

## REVIEW ARTICLE

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# Proposed New Diagnostic Criteria for Complex Regional Pain Syndrome

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### ABSTRACT

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This topical update reports recent progress in the international effort to develop a more accurate and valid diagnostic criteria for complex regional pain syndrome (CRPS). The diagnostic entity of CRPS (published in the International Association for the Study of Pain's Taxonomy monograph in 1994; International Association for the Study of Pain [IASP]) was intended to be descriptive, general, and not imply etiopathology, and had the potential to lead to improved clinical communication and greater generalizability across research samples. Unfortunately, realization of this potential has been limited by the fact that these criteria were based solely on consensus and utilization of the criteria in the literature has been sporadic at best. As a consequence, the full potential benefits of the IASP criteria have not been realized. Consensus-derived criteria that are not subsequently validated may lead to over- or underdiagnosis, and will reduce the ability to provide timely and optimal treatment. Results of validation studies to date suggest that the IASP/CRPS diagnostic criteria are adequately sensitive; however, both internal and external validation research suggests that utilization of these criteria causes problems of overdiagnosis due to poor specificity. This update summarizes the latest international consensus group's action in Budapest, Hungary to approve and codify empirically validated, statistically derived revisions of the IASP criteria for CRPS.

*Key Words.* Complex Regional Pain Syndrome; Reflex Sympathetic Dystrophy; Causalgia; Diagnostic Criteria

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### Introduction

Complex regional pain syndrome (CRPS) has been known by many names, but most commonly as reflex sympathetic dystrophy and causalgia (as attributed to Evans and Mitchell, respectively) [1,2]. In the past, it was diagnosed using a variety of nonstandardized and idiosyncratic diagnostic systems (e.g., [3–6], each of which

was derived solely from the authors' clinical experiences and none of which achieved wide acceptance. After much debate in the literature and at scientific meetings, the name was ultimately changed to complex regional pain syndrome (CRPS) at a consensus workshop in Orlando, Florida, in 1994 [7,8], with the new name and diagnostic criteria codified by the International Association for the Study of Pain (IASP) task force on taxonomy (Table 1) [9]. The new diagnostic entity of CRPS was intended to be descriptive, general, and not imply any etiopathology (including any direct role for the sympathetic nervous system). This pivotal effort finally provided an

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**Table 1** IASP diagnostic criteria for complex regional pain syndrome (CRPS)\* (adapted from [9])

1. The presence of an initiating noxious event, or a cause of immobilization<sup>†</sup>
2. Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain (can be sign or symptom)
4. This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction

\* If seen without "major nerve damage" diagnose CRPS I; if seen in the presence of "major nerve damage" diagnose CRPS II.

<sup>†</sup> Not required for diagnosis; 5–10% of patients will not have this.

officially endorsed set of standardized diagnostic criteria that had the potential to lead to improved clinical communication and greater generalizability across research samples [7]. However, realization of this potential has been somewhat limited by the fact that these criteria were based solely on consensus, utilization of the criteria in the literature has been sporadic at best [10], and certain influential groups have resisted the change (e.g., personal injury lawyers, who may benefit by a "looser" criteria, and some ill informed patient advocacy organizations that fear a "tighter" criteria may cause many previously diagnosed patients to be thrown into diagnostic limbo: see discussion of CRPS-not otherwise specified (NOS) below). As a consequence, the full benefits of the common, consensus-defined IASP criteria have not been completely realized.

