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# Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome

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## Abstract

Current IASP diagnostic criteria for CRPS have low specificity, potentially leading to overdiagnosis. This validation study compared current IASP diagnostic criteria for CRPS to proposed new diagnostic criteria (the "Budapest Criteria") regarding diagnostic accuracy. Structured evaluations of CRPS-related signs and symptoms were conducted in 113 CRPS-I and 47 non-CRPS neuropathic pain patients. Discriminating between diagnostic groups based on presence of signs or symptoms meeting IASP criteria showed high diagnostic sensitivity (1.00), but poor specificity (0.41), replicating prior work. In comparison, the Budapest clinical criteria retained the exceptional sensitivity of the IASP criteria (0.99), but greatly improved upon the specificity (0.68). As designed, the Budapest research criteria resulted in the highest specificity (0.79), again replicating prior work. Analyses indicated that inclusion of four distinct CRPS components in the Budapest Criteria contributed to enhanced specificity. Overall, results corroborate the validity of the Budapest Criteria and suggest they improve upon existing IASP diagnostic criteria for CRPS.

### Keywords

Complex Regional Pain Syndrome; Reflex sympathetic dystrophy; CRPS; RSD; Diagnosis; Validation

## 1. Introduction

The historical literature regarding the disorder now called Complex Regional Pain Syndrome (CRPS) reflects an array of idiosyncratic diagnostic schemes [1,4,11,17,28,35]. In response, an international meeting was held in 1993 in Orlando, Florida to develop

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consensus terminology (i.e., CRPS) and standardized diagnostic criteria to improve clinical recognition of the disorder and facilitate the selection of more generalizable research samples [33,36]. Since publication of these consensus-based criteria by the International Association for the Study of Pain (IASP) [23], the extent of their use in the clinical setting is unknown, but their application in the research setting has been shown to be inconsistent [28].

Despite the inherent advantages of having standardized, internationally-recognized diagnostic criteria for CRPS, it has been suggested that a lack of proven validity may be a barrier to their use by researchers and clinicians [6,13,17]. Incomplete understanding of CRPS pathophysiology and the resulting lack of a "gold standard" test make the design of validation studies more challenging [6,28]. However, studies conducted to date suggest that the IASP criteria for CRPS suffer from a lack of specificity [6,10,13]. That is, while the IASP criteria may accurately identify most cases of CRPS, they also tend to misidentify non-CRPS neuropathic pain conditions as CRPS, potentially contributing to overdiagnosis and either inappropriate or unnecessary treatments [6,13]. This inadequate specificity results from the fact that the IASP CRPS criteria can be met solely based on self-reported symptoms (which can be historical), and the use of overly liberal decision rules; for instance requiring only the report of edema and pain seemingly out of proportion to the injury as sufficient to make the diagnosis [6,10,13,23]. Failure of the IASP criteria to incorporate motor and trophic features commonly associated with CRPS also may adversely impact diagnostic accuracy [6,13].

To address these limitations, an international consensus meeting was held in Budapest in 2003 to review issues related to CRPS diagnosis with the goal of recommending improvements to the IASP criteria (Ref. [12]; see Appendix I for a list of participants). The resulting proposal for modified diagnostic criteria for CRPS (the "Budapest Criteria") was based primarily on empirically-derived criteria published previously [6,13]. Research evaluating these empirically-derived criteria since their publication in 1999 indicates they result in improved diagnostic consistency between clinicians (kappa = 0.66–0.69) compared to existing IASP criteria (kappa = 0.43–0.66) [9]. Moreover, these modified criteria result in less frequent diagnoses of CRPS [9,27], potentially reflecting improved specificity. However, no published studies have yet directly compared the current standard IASP criteria to these proposed Budapest Criteria vis-à-vis diagnostic sensitivity and specificity. In a manner similar to our prior published work [6,10], this study sought to compare the relative diagnostic efficiency of these alternative diagnostic criteria in discriminating between CRPS and non-CRPS neuropathic pain patients.

## 2. Method

### 2.1. Design

An international, multi-site, between-subjects design was used to compare the ability of the IASP and Budapest diagnostic criteria to distinguish between CRPS-I and non-CRPS neuropathic pain patients.

