External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria

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Abstract

Recent work in our research consortium has raised internal validity concerns regarding the current IASP criteria for Complex Regional Pain Syndrome (CRPS), suggesting problems with inadequate sensitivity and specificity. The current study explored the external validity of these IASP criteria for CRPS. A standardized evaluation of signs and symptoms of CRPS was conducted by study physicians in 117 patients meeting IASP criteria for CRPS, and 43 patients experiencing neuropathic pain with established non-CRPS etiology (e.g. diabetic neuropathy, post-herpetic neuralgia). Multiple discriminant function analyses were used to test the ability of the IASP diagnostic criteria and decision rules, as well as proposed research modifications of these criteria, to discriminate between CRPS patients and those experiencing non-CRPS neuropathic pain. Current IASP criteria and decision rules (e.g. signs or symptoms of edema, or color changes or sweating changes satisfy criterion 3) discriminated significantly between groups (P < 0.001). However, although sensitivity was quite high (0.98), specificity was poor (0.36), and a positive diagnosis of CRPS was likely to be correct in as few as 40% of cases. Empirically-based research modifications to the criteria, which are more comprehensive and require presence of signs and symptoms, were also tested. These modified criteria were also able to discriminate significantly, between the CRPS and non-CRPS groups (P < 0.001). A decision rule, requiring at least two sign categories and four symptom categories to be positive optimized diagnostic efficiency, with a diagnosis of CRPS likely to be accurate in up to 84% of cases, and a diagnosis of non-CRPS neuropathic pain likely to be accurate in up to 88% of cases. These results indicate that the current IASP criteria for CRPS have inadequate specificity and are likely to lead to overdiagnosis. Proposed modifications to these criteria substantially improve their external validity and merit further evaluation.

Keywords: Complex regional pain syndrome; Reflex sympathetic dystrophy; Causalgia; Validation; Diagnosis; Diagnostic criteria

1. Introduction

The publication in 1994 of standardized, consensus-based diagnostic criteria for Complex Regional Pain Syndrome (CRPS) was a step forward in the diagnosis of regional pain disorders associated with vasomotor or sudomotor changes (Merskey and Bogduk, 1994). This syndrome was known previously by various names, most commonly reflex sympathetic dystrophy and causalgia, and was diagnosed using a variety of non-standardized or incompatible diagnostic schemes (Kozin et al., 1981; Amadio et al., 1991; Blumberg, 1991; Gibbons and Wilson, 1992). The standardized CRPS criteria published by the International Associa-
tion for the Study of Pain (IASP; Merskey and Bogduk, 1994) are intended to improve clinical recognition of the disorder, and facilitate selection of more generalizable samples for treatment outcome and basic science research (Stan-

ton-Hicks et al., 1995; Wilson et al., 1996).

Widespread use of these standardized CRPS diagnostic criteria has the potential to lead to improved understanding and treatment of the disorder. However, realization of this potential is limited by the fact that the criteria were derived rationally, based upon the consensus of a group of expert clinicians. While this was an appropriate first step towards developing criteria, experience regarding criterion development in the areas of headache and psychiatric diagnosis highlight the necessity of validating, and if necessary modifying, these initial consensus-based criteria based upon results of validation research and further clinical experience (Merikangas and Frances, 1993). Although the IASP criteria were published nearly 4 years ago, research to validate them empirically has been quite limited. In the absence of ade-

quate research, the validity of these criteria remains uncertain, and the possibility of significant under- or over-
diagnosis cannot be excluded (Galer et al., 1998).