## Methods

A "closed" workshop (by invitation only) was held in Budapest, Hungary, in the fall of 2003. One day was devoted to a discussion of the diagnostic criteria with a stated goal of "to review the terminology of complex regional pain syndromes in light of experience gained since its introduction as component of the taxonomy of chronic pain." There were 35 professionals attending from seven countries (see Table 2 for list of attendees). The diagnostic criteria workshop loosely followed a "Dahlem" think tank type of format with didactic presentations followed by breakout working groups, full group discussion, a second round of breakout sessions, and a final full session. Formal recommendations were made to endorse the recommended research criteria that had been previously formulated by empiric research [11,12]. This was followed by a day to discuss the treat-

ment of CRPS and half a day of presentations to an open audience. A book was published concerning diagnostic and therapeutic issues by workshop attendees on the basis of these recommendations [13]. The recommendations of this panel have been formally submitted to the IASP's task force on taxonomy for consideration in the third edition of the classification of chronic pain: descriptions of chronic pain syndromes and definition of pain terms (published by IASP Press).

There is controversy about the value of the consensus process in this setting. There has been an almost complete absence of evidence-based information about this condition since it was newly defined. It is therefore not possible to apply the usual scientific tools to the problem of diagnosis and therapy. The consensus process has been widely accepted in medicine, and is the subject of study by groups such as the National Institutes of Health (see <http://www.consensus.nih.gov/about/references.htm>). For example, experience has been gained in developing diagnostic criteria for headache and psychiatric disorders. These highlight the necessity of validating and modifying initial consensus-based criteria in the light of systematic validation research [14]. Consensus-derived criteria that are not subsequently validated may lead to over- or underdiagnosis, and will reduce the ability to provide timely and optimal treatment. This review summarizes the latest international consensus group's action in Budapest, Hungary, to approve and codify empirically validated revisions of the IASP criteria for CRPS [15].

Results of validation studies to date suggest that the IASP/CRPS diagnostic criteria are adequately sensitive (i.e., rarely miss a case of actual CRPS). However, both internal and external validation research suggests that using these criteria causes problems of overdiagnosis due to poor specificity [11,12,16]. The current IASP criteria implicitly assume that signs and symptoms of vasomotor, sudomotor, and edema-related changes provide redundant diagnostic information; that is, the presence of any one of these is sufficient to meet criterion 3. This combination of multiple distinct elements of the syndrome into a single diagnostic criterion in the current IASP system appears to be one element compromising specificity [11,15]. Wording of the current IASP criteria that permits diagnosis based solely on patient-reported historical symptoms may also contribute to overdiagnosis. An additional weakness of the current criteria is their failure to include motor/trophic signs and symptoms, which can lead to important informa-

**Table 2** Workshop attendees, Budapest, Hungary, fall 2003

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Stephen Bruehl, PhD Vanderbilt University TN, USA	Joshua Prager, MD California Pain Management Center CA, USA
Allen W. Burton, MD MD Anderson Cancer Center TX, USA	Gabor Racz, MD Texas Tech University Health Sciences TX, USA
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tion being ignored that may discriminate CRPS from other syndromes [16–18].

The conclusions above are supported by the results of a factor analysis that was conducted in a series of 123 CRPS patients. These results indicated that signs and symptoms of CRPS actually clustered into four statistically distinct subgroups [11]. The first of these subgroups is a unique set of signs and symptoms indicating abnormalities in pain processing (e.g., allodynia, hyperalgesia). Skin color and temperature changes, which are indicative of vasomotor dysfunction, characterize the second subgroup. Edema and sudomotor dys-

function (e.g., sweating changes) combined to form a third unique subgroup. The finding that vasomotor signs and symptoms were statistically distinct from those reflecting sudomotor changes/edema is in contrast to the IASP criteria, which treat all three of these as diagnostically equivalent. A fourth and final separate subgroup was identified that included motor and trophic signs and symptoms. Numerous studies have described various signs of motor dysfunction (e.g., dystonia, tremor) as important characteristics of this disorder, and trophic changes have frequently been mentioned in historical clinical descriptions [6,17,19]. The

absence of these features from the current IASP criteria is notable, especially given factor analytic findings that this subgroup of signs and symptoms does not overlap significantly with the other characteristics of CRPS used in the IASP criteria.