### 2.2. Subjects

Subjects included a series of 113 CRPS-I patients and 47 patients with non-CRPS neuropathic pain ("non-CRPS") who presented for evaluation and treatment at the data collection sites. Due to the clinical nature of the sample accrual, matching of CRPS and non-CRPS groups in terms of sample size, type of initiating injury, or other relevant characteristics was not possible. The CRPS sample for this study was restricted to CRPS-I patients to maximize sample homogeneity given the small proportion of CRPS-II patients in

the overall sample (13%) which prevented separate analyses by CRPS subtype. Non-CRPS neuropathic pain affecting the limbs appeared to be the most appropriate comparison group given that CRPS-I is associated with signs and symptoms characteristic of other known neuropathic pains (e.g., allodynia, hyperalgesia) and evidence that CRPS-I may be associated with some type of peripheral nerve injury [2,24]. All patients in the CRPS-I group met published IASP criteria for this disorder [23]. Fracture was the single most common initiating event in the CRPS group (41.6%), with surgery and crush injuries contributing in an additional 32% of CRPS cases. Distribution of CRPS patients across the study sites was: Reuth Medical Center (Israel; 31%), University of Erlangen-Nuremberg (Germany; 16.8%), VU University Medical Center (Netherlands; 15.9%), University Medical Center Mainz (Germany; 12.4%), Rehabilitation Institute of Chicago (US; 10.6%), Leiden University Medical Center (Netherlands; 9.7%), and Rush University Medical Center (US; 3.5%). The two German sites evaluated patients primarily with short-term CRPS (mean of less than 5 months in duration), whereas the other study sites evaluated primarily patients with long-term CRPS (all means greater than 30 months in duration).

Diagnoses in the non-CRPS group included peripheral neuropathy in a single extremity isolated to a specific nerve distribution (45%), radiculopathy (30%), diabetic peripheral neuropathy (15%), and carpal or tarsal tunnel syndrome (10%). Most common initiating events for the non-CRPS pain conditions were surgery (50%) and crush injuries (30%). Non-CRPS neuropathic pain disorders were diagnosed by presence of persistent pain with clear neuropathic etiology supported by relevant testing where appropriate (e.g., EMG and clinical examination consistent with pain and symptoms restricted to a specific peripheral nerve distribution following known injury to that nerve, extremity pain coexisting with known diabetes mellitus, pain in a radicular pattern with disk herniation confirmed by MRI, etc.). A lower extremity pain location was significantly more common in the non-CRPS patients than in the CRPS patients (74.4% versus 47.7%, $p < .001$). Distribution of non-CRPS patients across the study sites was: Reuth Medical Center (Israel; 12.8%), VU University Medical Center (Netherlands; 23.4%), University Medical Center Mainz (Germany; 21.3%), Leiden University Medical Center (Netherlands; 19.1%), Stanford University Medical Center (US; 12.8%), and Rush University Medical Center (US; 10.6%).

## 2.3. Measures

**2.3.1. CRPS database checklist—**In order to insure standardized assessment of signs and symptoms across study sites, a CRPS database checklist similar to that used in our past multi-site research work was employed [6,7,13]. This checklist presented a complete list of the signs and symptoms used to diagnose CRPS, as well as other signs/symptoms (e.g., trophic changes, motor abnormalities) reported to be associated with the disorder in previous literature but not incorporated in the IASP diagnostic criteria [16,23,31–35]. Based on previous suggestions of sensory deficits in CRPS patients beyond the region of pain [30], an evaluation of light touch sensitivity (categorized as hypoesthetic, normal, or allodynic) was included in the CRPS database checklist and was assessed bilaterally on the face, chest, and upper and lower extremities. Categorical measures (e.g., presence or absence) were used to assess all signs and symptoms because of the potential for decreased inter-rater reliability using interval rating scales [15,25]. Written standardized procedures and an instructional video to demonstrate the data collection procedures were provided with the checklist to maximize uniform assessment across sites. Investigators at all sites were highly proficient in English, thereby minimizing the potential impact of language issues. Copies of the database checklist and instructions are available from the authors.

**2.3.2. Visual analog pain intensity scale—**At all study sites, a 100 mm visual analog scale (VAS) was used to assess overall pain intensity. This VAS was anchored with “no pain” and “worst possible pain” in the patients’ native language.