The limited available work in this area suggests several problems with the current IASP criteria. One validity issue is internal validity, which addresses the extent to which interrelationships between CRPS signs and symptoms observed in clinical patients correspond to the IASP criteria. Recent work by the current authors used principal compo-
nents factor analysis (PCA) to study the internal validity of the IASP criteria (Bruehl et al., 1998). PCA is a statistical technique which identifies coherent, and presumably conceptually-linked, subsets of variables within a dataset. Unlike the IASP diagnostic scheme which treats edema, vasomotor, and sudomotor changes as a unitary criterion, PCA indicated that signs and symptoms of vasomotor change form a factor which is statistically-distinct from sudomotor changes and edema (which did group together). The fact that these two statistically-distinct groups of signs and symptoms are combined into a single criterion in the IASP criteria, may contribute to their poor specificity (Bruehl et al., 1998). In addition to the findings above, PCA revealed the presence of statistically-distinct compo-
nents of CRPS which are not incorporated in the current criteria: weakness, movement disorder, tremor, dystonia, diminished range of motion and trophic changes of the hair, skin and nails (Bruehl et al., 1998). These signs and symptoms form a distinct cluster which is referred to, here-
after, as a motor/trophic cluster.

External validity of the IASP criteria is another important issue to be addressed. External validity of diagnostic criteria refers to their usefulness for distinguishing between patients on the basis of some external reference or ‘gold standard’ (Merikangas et al., 1994). The external validity of the IASP criteria was recently examined in a small pilot study by members of our CRPS research consortium (Galer et al., 1998). This study examined the ability of the IASP diag-
nostic criteria to distinguish between CRPS and diabetic neuropathy patients. Use of current IASP criteria and deci-
sion rules (e.g. criterion 3 is satisfied by presence of edema or skin blood flow changes or sweating changes) to make diagnostic decisions led to substantial overdiagnosis. If objective test results to identify diabetes were unavailable and diagnosis were made solely on the pattern of signs and symptoms, up to 37% of diabetic neuropathy patients were likely to be misdiagnosed as having CRPS (Galer et al., 1998). Although based on a small sample, results of this study also suggested that modification of the IASP criteria and decision rules might substantially improve their diag-
nostic accuracy.

The current study was designed to provide a more comprehensive evaluation of the external validity of the IASP CRPS criteria. As in the Galer et al. (1998) study, the current study was based upon the premise that if the IASP criteria and decision rules for diagnosing CRPS cannot dis-
criminate between it and neuropathic pain disorders which do not have a substantial autonomic component, these criteria are likely to be of limited use clinically or for defining research samples. This study also sought to evaluate proposed empirically-derived research modifications to CRPS criteria previously suggested by our research consortium (Bruehl et al., 1998).

2. Methods

2.1. Design

The study is a multi-site between-subjects design comparing CRPS to non-CRPS neuropathic pain patients.

2.2. Participants

Participants included a series of 117 CRPS patients and 43 patients diagnosed with non-CRPS neuropathic pain (non-CRPS) who presented for evaluation and treatment at the data collection sites. CRPS was diagnosed in all patients according to published IASP criteria (see Appendix A; Merskey and Bogduk, 1994). Objective tests of nerve dysfunction (EMG/nerve conduction) were available in a subset of CRPS patients, which if used as a diagnostic cri-
terion, would have led to the diagnosis of CRPS-Type I in approximately two-thirds of the sample (Merskey and Bog-
duk, 1994; Baron et al., 1996). Comparison of known Type I and Type II CRPS patients (based on absence or presence of objective EMG/nerve conduction abnormalities, respec-
tively) revealed no differences in frequency of any sign or symptom between diagnostic groups (all $P > 0.10$), and therefore, the remaining analyses did not separate these diagnostic subcategories. The non-CRPS group reflected several known non-CRPS diagnoses including diabetic neu-
ropathy (44.2%), polyneuropathy (14.0%), post-herpetic neuralgia (20.9%) and radiculopathy (20.9%). To avoid
confounding the two groups, the non-CRPS patients were not identified by process of exclusion (i.e. simply failing to meet CRPS criteria). Rather, each of the non-CRPS disorders was diagnosed using criteria distinct from CRPS criteria, such as extremity pain coexisting with known diabetes mellitus, or pain in a radicular pattern with disc herniation confirmed by MRI.