External validity, which addresses the ability of the diagnostic criteria to distinguish CRPS patients from those with other types of pain conditions (specificity), is obviously an important issue. In the absence of a definitive pathophysiology of CRPS and thus the absence of a definitive objective test to serve as a “gold standard,” providing evidence for external validity of a diagnostic criteria is challenging [12]. However, the upper limit on external validity can be evaluated by using the original criteria themselves as a reference point [12,16]. In this methodology, the researcher must employ a strict application of the IASP/CRPS criteria in order to distinguish a CRPS patient group from a comparison group of non-CRPS neuropathic pain patients who are defined by independent diagnostic information (e.g., chronic diabetes with ascending symmetrical pain, corroborated by electrodiagnostic studies). Existing criteria and modifications to these criteria can then be evaluated with regard to their ability to distinguish between these two groups based on patterns of signs and symptoms. While a defined disorder such as diabetic neuropathy is not likely to present a differential diagnostic challenge in actual clinical practice, use of such disorders for testing the discriminative utility of CRPS diagnostic signs and symptoms provides a model for examining external validity issues.

This model was used to test the accuracy of the IASP/CRPS criteria for discriminating between 117 patients meeting IASP criteria and 43 neuropathic pain patients with established non-CRPS etiology. The IASP/CRPS criteria and decision rules (e.g., “evidence at some time” of edema *or* color changes *or* sweating changes that satisfy criterion 3) did discriminate significantly between the CRPS and non-CRPS groups. However, closer examination of the results indicated that while diagnostic sensitivity (i.e., the ability to detect the disorder when it is present) was quite high (0.98), specificity (i.e., minimizing false-positive diagnoses) was poor (0.36); thus a positive diagnosis of CRPS was likely to be correct in as few as 40% of cases [12].

For clinical purposes, sensitivity is extremely important. On the other hand, specificity is critical in the selection of research samples. High sensitivity at the expense of specificity in a diagnostic criteria may lead to overdiagnosis and, ultimately,

unnecessary, ineffective, and potentially invasive treatments. Such diagnostic criteria also have the significant downside of identifying pathophysiologically heterogeneous groups for research, potentially contributing to negative results in clinical trials. Such overdiagnosis (due to poor specificity) must be balanced with the equally undesirable consequences of failing to identify clinically relevant syndromes and treat patients inadequately (due to poor sensitivity).

#### Statistically Derived Revision of CRPS Criteria

A set of modified diagnostic criteria for further exploration was developed based on results of validation studies [11,12]. These modified criteria assessed CRPS characteristics within each of the four statistically derived factors described above. Given evidence from Galer et al. [16] and Harden et al. [11] that objective signs on examination and patient-reported symptoms both provide useful and nonidentical information, the modified criteria required the presence of signs and symptoms of CRPS for diagnosis [11,16]. A study of these modified criteria testing their ability to discriminate between the CRPS and non-CRPS neuropathic pain groups indicated that they could increase diagnostic accuracy [12]. Results indicated that a decision rule requiring two of four sign categories and three of four symptom categories for a diagnosis to be made resulted in a sensitivity of 0.85 and a specificity of 0.69 (Table 3). This decision rule represented a good compromise between identifying as many patients as possible in the clinical context while substantially reducing the high level of false-positive diagnoses associated with current IASP criteria. This decision rule was therefore adopted in a set of *Clinical Diagnostic Criteria* endorsed by the Budapest group (summarized in Table 3).