## 2.4. Procedures

For all patients in both groups, the study physician conducted an evaluation of signs and symptoms 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. As part of the physical examination, an evaluation of mechanical wind-up (to repetitive light pinprick) was conducted using a punctate mechanical stimulator (diameter: 0.2 mm; force: 256 mN) provided to all study sites by one of the authors (C.M.) and based on procedures described previously [8,29]. To better characterize the degree of temperature asymmetry, temperatures in the center of the affected hand (palmar surface) or foot (plantar surface) and the contralateral hand/foot were determined while in a room temperature environment (minimum 30 min of acclimatization) using standard infrared (IR) thermometers provided to all study sites (Exergen Corp., Watertown, MA). This simple temperature assessment methodology was designed solely to provide objective documentation of the clinically-determined temperature asymmetry used in making the diagnoses. Repeated assessment of temperature asymmetry over time would be necessary to optimize the accuracy of these temperature evaluations (e.g., [18]).

Thermal Quantitative Sensory Testing (tQST; Medoc TSA-II, Medoc Inc., Tel Aviv, Israel) data were available for patients at the study sites in Israel and Germany, as well as for a subset of patients at the Rehabilitation Institute of Chicago and Stanford sites. tQST data were available for a total of 61 CRPS patients and 13 non-CRPS patients. A standardized protocol was used across all study sites obtaining these data. The tQST protocol employed a computer-controlled 30 × 30 mm Peltier thermistor probe that was used to evaluate cold and warmth perception thresholds and heat pain threshold (mean of three trials each) using the method of limits. For upper extremity CRPS, the probe was placed sequentially on three adjacent sites on the volar forearm of the affected extremity. For lower extremity CRPS, the probe was similarly placed on three adjacent sites on the dorsal mid-calf. Prior to each trial, the probe was maintained at an adaptation temperature of 32 °C.

All study procedures were approved by the appropriate ethical review boards at participating institutions.

## 2.5. Statistical analysis

Analyses were conducted using the SPSS for Windows Version 17 statistical package (SPSS Inc., Chicago, IL). Preliminary analyses used *t*-tests to compare mean values across diagnostic groups and the nonparametric phi correlation to evaluate direction and strength of associations of categorical measures across groups.

For correlational analyses of highly skewed continuous variables, Spearman’s rho was used to minimize the influence of the skewed distribution. The underlying rationale for the approach taken in primary analyses is detailed in our similar prior work (see Refs. [6,10]). Primary analyses derived measures of diagnostic efficiency (see below) to provide relative comparisons between the IASP and Budapest Criteria in distinguishing CRPS from non-CRPS neuropathic pain patients. Similar models have been used in validation of diagnostic criteria for headache and psychiatric disorders [21,22].

In analyses of diagnostic efficiency, IASP criteria were evaluated as written and typically applied in clinical practice, i.e., criteria can be met by presence of self-reported symptoms or

signs noted during the physical examination. For the Budapest Criteria (detailed in Ref. [14]), both the *clinical* decision rules (CRPS characteristics present in at least 3 of 4 symptom categories and at least 2 of 4 sign categories) and *research* decision rules (CRPS characteristics present in all 4 symptom categories and at least 2 of 4 sign categories) were evaluated. Appendix II summarizes the Budapest clinical criteria. Based on fulfillment of the various diagnostic criteria as a function of patient group membership, several indices of diagnostic efficiency were derived, 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. Potentially of more importance clinically, given the need to maximize probability of correct diagnosis when actual disease status is unknown, are PPP and NPP [19]. In this study, PPP indicated the probability of accurate categorization to the CRPS group based on the diagnostic criteria being tested, whereas NPP indicated the probability of accurate categorization to the non-CRPS neuropathic pain group. Both PPP and NPP are dependent on the prevalence of the targeted disorder (CRPS) in the population being examined, and these were derived as described by Meehl and Rosen [20]. PPP was defined as: (CRPS prevalence * true positive rate)/((CRPS prevalence * true positive rate) + (1 − CRPS prevalence * false positive rate)). NPP was defined as: ((1 − CRPS prevalence) * true negative rate)/((1 − CRPS prevalence * true negative rate) + (CRPS prevalence * false negative rate)). PPP and NPP were derived for scenarios in which 50% and 70% of patients referred to rule in or out CRPS actually have the disorder, a prevalence range like that which might occur in a specialty pain clinic to which suspected cases of CRPS are often referred [26]. These four indicators of diagnostic efficiency were contrasted across different criteria to evaluate relative accuracy and likely diagnostic utility of each.