2.3. CRPS database checklist

In order to insure standardized assessment of signs and symptoms across sites, a database checklist was used. This CRPS checklist presents a complete list of the signs and symptoms used to diagnose CRPS, as well as other signs/symptoms (e.g. trophic changes, motor abnormalities) which are reported to be associated with the disorder in previous literature, but are not incorporated in the IASP diagnostic criteria (Schwartzman and McLellan, 1987; Stanton-Hicks et al., 1990, 1995; Merskey and Bogduk, 1994; Janig and Stanton-Hicks, 1996; Wilson et al., 1996). As recommended by Janig et al. (1991), dichotomous measures (i.e. presence or absence) were used to assess signs and symptoms due to the potential for inter-rater unreliability using interval rating scales. Standardized procedures for evaluating the different signs are provided with the checklist to maximize uniform assessment across sites. Signs and symptoms in the checklist are summarized in Appendix B.

2.4. Procedures

For all patients in both groups, an evaluation of signs and symptoms was conducted by a study physician using the CRPS checklist described above. This involved obtaining a patient history to assess symptoms, as well as conducting a physical examination to assess signs.

2.5. Statistical analysis

The primary analyses tested whether CRPS and non-CRPS neuropathic pain can be distinguished based upon patterns of signs and symptoms. These analyses were more specifically designed to test the ability of current IASP criteria and decision rules to distinguish between the CRPS and non-CRPS groups. The differential diagnosis of CRPS is disorders such as diabetic neuropathy and post-herpetic neuralgia, as in the current study, is unlikely in clinical practice. However, statistical examination of the ability of the IASP criteria to discriminate CRPS from ‘known’ non-CRPS disorders (i.e. without autonomic dysfunction) is an appropriate model for testing the external validity of the diagnostic criteria. Similar statistical models have been used in the validation of diagnostic criteria for headache and psychiatric disorders (Merikangas and Frances, 1993; Merikangas et al., 1994).

Due to the suspected inadequacies in current IASP CRPS criteria suggested by Galer et al. (1998), the current study was also used to test a set of proposed research diagnostic criteria for CRPS which were empirically-derived using principal components factor analysis (PCA; Bruehl et al., 1998). Results of this study are presented in detail in a separate manuscript currently under review. As a pattern recognition technique, PCA provided an empirical basis for determining the proper manner in which to group together signs and symptoms included in a set of proposed CRPS research diagnostic criteria (see Appendix C). Briefly, these research criteria require the presence of both signs and symptoms, each of which are divided into four categories: (1) sensory (2) vasomotor (3) sudomotor/edema and (4) motor/trophic. While PCA allowed determination of the proper groupings of CRPS signs/symptoms, it did not permit determination of the optimal decision rules (i.e. number of signs/symptom categories which must be positive) for determining presence or absence of CRPS. The methodology of the current study was designed to address this latter issue, and therefore, a series of decision rules based upon these research criteria was tested, each differing in the number of sign and symptom categories required to be positive to meet the diagnostic threshold for CRPS.

Discriminant function analyses (DFAs) were conducted using IASP and proposed research criteria/decision rules to discriminate between the CRPS and the non-CRPS groups. DFA determines a discriminant score for each case, and then applies Bayes’ theorem to derive a general rule for classifying cases into one of two groups. Results of DFA were then used to derive indices of discriminative efficiency, including sensitivity, specificity, positive predictive power (PPP) and negative predictive power (NPP). Sensitivity is defined as true positive rate/true positive + false negative rates, reflecting the percentage of true positive (CRPS) cases classified accurately. Specificity is defined by true negative rate/true negative + false positive rates, and reflects the proportion of true negative (non-CRPS) cases classified accurately. Of more importance clinically, given the need to maximize probability of correct diagnosis when actual disease status is unknown, are PPP and NPP (Landau et al., 1991). In this study, PPP indicates the probability that a diagnosis of CRPS is accurate, whereas NPP indicates the probability that a diagnosis of non-CRPS neuropathic pain is accurate. Both PPP and NPP are in part a function of the base rate (prevalence) for the targeted disorder (CRPS) in the population being examined, and these were derived as described by Meehl and Rosen (1955). PPP was defined as: (CRPS base rate × true positive rate)/(CRPS base rate × true positive rate + (1 – CRPS base rate × false positive rate)). NPP was defined as: ((1 – CRPS base rate) × true negative rate)/(1 – CRPS base rate × true negative rate + (CRPS base rate × false negative rate)). These four indicators of diagnostic efficiency were contrasted across different criteria and/or decision rules to determine relative accuracy and likely diagnostic utility of each.