Both sensitivity and specificity can be strongly influenced by the decision rules employed [12], and optimization of decision rules depends on the purpose for which they are intended, such as identifying stringent research samples (minimizing false positives) vs clinically identifying as many CRPS patients as possible (minimizing false negatives). The proposed clinical diagnostic criteria described above reflected an improvement over current IASP criteria for clinical purposes, but still suffered from less than optimal specificity for use in the research context. Tests of the modified CRPS criteria above indicated that modifying the decision rules to require that two of four sign

**Table 3** Proposed clinical diagnostic criteria for CRPS**General definition of the syndrome:**

CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time

**To make the clinical diagnosis, the following criteria must be met:**

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three of the four* following categories:
  - Sensory:** Reports of hyperesthesia and/or allodynia
  - 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 **at time of evaluation** in *two or more* of the following categories:
  - Sensory:** Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
  - Vasomotor:** Evidence of temperature asymmetry (>1°C) 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)
4. There is no other diagnosis that better explains the signs and symptoms

**For research purposes,** diagnostic decision rule should be at least one symptom **in all four** symptom categories and at least one sign (observed at evaluation) in two or more sign categories.

categories and four of four symptom categories be positive for diagnosis to be made in a research setting resulted in a sensitivity of 0.70 and a specificity of 0.94. Of all the permutations tested, this decision rule resulted in the greatest probability of accurate diagnosis for both CRPS and non-CRPS patients (approximately 80% and 90% accuracy, respectively; see Table 4 for a summary of decision rules considered) [12]. This high level of specificity was considered desirable in the research context by the Budapest consensus group, and therefore was adopted as distinct *Research Diagnostic Criteria*. Thus, the proposed revision to the CRPS criteria endorsed by the Budapest group resulted in two similar sets of diagnostic criteria, differing only in the decision rules employed to optimize their use for clinical vs research purposes.

**Table 4** Summary of decision rules considered (modified from [12])

Criteria/Decision Rules for Proposed Criteria	Sensitivity	Specificity
2+ sign categories & 2+ symptom categories	0.94	0.36
2+ sign categories & 3+ symptom categories	0.85	0.69
2+ sign categories & 4 symptom categories	0.70	0.94
3+ sign categories & 2+ symptom categories	0.76	0.81
3+ sign categories & 3+ symptom categories	0.70	0.83
3+ sign categories & 4 symptom categories	0.86	0.75

Current distinctions between CRPS type I and CRPS type II subtypes, reflecting, respectively, the absence and presence of evidence of peripheral nerve injury, were retained by consensus despite ongoing questions as to whether such distinctions have clinical utility. The consensus group also was concerned about the approximately 15% of patients previously diagnosed with CRPS who would now be without a diagnosis. A third diagnostic subtype called CRPS-NOS was recommended that would capture those patients who did not fully meet the new clinical criteria, but whose signs and symptoms could not better be explained by another diagnosis [15]. In other words, those patients who have fewer than three symptom or two sign categories, or who were not showing a sign at the time of the examination, but had exhibited this previously, and whose signs and symptoms were felt to be best explained by CRPS, would receive a diagnosis of CRPS-NOS.

**Conclusions and Clinical Implications**

The IASP diagnostic criteria were designed to provide a standardized, common methodology for making decisions as to whether unidentified pain conditions represent CRPS or not. Treatment for two distinct conditions should differ, and application of inappropriate (and possibly expensive and/or dangerous) treatments due to misdiagnosis can contribute to excessive medical costs, or worse, may delay the appropriate treatment. Thus, the statistically derived revisions of CRPS diagnostic

criteria endorsed by the Budapest consensus group may impact positively on problems of medical overutilization and patient quality of life. These revisions should also assist in identifying more homogeneous research samples to evaluate and improve therapeutic options [15,20]. A test of the modified research diagnostic criteria indicates that it is possible to reduce the rate of overdiagnosis dramatically, although such changes modestly diminish diagnostic sensitivity as well [12]. The relative merits of enhanced specificity at the expense of diagnostic sensitivity were discussed extensively by the consensus group, with the result being that two similar sets of criteria were adopted specifically for use in clinical vs research settings, differing only in the decision rules employed (summarized in Table 1). These new criteria will now, of course, need to be further validated. The closed consensus workshop in Budapest adopted and codified the revised criteria described above (Table 3), and they are being proposed to the Committee for Classification of Chronic Pain of the IASP for inclusion in future revisions of their formal taxonomy and diagnostic criteria for pain states.

