



Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome?

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Abstract

This study tested for evidence supporting the clinical lore of three sequential stages of complex regional pain syndrome (CRPS) and examined the characteristics of possible CRPS subtypes. A series of 113 patients meeting IASP criteria for CRPS underwent standardized history and physical examinations to assess CRPS signs and symptoms in four domains identified in previous research: pain/sensory abnormalities, vasomotor dysfunction, edema/sudomotor dysfunction, and motor/trophic changes. K-Means cluster analysis was used to derive three relatively homogeneous CRPS patient subgroups based on similarity of sign/symptom patterns in these domains. The resulting CRPS subgroups did not differ significantly regarding pain duration as might be expected in a sequential staging model. However, the derived subgroups were statistically-distinct, and suggested three possible CRPS subtypes: (1) a relatively limited syndrome with vasomotor signs predominating, (2) a relatively limited syndrome with neuropathic pain/sensory abnormalities predominating, and (3) a florid CRPS syndrome similar to 'classic RSD' descriptions. Subtype 3 showed the highest levels of motor/trophic signs and possible disuse-related changes (osteopenia) on bone scan, despite having directionally the briefest pain duration of the three groups. EMG/NCV testing suggests that Subtype 2 may reflect CRPS-Type 2 (causalgia). Overall, these results are consistent with limited previous work that argues against three sequential stages of CRPS. However, several distinct CRPS subtypes are suggested, and these could ultimately have utility in targeting treatment more effectively. © 2002 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

The clinical entity of complex regional pain syndrome (CRPS) remains only incompletely understood despite growing basic knowledge regarding its pathophysiology (Gracely et al., 1992; Woolf et al., 1992; Harden et al., 1994; Baron and Maier, 1996; Birklein et al., 1998; Kurvers et al., 1998; Wasner et al., 2001). If the treatment of CRPS is to be advanced, clinical research must address ways of improving the recognition and diagnosis of the disorder (Bruehl et al., 1999; Harden et al., 1999). One important target for clinical research is the identification of stages or subtypes of the syndrome, such as those based on severity or time course (Stanton-Hicks et al., 1995). If clear CRPS

stages or subtypes can be identified, the ability to discriminate these accurately might ultimately permit more specific targeting of treatments for CRPS patients (Janig, 1991, 1992; Stanton-Hicks et al., 1995). Equally important is the fact that identification of distinct subtypes or stages of CRPS would facilitate selection of more homogeneous research samples, thus allowing improved research into the mechanisms underlying the syndrome (Janig, 1991).

The current IASP diagnostic criteria make a distinction only between two general subtypes of CRPS: Type I (RSD) and Type II (Causalgia), with the latter reflecting clear evidence of nerve injury whereas the former does not (Merskey and Bogduk, 1994). In addition to these two broad diagnostic subcategories of CRPS, there is a long-standing belief expressed in the literature that untreated CRPS develops through distinct sequential stages, each characterized by

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a different pattern of signs and symptoms (Schwartzman and McLellan, 1987; Bonica, 1990; Schwartzman and Kerrigan, 1990; Gibbons and Wilson, 1992; Veldman et al., 1993). While the clinical descriptions of these hypothesized stages have differed somewhat between authors in the details, most conform to the description by Bonica (1990). The early, acute stage of CRPS (Stage I) is believed to be characterized primarily by pain/sensory abnormalities (e.g. hyperalgesia, allodynia), signs of vasomotor dysfunction, and prominent edema and sudomotor disturbance. Stage II (dystrophic stage) is proposed to occur 3–6 months after onset, and is characterized by more marked pain/sensory dysfunction, continued evidence of vasomotor dysfunction, with development of significant motor/trophic changes. Stage III (atrophic stage) is characterized by decreased pain/sensory disturbance, continued vasomotor disturbance, and markedly increased motor/trophic changes. Although there have been only limited empirical tests of this hypothesized staging of CRPS, the concept has been frequently accepted as fact in the CRPS literature (e.g. DeTakats, 1937; Schwartzman and McLellan, 1987; Bonica, 1990).