Actual sample size values varied slightly across analyses due to missing data. The maximum available number of
subjects was used for all analyses. All probability values are two-tailed.

3. Results

3.1. Demographics and pain characteristics

A comparison of the demographics and pain characteristics across the CRPS and non-CRPS groups is presented in Table 1. The two subsamples differed significantly on several variables. CRPS patients were younger ($t (131) = 9.50$, $P < 0.001$), had shorter pain duration ($t (149) = 5.18$, $P < 0.001$), and were more likely than non-CRPS patients to be experiencing upper extremity (Phi $(146) = 0.54$, $P < 0.001$) and/or unilateral pain (Phi $(147) = 0.67$, $P < 0.001$).

3.2. Discriminant function analyses (DFA)

Current IASP criteria (see Appendix A) for CRPS were examined first. IASP criterion 2 (continuing pain, allodynia, or hyperalgesia with pain disproportionate to the inciting event) and criterion 3 (edema, changes in surface blood flow, or abnormal sudomotor activity) were combined in a DFA to distinguish between CRPS and non-CRPS groups. A literal interpretation of current IASP criteria as written (‘evidence at some point of…’), which allows criteria to be met by presence of current objective signs or historical symptom reports, distinguished significantly between the two groups (chi-square $(2) = 40.9$, $P < 0.001$). Requiring the presence of objective signs (strict interpretation) for a diagnosis of CRPS to be made also resulted in significant discrimination between groups (chi-square $(2) = 23.9$, $P < 0.001$).

Proposed research criteria (Appendix C) were also tested using a variety of decision rules for determining the threshold for diagnosis of CRPS. Decision rules ranging from a requirement that at least two of four sign categories and at least two of four symptom categories be positive (chi-square $(2) = 18.8$, $P < 0.0010$), to a more stringent rule that three + sign categories and four symptom categories be positive (chi-square $(2) = 68.1$, $P < 0.001$), all discriminated significantly between the CRPS and non-CRPS groups (see Table 2 for complete list of decision rules tested).

4. Diagnostic efficiency

Although it might be assumed that the various diagnostic criteria and decision rules tested are roughly comparable, given that all DFAs were significant, examination of data regarding diagnostic efficiency of each revealed substantial differences. Table 2 presents sensitivity and specificity for all criteria and decision rules tested. The literal interpretation of current IASP criteria (satisfied by presence of signs or symptoms) resulted in a high level of sensitivity, but quite poor specificity. A strict interpretation of IASP criteria (must display objective signs) was also associated with good sensitivity, but only moderately improved specificity. Results for both interpretations of IASP criteria were consistent with results of similar analyses reported by Galer et al. (1998) which found specificities of 0.27
and 0.55 for the literal and strict interpretations of IASP criteria.

As noted above, positive (PPP) and negative (NPP) predictive power may be of more relevance clinically, given that they directly reflect the probability that a given diagnosis of CRPS or Non-CRPS pain, respectively, is correct. Fig. 1A–E display PPP and NPP for the five decision rules which displayed the best combinations of sensitivity and specificity in Table 2. Since the actual PPP and NPP of a given diagnostic decision rule is in part a function of the prevalence of CRPS in the pain population of interest (Meehl and Rosen, 1955), each of these figures displays PPP and NPP for all possible CRPS prevalence rates. For example, in Fig. 1B, the PPP line represents the probability of an accurate CRPS diagnosis across all hypothetical base rates (prevalence) for CRPS within the larger population of neuropathic-type disorders seen in tertiary pain management centers. PPP and NPP values refer to probability that a diagnosis of CRPS is accurate (PPP) or a diagnosis of non-CRPS pain is accurate (NPP). (B) Two + sign and four symptom decision rule. (C) Three + sign and two + symptom decision rule. (D) Three + sign and three + symptom decision rule. (E) Three + sign and four symptom decision rule.