Secondary analyses were conducted to evaluate the extent to which each of the diagnostic components included in the Budapest Criteria (sensory, vasomotor, sudomotor/edema, and motor/trophic) contribute to diagnostic accuracy. This was addressed by contrasting the ability of each individual diagnostic component to discriminate between CRPS and non-CRPS neuropathic pain patients with the ability of all four components to discriminate these groups simultaneously. Continuous component scores were derived reflecting the total number of signs and symptoms observed in each of the four categories above for each subject (total score combining all four components in CRPS = 12.0 ± 2.59, non-CRPS = 5.4 ± 3.59; $t(164) = 12.84$, $p < .001$).

These component scores were then included as independent variables (individually and in combination) in a series of binary logistic regressions, with resulting classification tables used to derive sensitivity and specificity values.

All analyses used the maximum number of cases available and a two-tailed probability value of $p < .05$ was used as the criterion for statistical significance. All means are presented as mean ± SD. For highly skewed continuous variables, medians are presented with interquartile range.

## 3. Results

### 3.1. Preliminary analyses

Table 1 summarizes differences between the CRPS and non-CRPS groups with regards to demographics and non-diagnostic clinical characteristics. The CRPS group was significantly younger, more likely to be female, and had experienced their pain condition for a significantly shorter time than the non-CRPS patients. Overall clinical pain intensity was

statistically comparable across groups. However, CRPS patients displayed significantly greater acute pain sensitivity (lower heat pain threshold) on tQST evaluation compared to non-CRPS patients. Additionally, CRPS patients were significantly more sensitive to non-noxious warmth (lower warmth perception threshold) and cold (higher cold perception threshold) during tQST evaluation compared to non-CRPS patients. Sensitivity to light touch was comparable between groups for most body regions evaluated with two exceptions: significantly greater frequency of abnormal sensation (hypoesthesia) on the contralateral side of the face and the unaffected (contralateral) thigh among non-CRPS patients. In general, rates of abnormal light touch sensitivity were relatively low in both groups.

Table 2 compares the two groups with regards to CRPS signs and symptoms. Significant differences were observed across groups on nearly every diagnostic characteristic. Although hypoesthesia and altered local reflexes were significantly more common in the non-CRPS group, other neurological signs and symptoms usually associated with CRPS were more common in the CRPS group. Quantitative evaluation of temperature asymmetry by IR thermometry supported the clinical examination, indicating that the majority of CRPS patients with temperature asymmetry exhibited a “cold CRPS” pattern, with the affected extremity on average more than 0.6 °C colder than the unaffected extremity, consistent with the diagnostic temperature asymmetry cutoff suggested in previous work [5]. The CRPS group was noted to have directionally greater mechanical wind-up to repetitive light pinprick, although these wind-up data failed to achieve even the level of a statistical trend.

The significantly higher frequency of diminished active range of motion (AROM) in CRPS compared to non-CRPS patients noted in Table 2 reflects impairments throughout the affected extremity. Quantitative goniometric assessment of AROM bilaterally in the affected region (i.e., elbow and wrist for upper extremity CRPS, knee and ankle for lower extremity CRPS) indicated that elbow/knee flexion (affected side: 115.3° ± 34.16; unaffected side: 127.0° ± 27.87), wrist/ankle flexion (affected side: 35.6° ± 33.30; unaffected side: 53.9° ± 33.27), and wrist/ankle extension (affected side: 37.4° ± 30.90; unaffected side: 58.8° ± 26.46) were significantly reduced in the CRPS affected side compared to the unaffected side ($t$s > 4.1, $p$s < .001).