Limited prospective research that has followed patients who develop CRPS-like symptoms after surgery, fracture, or severe hand injury (Veldman et al., 1993; Bickerstaff and Kanis, 1994; Zyluk, 1998) suggests that, in most cases, the condition does not progress through increasingly problematic stages like those described above. Retrospective surveys completed by CRPS patients with an average pain duration of over 3 years (Galer et al., 2000) similarly indicate that CRPS symptoms most often tend to remain stable or improve, rather than progressively deteriorate. Findings such as these raise the possibility that the presumed sequential ‘stages’ often reported by clinicians may reflect CRPS subtypes, rather than an actual staging that follows a progressive, deteriorating course.

The present study sought to investigate these issues using a statistical pattern recognition methodology that has not yet been applied to this problem. It was hypothesized that if the three sequential stages of CRPS described above exist, then statistical grouping of CRPS patients into three subgroups based on similarity of sign/symptom patterns should yield distinct patient subgroups differing in pain duration. It was also presumed that CRPS characteristics exhibited by patients within these three statistically-derived subgroups would correspond to the three stages described above.

2. Methods

2.1. Subjects

Subjects included a series of 113 patients meeting IASP criteria for CRPS (Merskey and Bogduk, 1994) who presented for evaluation and treatment at the data collection sites. Sites included the University of Washington Medical School (28% of the sample), the Rehabilitation Institute of

Chicago (22%), Wright Patterson Air Force Base (13%), University of Wisconsin–Madison (17%), the Cleveland Clinic (8%), Johns Hopkins School of Medicine (8%), and Space Coast Anesthesiology (a private clinic; 4%). The sample was 62.5% female, and predominately Caucasian (92%), with 3% of the sample being African-Americans. The mean age of the sample was 41 years (SD 10.2), and mean pain duration was 26.9 months, with a high degree of interpatient variability (SD 28.8). Lower extremity CRPS was slightly more common (52%) than upper extremity CRPS (46%), with the remaining 2% of the sample displaying CRPS pain in both upper and lower extremities. CRPS was slightly more common on the left side (51% versus 47% on the right), with bilateral CRPS in 2% of the sample. The most common initiating event was surgery (24%), with other common precipitants being crush injuries (16%), fractures (15%), and sprains (9%).

All patients received criterion-based diagnoses of CRPS based upon the published IASP criteria for CRPS (Merskey and Bogduk, 1994). To maximize uniform assessment across sites, standardized procedures for evaluating CRPS signs were provided, and a database checklist developed in our previously published work was used to guide and record the history and physical examination data (Bruehl et al., 1999; Harden et al., 1999). Results of EMG/nerve conduction velocity testing (EMG/NCV) were available in 55 patients and were used as a conservative means of distinguishing CRPS Type I from Type II. Using this criterion, 67% of the sample would be diagnosed with CRPS-Type I (Merskey and Bogduk, 1994; Baron et al., 1996).

2.2. Procedures

For each patient, a study physician conducted an evaluation of CRPS signs and symptoms using the checklist described above. This evaluation involved obtaining a patient history to assess symptoms, as well as conducting a physical examination using standardized procedures to assess signs. The results of this evaluation were used to determine that all patients in the study met IASP diagnostic criteria for CRPS (Merskey and Bogduk, 1994).

2.3. Statistical analysis

All analyses were conducted using the SPSS for Windows Version 9.0 statistical package (SPSS Inc., Chicago, IL). Previous work using factor analysis had revealed four distinct subgroups of CRPS signs and symptoms (Bruehl et al., 1999; Harden et al., 1999). These factor analytic results were used as the basis for creating a set of empirically-supported research diagnostic criteria for CRPS (Bruehl et al., 1999; Harden et al., 1999). For each patient in the current study, the number of CRPS characteristics present within each of the four sign and four symptom categories incorporated in these research diagnostic criteria (sensory/pain, vasomotor, sudomotor/edema, motor/trophic) was calculated. Because of different total numbers

Table 1
Pain characteristics and demographics across CRPS patient subgroups^a

Variable	Patient subgroup		
	Subgroup 1	Subgroup 2	Subgroup 3
Pain duration (months)	27.0 (27.0)	34.6 (43.1)	23.3 (20.3)
Age (years)	43.6 (9.3)	40.4 (9.3)	39.8 (11.0)
Gender (% female)	62.1	57.7	64.9
Pain location (%)*:			
Upper extremity	56.7	29.2	47.2
Lower extremity	43.3	62.5	52.8
Affected side (% right)	43.3	44.0	50.9
Initiating event (%):			
Surgery*	30.0	34.6	14.8
Crush injury	20.0	7.7	18.5
Fracture	10.0	7.7	20.4