Fig. 1. (A) Positive predictive power (PPP) and negative predictive power (NPP) for proposed research diagnostic criteria with 2 + sign and 3 + symptom decision rule. The x-axis reveals how PPP and NPP vary across all hypothetical base rates (prevalence) for CRPS within the larger population of neuropathic-type disorders seen in tertiary pain management centers. PPP and NPP values refer to probability that a diagnosis of CRPS is accurate (PPP) or a diagnosis of non-CRPS pain is accurate (NPP). (B) Two + sign and four symptom decision rule. (C) Three + sign and two + symptom decision rule. (D) Three + sign and three + symptom decision rule. (E) Three + sign and four symptom decision rule.
tive would provide the highest combination of PPP and NPP across the widest range of possible CRPS prevalence rates.

5. Discussion

The IASP criteria for CRPS were developed by a group of clinicians and basic scientists during a Dahlem-type workshop (Stanton-Hicks et al., 1995). The resulting criteria were intended to facilitate the diagnosis of CRPS and promote research through the use of a descriptive system, rather than one relying on assumptions about pathophysiology (Stanton-Hicks et al., 1995). The authors of the new taxonomy expressed the goal that uniform criteria would improve the clinical recognition of the disorder, facilitate more generalizable treatment outcome research, and lead to identification of possible new subcategories of the disorder (Stanton-Hicks et al., 1995). However, a Medline search reveals only one study to date specifically addressing the validity of these IASP criteria (Galer et al., 1998). The current study is an empirical evaluation of the IASP CRPS criteria and their external validity, and an effort to acquire data for use in guiding future revisions of these criteria.

Consistent with pilot work by Galer et al. (1998), the results of the current study indicate that the external validity of the IASP criteria can be challenged; their application as currently written may result in the over-diagnosis of CRPS. A proposed set of research diagnostic criteria for CRPS, based upon results of the current study and previous factor analysis research (Bruehl et al., 1998) appears to be more specific than current IASP criteria, and may substantially improve the ability to discriminate accurately between CRPS and other types of neuropathic pain. Decision rules tested in this study based on these modified research criteria suggest that a rule requiring at least two of four sign categories and four symptom categories to be positive maximized diagnostic accuracy across the widest range of CRPS prevalence rates. The discriminative ability of the modified research criteria tested in this study suggests that further research regarding these criteria is merited. It is hoped that data from this and other similar studies may provide data-based guidelines for future revisions of the criteria by the IASP taxonomy committee.

One issue not addressed in the current study is the possible impact of CRPS with nerve injury (Type II) versus CRPS without such injury (Type I) on the diagnostic efficiency of CRPS criteria. The developers of the IASP criteria for CRPS did not assume that it was a unitary phenomenon, and this was reflected in the requirement that CRPS Type I versus Type II be specified when making a diagnosis. In the current study, this issue was not specifically examined given that analyses of these data had revealed no significant differences in frequency of various signs and symptoms between patients with and without nerve injury as documented by EMG/NCV (Bruehl et al., 1998). This finding suggested that it was unlikely that the presence or absence of nerve injury would have a significant impact on the ability of the IASP criteria and the proposed research criteria to identify CRPS accurately. However, when a larger set of data is available, it would be useful to test this issue by replicating the current study using CRPS groups with and without documented nerve injury.