#### References

- 1 Evans J. Reflex sympathetic dystrophy. *Surg Clin N Am* 1946;26:780.
- 2 Mitchell SW. *Injuries of the Nerves and Their Consequences*. Philadelphia, PA: J.B. Lippincott & Co; 1872.
- 3 Bonica JJ. *The Management of Pain*. Philadelphia, PA: Lea and Feibiger; 1953.
- 4 Gibbons JJ, Wilson PR, Score RSD. Criteria for the diagnosis of reflex sympathetic dystrophy and causalgia. *Clin J Pain* 1992;8:260-3.
- 5 Kozin F, Ryan LM, Carerra GF, Soin JS, Wortmann RL. The reflex sympathetic dystrophy syndrome III: Scintigraphic studies, further evidence for the therapeutic efficacy of systemic corticosteroids, and proposed diagnostic criteria. *Am J Med* 1981;70:23-30.
- 6 Wilson PR, Low PA, Bedder MD, Covington EC, Rauck RL. Diagnostic algorithm for complex regional pain syndromes. In: Janig W, Stanton-Hicks M, eds. *Reflex Sympathetic Dystrophy: A Reappraisal*. Seattle, WA: IASP Press; 1996:93-106.
- 7 Boas R. Complex regional pain syndromes: Symptoms, signs and differential diagnosis. In: Janig W, Stanton-Hicks M, eds. *Reflex Sympathetic Dystrophy: A Reappraisal*. Seattle, WA: IASP Press; 1996:79-92.
- 8 Stanton-Hicks M, Janig W, Hassenbusch S, et al. Reflex sympathetic dystrophy: Changing concepts and taxonomy. *Pain* 1995;63:127-33.
- 9 Merskey H, Bogduk N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. Seattle, WA: IASP Press; 1994.
- 10 Reinders MF, Geertzen JH, Dijkstra PU. Complex regional pain syndrome type I: Use of the International Association for the Study of Pain diagnostic criteria defined in 1994. *Clin J Pain* 2002;18:207-15.
- 11 Harden RN, Bruehl S, Galer B, et al. Complex regional pain syndrome: Are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain* 1999;83:211-9.
- 12 Bruehl S, Harden RN, Galer BS, et al. External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. *Pain* 1999;81:147-54.
- 13 Wilson P, Stanton-Hicks M, Harden R, eds. *CRPS: Current Diagnosis and Therapy*. Seattle, WA: IASP Press; 2005.
- 14 Merikangas KR, Frances A. Development of diagnostic criteria for headache syndromes: Lessons from psychiatry. *Cephalalgia* 1993;13(suppl 12):34-8.
- 15 Harden R, Bruehl S. Diagnostic criteria: The statistical derivation of the four criterion factors. In: Wilson PR, Stanton-Hicks M, Harden RN, eds. *CRPS: Current Diagnosis and Therapy*. Seattle, WA: IASP Press; 2005:45-58.
- 16 Galer BS, Bruehl S, Harden RN. IASP diagnostic criteria for complex regional pain syndrome: A preliminary empirical validation study. *Clin J Pain* 1998;14:48-54.
- 17 Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. *Neurology* 1990;40:57-61.
- 18 Schwartzman RJ, McLellan TL. Reflex sympathetic dystrophy: A review. *Arch Neurol* 1987;44:555-61.
- 19 Galer BS, Butler S, Jensen MP. Case report and hypothesis: A neglect-like syndrome may be responsible for the motor disturbance in Reflex Sympathetic Dystrophy (Complex Regional Pain Syndrome-1). *J Pain Symptom Manage* 1995;10:385-91.
- 20 Stanton-Hicks M, Baron R, Boas R, et al. Consensus report: Complex regional pain syndromes: Guidelines for therapy. *Clin J Pain* 1998;14:155-66.