^a Pain duration and age are expressed as mean (SD) values. Frequency data for only the three most common initiating events are presented. * $P < 0.10$ for comparison across clusters.

of signs and symptoms in each category, standardized scores (Z scores) for each of these eight sign/symptom categories were derived. These standardized sign/symptom category scores were then used as the dependent variables in a K-means cluster analysis. This procedure uses a nonhierarchical, partitioning method of clustering using an algorithm that employs iteratively derived cluster centers (Milligan and Cooper, 1987). The K-Means cluster analytic procedure is a pattern recognition technique that was used to identify relatively homogeneous patient subgroups based on the patterns observed within the four sign and four symptom categories. Based upon the hypothesized presence of three distinct stages of CRPS, the cluster analysis procedure specified the derivation of three clusters.

One-way analysis of variance with linear contrasts was used for comparing continuous variables across the three cluster-derived groups. Comparisons of frequencies across patient subgroups were performed using the nonparametric phi statistic. A two-tailed significance level of $P < 0.05$ was used for all analyses.

Table 2
Mean (SD) number of signs or symptoms of CRPS within each CRPS patient subgroup^a

Sign/symptom category	CRPS patient subgroup		
	Subgroup 1	Subgroup 2	Subgroup 3
Sensory symptom	0.10 (0.31) ^{A,B}	0.88 (0.33) ^B	0.82 (0.38) ^A
Sensory sign	0.40 (0.50) ^{A,B}	1.92 (0.27) ^{B,C}	1.70 (0.60) ^{A,C}
Vasomotor symptom	1.23 (0.90) ^A	1.00 (0.85) ^C	1.95 (0.23) ^{A,C}
Vasomotor sign	0.93 (0.78) ^{A,B}	0.50 (0.58) ^{B,C}	1.72 (0.49) ^{A,C}
Sudomotor/edema symptom	0.93 (0.64) ^A	1.15 (0.73) ^C	1.58 (0.57) ^{A,C}
Sudomotor/edema sign	0.53 (0.57) ^A	0.35 (0.49) ^C	1.16 (0.75) ^{A,C}
Motor/trophic symptom	1.30 (0.95) ^A	1.42 (1.06) ^C	2.63 (0.56) ^{A,C}
Motor/trophic sign	1.00 (0.95) ^A	0.88 (0.95) ^C	2.33 (0.69) ^{A,C}

^a All values with the same superscript are significantly different at $P < 0.05$. The sign and symptom categories above are taken from a set of empirically-derived research diagnostic criteria for CRPS that were based on results of factor analysis (8,9). For interpretive clarity, values presented reflect actual means rather than the standardized means used in cluster analysis.

3. Results

3.1. Pain characteristics and demographics across CRPS patient subgroups

Examination of Table 1 indicates that the three CRPS patient subgroups resulting from cluster analysis were not significantly different regarding duration of CRPS. Patients in Subgroup 2 displayed the greatest average pain duration, but were not significantly different from either of the other cluster-derived subgroups ($P > 0.10$). Substantial variability in pain duration was noted within all three patient subgroups, although Subgroup 2 displayed the greatest variability. Pain duration analyses excluding statistical outliers did not alter these results ($P > 0.10$).

Patient age and gender were comparable across groups. However, distribution of pain location (upper versus lower extremity) displayed a nonsignificant trend towards less frequent upper extremity problems in Subgroup 2 ($P < 0.10$). With regards to the presumed initiating event, there was a nonsignificant trend towards surgery being a more frequent antecedent of CRPS among those in Subgroups 1 and 2, compared with those in Subgroup 3 ($P < 0.10$).

3.2. Characterization of CRPS patient subgroups

Table 2 describes the pattern of signs and symptoms observed within the three CRPS patient subgroups. Values in this table reflect the mean number of CRPS characteristics observed within each sign or symptom category across the three patient subgroups. Despite the fact that cluster analysis is designed to maximize differences between the groups, Subgroups 1 and 2 did not differ significantly with regard to frequency of sudomotor/edema or motor/trophic characteristics of CRPS. Patients in Subgroup 1 were, however, found to exhibit significantly fewer pain/sensory signs and symptoms, and significantly more vasomotor signs than those in Subgroup 2.