The differential diagnosis specifically between CRPS and post-herpetic neuralgia or diabetic neuropathy is likely to be uncommon in typical clinical situations. However, this study used a methodology similar to that used in other diagnostic validity research (Merikangas and Frances, 1993; Merikangas et al., 1994; Galer et al., 1998) which allowed a controlled test of a statistical model analogous to the clinical process of CRPS diagnosis. The pain physician is frequently presented with a patient experiencing an unidentified pain complaint suspected to be neuropathic, with the task of identifying it properly and planning treatment accordingly. The IASP diagnostic criteria are designed to provide an objective means of making decisions as to whether such unidentified conditions are CRPS (i.e. in which autonomic dysfunction is present) or some other type of neuropathic pain. Treatment for these two types of conditions will differ, and application of inappropriate (and possibly expensive) treatments due to misdiagnosis may contribute to excessive medical costs, or worse, delay more appropriate treatment in some cases. Therefore, empirically-guided revisions which improve the validity of the CRPS diagnostic criteria may impact positively on problems of medical over-utilization and patient quality-of-life. Such improvements to the CRPS criteria will also assist in identifying more appropriate research samples to evaluate and improve therapeutic outcomes (Stanton-Hicks et al., 1998).

One potential issue regarding the methodology of this study is that CRPS criteria were used to define the CRPS group, but in some analyses were also used to discriminate between diagnostic groups. This procedure was used because there is no ‘gold standard’ (i.e. single known pathophysiology) for identifying CRPS independent of the current consensus-based IASP criteria. Although not ideal, this methodology is unlikely to have confounded the results for several reasons. First, the non-CRPS group was defined using criteria which were independent of the CRPS criteria, rather than simply reflecting failure to meet CRPS criteria. Selection of the non-CRPS group using this latter methodology would clearly have produced invalid results. Second, if this methodology had confounded the results, it should have maximized group differences, thus making it easier to discriminate statistically between groups. The fact that the current IASP criteria displayed poor specificity despite this possible exaggeration of group differences reaffirms the need for more thorough validation of the current criteria in large clinical populations. Finally, tests of the proposed research modifications to the IASP CRPS criteria and decision rules did not suffer from this same potential confound.
Methodology similar to that described above has been used in the process of validating headache diagnostic criteria as well, given a similar absence of clear diagnostic markers for those disorders (Merikangas and Frances, 1993; Merikangas et al., 1994). Researchers attempting to validate headache diagnostic criteria have accepted the fact that with a lack of a defined pathophysiology, and therefore, an absence of definitive validation studies, the emphasis must be on repeated evaluation of the validity of diagnostic criteria using the best means that are available (Merikangas et al., 1994). It is hoped that the current study will spur additional research focused on evaluation of CRPS diagnostic validity.

Results of this study confirm the existence of a syndrome which is statistically distinguishable from other types of known neuropathic pain, and suggest modifications which may enhance CRPS diagnostic accuracy. Although the modified research criteria examined in this study appear promising and deserve further research, use of these modified criteria for ‘clinical’ diagnosis is clearly premature. This would encourage a reversion to the situation prior to 1994 in which there was no universal standard for CRPS diagnosis, and would consequently, defeat the original purpose of the standardized IASP criteria. The proposed modified research criteria should, therefore, be used only for research until sufficient validation data are available to justify a formal revision of the CRPS criteria through the IASP taxonomy committee. Further exploration of potential modifications to the IASP diagnostic scheme for CRPS may be invaluable for guiding such revisions of the CRPS criteria, and ultimately will contribute to improved clinical diagnosis.

Appendix A IASP diagnostic criteria for Complex Regional Pain Syndrome

(1) The presence of an initiating noxious event, or a cause of immobilization.

(2) Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.

(3) Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.

(4) This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Appendix B Signs and/or symptoms on CRPS checklist

‘Burning’ pain

Hyperesthesia

Temperature asymmetry

Color changes

Sweating changes

Edema

Nail changes

Hair changes

Skin changes

Weakness

Tremor

Dystonia

Decreased range of motion

Hyperalgesia

Allodynia

Appendix C Proposed modified research diagnostic criteria for CRPS

(1) Continuing pain which is disproportionate to any inciting event

(2) Must report at least one symptom in each of the four following categories

Sensory: reports of hyperesthesia

Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry

Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry

Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

(3) Must display at least one sign in two or more of the following categories

Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)

Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry

Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry

Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

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