Pain duration may impact the pattern of CRPS characteristics. For example, patients with longer duration CRPS displayed a significantly larger number of sensory signs and symptoms (hyperalgesia, allodynia, hyperesthesia; Spearman’s rho = 0.22, $p < .05$) and significantly fewer vasomotor signs and symptoms (skin temperature and color changes; Spearman’s rho = −0.24, $p < .05$). Prior work suggested that CRPS patients over time may transition from a predominately “warm CRPS” pattern (affected extremity warmer with reddish skin color) to a predominately “cold CRPS” pattern (affected extremity colder with pale or bluish skin color; [3]). Consistent with this idea, among CRPS patients in the current study exhibiting notable temperature asymmetry detectable on clinical examination, those displaying a “cold CRPS” pattern had experienced CRPS for a significantly longer duration than those with a “warm CRPS” pattern (median (IQR) for cold CRPS: 20.1 (38.2) months, warm CRPS: 3.9 (19.1) months; Mann–Whitney $U = 392.00$, $p < .05$). On tQST evaluation, patients with CRPS of longer duration exhibited significant hypoesthesia on evaluation of cold (Spearman’s rho = −0.37, $p < .01$) and warmth perception thresholds (Spearman’s rho = 0.33, $p < .05$) relative to patients with CRPS of shorter duration.

### 3.2. Diagnostic efficiency

Indices of diagnostic efficiency reflecting the relative ability of the different CRPS criteria to discriminate between CRPS-I and non-CRPS neuropathic pain patients are summarized in Table 3. The current IASP criteria resulted in excellent sensitivity, but poor specificity.

Table 3 indicates that the Budapest clinical criteria retained excellent sensitivity that was nearly identical to the IASP criteria, but also displayed much improved specificity compared to the latter criteria. Given the intent of the Budapest research criteria to maximize specificity (minimize false positives) at the expense of sensitivity, it is not surprising that these criteria had the highest specificity but also the lowest sensitivity of the various criteria examined. Consistent with sensitivity and specificity findings, the IASP criteria showed the lowest probability of accurate CRPS diagnosis (PPP) and the Budapest research criteria showed the highest probability of accurate diagnosis. The Budapest clinical criteria were clearly better in terms of overall diagnostic accuracy (balancing PPP and NPP) compared to the IASP criteria. Of note, and somewhat surprising, was the fact that PPP was only marginally higher for the Budapest research criteria compared to the Budapest clinical criteria.

Analyses were conducted to evaluate the relative contributions of each of the diagnostic components included in the Budapest Criteria (sensory, vasomotor, sudomotor/edema, and motor/trophic) to overall diagnostic accuracy. Table 4 indicates that while each of the four individual diagnostic components are reasonably sensitive, they are not as specific (0.57–0.71) as the combination of all components. Of the four diagnostic components, vasomotor characteristics appear to be the most sensitive for distinguishing between CRPS and non-CRPS neuropathic pain, but lack the specificity of the combined components. Combining all four diagnostic components in diagnostic decision making maximizes sensitivity (0.95), but also improves specificity substantially (0.81). This supports inclusion of all four components in the diagnostic decision making process as suggested in the Budapest Criteria. It should be noted that the higher specificity values exhibited in these analyses compared to those involving the Budapest Criteria reported in Table 3 resulted from use of continuous component scores in the former. While continuous sign/symptom scores may optimize statistical prediction, they do not reflect the clinical reality of having to set a cutoff for making diagnostic decisions as in the actual Budapest Criteria.

## 4. Discussion

The current study replicated previous findings suggesting relatively poor diagnostic accuracy for the extant IASP diagnostic criteria for CRPS. Results indicated that the IASP criteria as written (i.e., criteria can be met by either self-reported symptoms or objective signs) were highly sensitive but had poor specificity (0.41). This finding is consistent with prior results [6,10], which found specificity values of 0.36 and 0.27, respectively, for the IASP criteria. These findings indicate that current IASP criteria may result in a relatively high rate of false positive diagnoses, potentially leading to unnecessary or inappropriate treatments [12]. Unlike the IASP criteria, proposed modified diagnostic criteria (“Budapest Criteria”; [12]) require presence of both signs and symptoms of CRPS to make the diagnosis, a change that should reduce false positive diagnoses.