Patients in Subgroup 1 were characterized most prominently by vasomotor dysfunction (i.e. color or temperature asymmetry) and motor/trophic changes (e.g. weakness, tremor, hair/nail changes). Patients in Subgroup 2 were characterized by the greatest frequency of pain/sensory abnormalities (e.g. allodynia and hyperalgesia) and the fewest signs of vasomotor dysfunction (temperature or color changes) of any of the three groups.

Patients in Subgroup 3 were clearly the most distinct from the other two subgroups, displaying higher levels in all sign/symptom categories (pain/sensory, vasomotor, sudomotor/edema, and motor/trophic) compared with Subgroup 1, and in all but one category relative to Subgroup 2. Patients in this subgroup exhibited the most florid overall CRPS syndrome. The most prominent CRPS characteristic among this subgroup was high levels of motor/trophic changes, with notable vasomotor dysfunction as well.

3.3. Objective test results across CRPS patient subgroups

Results of objective tests traditionally used in the assessment of CRPS were available for only a subset of patients. However, examination of these test results help to clarify objectively the differences between the cluster-derived patient subgroups. As noted above, data regarding abnormalities observed upon EMG/NCV testing were available for 55 patients. Patients in Subgroup 3 (florid CRPS) demonstrated a significantly lower rate of EMG/NCV abnormalities (20%) than were displayed by Subgroup 2 (50%; $\phi = -0.312$, $P < 0.05$). The rate of EMG/NCV abnormalities among patients in Subgroup 1 (38%) fell between, but was not significantly different from, those in the other two groups (both $P > 0.10$).

Results for bone scan were available for 38 patients. Despite this small sample size, positive bone scans (e.g. increased uptake in phase 3) were significantly less frequent among Subgroup 1 patients (8% positive for CRPS) than those in Subgroup 3 (47% positive; $\phi = 0.41$, $P < 0.05$), although comparisons with Subgroup 2 (33% positive) were not statistically significant ($P > 0.10$).

4. Discussion

The present study used a statistical pattern recognition technique, cluster analysis, to test for evidence of homogeneous CRPS subgroups consistent with hypothesized CRPS stages. The existence of sequential stages of CRPS as described in clinical lore (Schwartzman and McLellan, 1987; Bonica, 1990; Schwartzman and Kerrigan, 1990; Gibbons and Wilson, 1992; Veldman et al., 1993) was not supported. No significant differences were found in pain duration between the three CRPS patient subgroups that were derived, thus arguing against a specific, temporally-determined staging of CRPS.

Evidence regarding the spectrum of signs and symptoms observed within the three empirically-derived CRPS

subgroups provided only mixed support for the traditional characterization of CRPS stages. Patients in Subgroup 3 (florid CRPS) displayed significantly fewer signs of pain/sensory dysfunction than Subgroup 2, which might be expected in comparing Stage III to Stage II CRPS according to traditional conceptions (Bonica, 1990). The significantly greater frequency of motor/trophic changes in Subgroup 3 relative to the other subgroups is also consistent with classic descriptions of Stage III. However, according to the CRPS staging described by Bonica (1990), patients in Stage II are expected to display substantially more motor/trophic signs than those in Stage I. No such difference was found between Subgroups 1 and 2 in this study. Although differences in motor/trophic signs between these two subgroups did not parallel expected differences between Stage I and II CRPS, the greater signs of pain/sensory abnormalities observed in Subgroup 2 relative to Subgroup 1 were consistent with expected differences between Stage II and Stage I, respectively.

Despite some similarities in patient characterizations between the three empirically-derived patient subgroups and the hypothesized stages of CRPS, the lack of pain duration differences between groups argues strongly against *sequential* stages of CRPS as traditionally proposed. It is notable that the CRPS subgroup with the greatest average pain duration (Subgroup 2) displayed half the number of motor/trophic changes as did Subgroup 3, the group with the briefest pain duration. This argues against viewing severe motor/trophic changes as an inevitable result of greater duration of CRPS. The negative overall findings in the present study regarding sequential CRPS stages are consistent with other related work using different experimental methodologies (Veldman et al., 1993; Bickerstaff and Kanis, 1994; Zyluk, 1998; Galer et al., 2000).

