$), saphenous nerve at the ankle ($n = 2$), sural nerve at the ankle ($n = 3$), and lateral and medial plantar nerves ($n = 1$) and medial plantar nerve ($n = 1$). In all of these patients, the reported pattern of injury was consistent with the distribution of the cutaneous findings in the course of the involved nerves.

Secondary univariate and multivariate regression analyses were performed to identify clinical factors associated with QST abnormalities. Using multivariate logistic regression with a backward selection procedure, each analysis considered four candidates (age, gender, duration of pain, and presence or absence of cutaneous mechanical dynamic allodynia) as predictors of the risk of thermal and vibratory QST abnormalities (i.e., values outside the normal range). Presence or absence of mechanical dynamic allodynia emerged as the only factor significantly associated with a risk for cold ($P = 0.006$) and heat ($P = 0.012$) allodynia. None of the four variables predicted abnormal WS and CS detection thresholds, and age only weakly ($P = 0.036$) predicted abnormal vibratory detection thresholds. Adjusting for age, gender, and duration of pain, the presence of mechanical dynamic allodynia remained significantly predictive of cold or heat allodynia. In particular, all 7 patients who showed allodynia to heat also showed mechanical dynamic and static allodynia.

4. Discussion

This is the first study to use QST and a structured neurological examination to analyze patterns of sensory

dysfunction and pain descriptors of children and adolescents with CRPS. The key clinical presentation in this study is in agreement with previous pediatric CRPS studies (Wilder et al., 1992; Stanton et al., 1993; Lee et al., 2002) and adult CRPS studies, with a few contrasting features (Veldman et al., 1993; Birklein et al., 2000). The onset of CRPS in early adolescence and presence of spontaneous pain in all patients in this study are most prevalent features that are consistent with findings of other pediatric studies (Wilder et al., 1992; Stanton et al., 1993; Lee et al., 2002). In adult CRPS prospective trials the incidence of spontaneous pain ranges from 77% to 93% (Veldman et al., 1993; Birklein et al., 2000) The female predominance is more pronounced in children (ratio of 5 – 13:1 vs. 3:1 in adults) with a marked predominance of lower extremity (ratio 5 – 16:1 vs. 2:3 in adults) (Wilder et al., 1992; Veldman et al., 1993; Lee et al., 2002).

Localized movement disorder was noticeably absent despite the chronicity of CRPS in children in this and other pediatric studies, compared to frequent tremor (49%) and myoclonus (36%) of the involved limb in a large adult study (Veldman et al., 1993). As with other pediatric CRPS reports, our patients exhibited milder and less frequent autonomic signs and infrequent trophic changes compared to adults with CRPS; trophic changes are present in more than 50% of patients in several adult case series (Veldman et al., 1993; Birklein et al., 2000).

In the present study, the patterns of abnormal sensory perceptions are in accordance with previous findings in adult studies of RSD/CRPS with respect to the diversity of type and severity of sensory abnormalities and range of mechanical and thermal abnormalities (Price et al., 1992; Verdugo and Ochoa, 1992; Sieweke et al., 1999). Recently, we noted a substantial disparity between children's self-reports and physician observations in the frequency of neurovascular, trophic, and pseudomotor symptoms in pediatric CRPS patients (Meier et al., 2006). Just as these autonomic abnormalities may fluctuate over time, it is plausible that the frequency and severity of sensory abnormalities may similarly fluctuate over time in these patients. In 76% of children in this study the mechanical dynamic allodynia, static allodynia or allodynia to punctate temporal summation was present, whereas in adult case series, mechanical allodynia occurred in 70–100% of patients (Price et al., 1989; Gracely et al., 1992; Price et al., 1992; Sieweke et al., 1999).

Distinct heat (16.7%) and cold (33.3%) allodynia were also present at lower frequency in our patients relative to adult case series; frequencies of heat hyperalgesia in adult studies range from 14% to 55% (Price et al., 1989; Price et al., 1992) to normal heat pain responses (Gracely et al., 1992; Sieweke et al., 1999; Birklein et al., 2001). Allodynia to cold is strikingly prevalent in adults, in the range of 74–100% (Gracely et al., 1992; Birklein et al., 2000).

Additionally, we observed wide variability in the detection thresholds of cold, warm, and vibration sensations that were not significantly different from control normal values; these findings are similar to those in adults with post-traumatic neuropathies and RSD/CRPS (Wahren et al., 1991; Koltzenburg et al., 1994; Kemler et al., 2000; Jorum et al., 2003).

Cold and heat hyperalgesia or allodynia may occur simultaneously or independently and are ascribed to dysfunction in small sensory fibers; they are commonly reported in peripheral nerve injuries or peripheral neuropathies in adults (Cline et al., 1989; Culp et al., 1989; Price et al., 1989; Price et al., 1992; Verdugo and Ochoa, 1992). Although heat hyperalgesia is attributed to abnormally sensitized C-fibers (Cline et al., 1989), mechanisms underlying cold hyperalgesia remain controversial. Possible support for involvement of central mechanisms in some patients with neuropathy and in human experimental models derives from the observation of paradoxically induced hot or burning sensation transduced by C-fibers in response to cold pain stimuli following loss of A-delta fibers' function (Craig and Bushnell, 1994; Ochoa and Yarnitsky, 1994; Jorum et al., 2003).

Concurrent mechanical dynamic and static allodynia and allodynia to punctate temporal summation were present in 62% of the patients. It has been suggested that allodynia to both light stroking and threshold-strength punctate stimuli is mediated by A-beta fibers and is maintained or generated through a sensitized state of WDR neurons induced by injury afferent input or chronically sensitized C-fibers (Cline et al., 1989; Culp et al., 1989; Price et al., 1989; Torebjork et al., 1992; Kilo et al., 1994; Ziegler et al., 1999). In certain neuropathic pain states, traumatic or ischemic injury sensitizes mechano-insensitive C-fibers, leading to primary sensitization of C-fibers, mechanical static allodynia/hyperalgesia and increased neural input necessary to maintain central sensitization and mechanical dynamic allodynia (Schmelz et al., 2000; Orstavik et al., 2003). Although it is plausible that both peripheral and central sensitization contributed to mechanical dynamic and static allodynia observed in our patients, the results of studies of QST in adults with CRPS 1 – and that of our study – suggest the abnormal hyperexcitable sensory patterns are consistent with a prominent role for central sensitization (Thimineur et al., 1998; Birklein et al., 2000; Rommel et al., 2001; Schwartzman et al., 2001; Eisenberg et al., 2005; Drummond and Finch, 2006). In multivariate analyses, presence or absence of mechanical dynamic allodynia was more highly predictive of cold and heat allodynia than a number of other clinical variables, including age, sex, or duration of symptoms.

No attempts were made to differentially test the function of unmyelinated C-fibers while transiently blocking impulse conduction of myelinated A-fibers under compression-ischemia (Wahren et al., 1989; Yarnitsky and Ochoa, 1989, 1990; Koltzenburg et al., 1994). We did not believe that pediatric patients would tolerate the duration of tourniquet application required to produce A-fiber blockade.

In 24% of our patients, mechanically evoked cutaneous pain was absent. This lack of pain does not exclude the possibility of sensitization of deep tissue unmyelinated afferent nociceptors of muscles and joints, because sensitization of deep tissue nociceptors may not be apparent unless evoked by pressure stimuli (static hyperalgesia). It is also possible that our patients were tested at a time wherein spontaneous recovery was in progress (Van Boven and Johnson, 1994; Sherry et al., 1999; Lee et al., 2002). Although we did not quantify hyperalgesia to deeper stimuli, we did observe markedly increased pain with deep palpation, percussion over joints, or firm grasping of the affected extremities that lacked cutaneous mechanically evoked pain. It is certainly plausible that, in limiting our testing paradigm to cutaneous rather than deeper tissue stimulation, we missed signs of selective deep tissue C-fiber sensitization that might have contributed to spontaneous pain in the absence of evoked cutaneous pain (Koltzenburg et al., 1992; Ochoa and Yarnitsky, 1993; Graven-Nielsen et al., 1997; Vatine et al., 1998).

There are several potential limitations of this study. Testing was performed at the site of maximum pain and it was not possible to distinguish primary from secondary uninjured areas. Some limitations imposed by testing in children and adolescents precluded the degree of detail and refinement using paradigms tolerated by adults. Serial testing would have improved the sensitivity of the methodology and the reproducibility of a particular sensory dysfunction (Rommel et al., 2001). Alternatively, concurrent comparison to other well-defined childhood neuropathies such as HIV or diabetes would have helped to characterize the specificity of these findings for CRPS as distinct from other neuropathies. However, most pediatric patients with cutaneous hypersensitivity pain do not tolerate noxious tests well, therefore, we chose the least noxious and most time efficient methods of stimulation, used a binary response of presence or absence of aberrant sensations, limited the use of suprathreshold stimuli, and avoided repetitive stimulation. Particular care was taken to not fatigue the patients and to avoid prolonged testing; most patients with allodynia dreaded all contacts, especially those with hyperpathia.

In conclusion, the present results indicate that brief QST can be successfully used in most children with CRPS to detect alterations in mechanical and thermal sensibilities; however, no single biological mechanism readily explains the various patterns of sensory dysfunctions observed. This is the first study to quantify aberrant sensations observed in childhood CRPS and should be considered exploratory. In future studies, it may be beneficial to examine in more detail the utility and reproducibility of the IASP diagnostic criteria for CRPS, to determine the significance of QST abnormalities and to investigate how sensory dysfunction changes over time in longitudinal trials.

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