Although the sequential staging model was not supported, results of this study indicate that at least three statistically-distinct CRPS patient subgroups can be identified. One interpretation of the data is that these patient subgroups broadly reflect differences in syndrome severity, with Subgroups 1 and 2 displaying significantly fewer signs and symptoms of CRPS than those in Subgroup 3. However, this interpretation is made less clear by the fact that Subgroups 1 and 2 differed not so much regarding number of CRPS characteristics, but rather, regarding the specific signs/symptoms that were most prominent.

It is suggested based on results of this study that CRPS might include the following three subtypes: (1) a relatively limited syndrome in which vasomotor signs predominate, (2) a relatively limited syndrome in which neuropathic pain/sensory abnormalities predominate, and (3) a florid CRPS syndrome similar to descriptions of 'classic RSD' (Gibbons and Wilson, 1992). Although signs of motor/trophic change were observed in all three groups, these were double in frequency among patients in Subgroup 3. Given that reliable pain rating data were not available for analysis, it is unclear whether the differences in extent and types of signs/symp-

toms between groups were paralleled by differences in pain severity.

It is notable that EMG/NCV abnormalities were numerically most common among patients in Subgroup 2, the subgroup that exhibited the highest frequency of traditional neuropathic pain characteristics (i.e. allodynia, hyperalgesia). This suggests that differences in clinical presentation between Subgroups 1 and 2 might reflect the differing diagnoses of CRPS Type I and II, respectively. This finding provides empirical support for making distinctions between these two currently-recognized subtypes of CRPS. However, the treatment utility of making this distinction is yet to be proven. For example, our previous work in limited samples has not suggested differences in sympathetic block efficacy between patients with CRPS Type I and those with Type II (Harden et al., 1999). The issue of treatment utility of CRPS subtypes must be addressed in future clinical research.

It is noteworthy that patients in Subgroup 3, who displayed the greatest frequency of positive bone scans, also exhibited the most florid overall CRPS syndrome and the greatest frequency of motor/trophic changes. Previous work in animals (Maeves and Smith, 1999; Ushida and Willis, 1999) and humans (Butler et al., 1999) suggests that disuse may contribute significantly to development of CRPS-like changes, such as allodynia, hyperalgesia, motor dysfunction, and temperature/color changes. Results of this study therefore would be consistent with a relationship between osteopenia, disuse, motor/trophic changes, and severity of the overall CRPS syndrome, although such connections remain to be tested directly.

One limitation of the current study is that the dependent variables used in the cluster analysis reflected only the presence or absence of CRPS characteristics within each of the four empirically derived sign and symptom categories (Harden et al., 1999). Thus, while the presence of temperature asymmetry was addressed, the specific direction of that asymmetry (i.e. affected side warmer or cooler) was not. Work by Birklein et al. (1998) and Wasner et al. (2001) indicates that temperature asymmetry characterized by relative warmth on the affected side is more common in short-term CRPS, whereas longer duration CRPS is more likely to be characterized by relative coolness in the affected extremity. It would therefore be valuable in replicating this cluster analysis to include specific direction of asymmetry as a variable to determine what impact this might have on the overall results.

The present findings indicate that additional research to identify and characterize CRPS subtypes is likely to be fruitful. This future research must address not only clinical characteristics but also pathophysiological mechanisms associated with these subtypes. Such research will be necessary to determine whether patient clusters like those identified in the current study reflect several subtypes of a single syndrome, or rather, whether they should be considered distinct clinical entities mislabeled under the broad rubric

of CRPS due to inadequate diagnostic specificity. In light of other negative findings on the topic of staging (Veldman et al., 1993; Bickerstaff and Kanis, 1994; Zyluk, 1998; Galer et al., 2000), results of the current study also suggest that the clinical lore regarding three sequential stages of CRPS should be reconsidered. The strength of such a conclusion must be tempered by the possibility that the traditional staging may apply only to *untreated* CRPS. Most patients in this sample, like those in all tertiary pain center research samples, had received previous treatments, and therefore detection of ‘pure’ sequential stages of CRPS might have been unattainable. Although results of this study need to be replicated, they do begin to shed light on clinical issues that have not received adequate research attention.

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