Prior work suggested that the Budapest Criteria were associated with improved diagnostic consistency between clinicians (kappa = 0.66–0.69) compared to existing IASP criteria (kappa = 0.43–0.66) [9]. To build on this work, the current study provided the first direct comparison of the Budapest Criteria to existing IASP diagnostic criteria for CRPS regarding relative diagnostic efficiency. The Budapest clinical criteria provided excellent sensitivity nearly identical to that for the IASP criteria (0.99), but with substantially improved specificity (0.68). Examination of positive and negative predictive power indicated that under conditions in which CRPS diagnoses were common (e.g., a clinic receiving many cases of suspected CRPS), CRPS diagnoses using the Budapest clinical criteria were likely to be accurate 88% of the time, with non-CRPS patients correctly diagnosed 97% of the time. These values represent improved accuracy in CRPS diagnosis compared to existing

IASP criteria. Overall, findings in this study suggest that the Budapest clinical criteria provide an incremental improvement in diagnostic accuracy compared to the current IASP criteria. Findings summarized in Table 4 suggest that all four diagnostic components included in the Budapest Criteria contribute to improved specificity. This improved specificity and diagnostic accuracy might account for the less frequent diagnosis of CRPS using the Budapest Criteria [9].

A unique feature of the Budapest Criteria is provision of two sets of decision rules, one for clinical diagnoses (placing relatively greater emphasis on sensitivity) and another for research purposes (emphasizing specificity to reduce false positives in research samples) [12]. In the current study, the Budapest research criteria demonstrated the highest specificity of the three sets of criteria examined, consistent with their designed purpose. Given that the Budapest research criteria decision rules require the presence of an extra symptom to reduce false positives, one would expect that these decision rules would lead to a notably higher probability that a positive CRPS diagnosis would be accurate (PPP). However, examination of PPP and NPP indicated that the Budapest clinical criteria show PPP nearly as high as for the Budapest research criteria, with much better NPP for the former. Indeed, advantages of the Budapest research criteria over the Budapest clinical criteria were minimal. This contrasts with findings of previous work on which the Budapest Criteria were based [6,13], which suggested that the Budapest research decision rules would result in dramatically increased specificity (0.94 versus 0.69) [6]. The current findings require replication as they could be due to some random unique feature of this sample. However, if confirmed, they would suggest that having separate clinical and research diagnostic decision rules may be unnecessary with the Budapest Criteria.

While sensitivity values in the current study for the IASP criteria were comparable to and specificity values were modestly higher than in prior work [6,10,13], specificity values for the Budapest Criteria were slightly lower than anticipated based on prior research evaluating similar criteria and decision rules [6,10]. This may be due in part to random sample variability and shrinkage normally expected on cross-validation. In addition, findings may also have been influenced by differences in the character of the non-CRPS sample in the current study compared to prior work, both of which were heterogeneous. Regardless of the absolute values of the indicators of diagnostic efficiency in the current study compared to prior work, the *relative* comparisons between the IASP and Budapest Criteria regarding these indicators are still meaningful. That is, the current findings suggest that the Budapest Criteria provide relatively more accurate CRPS diagnoses than the IASP criteria.

This study used a methodology similar to that used in other diagnostic validity research [6,10,13,21,22] which allowed a controlled test of a statistical model analogous to the clinical process of CRPS differential 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 were designed to provide a systematic means of making decisions as to whether such unidentified conditions are CRPS (i.e., in which autonomic dysfunction is prominent) or some other type of neuropathic pain. Treatment for these two types of conditions will differ, and application of inappropriate (and possibly expensive or even dangerous) treatments due to misdiagnosis may contribute to excessive medical costs, or worse, delay more appropriate treatment in some cases. Therefore, empirically-guided revisions that improve the validity of the CRPS diagnostic criteria may impact positively on problems of medical overutilization and patient quality of life. Such improvements to the CRPS criteria may also assist in identifying more appropriate research samples to evaluate and improve therapeutic outcomes [34].

One potential issue regarding the methodology of this study is that the IASP diagnostic criteria for CRPS 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 single known pathophysiology or objective test 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 not defined by a process of exclusion (i.e., failure to meet CRPS criteria), a situation which might have impacted negatively on study results. Second, if the methodology employed had confounded the results, it should have maximized group differences, thus making it easier to discriminate accurately between groups when using the IASP criteria. The fact that the current IASP criteria displayed poor specificity despite this possible "stacking of the deck" in favor of their discriminative ability underscores the relative superiority of the Budapest Criteria. Methodology similar to that described above has been used in the process of validating diagnostic criteria for headache and psychiatric disorders as well, given a similar absence of clear diagnostic markers for those disorders [21,22]. 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 [22].

Several potential study limitations bear mention. The non-CRPS group reflected a somewhat heterogeneous set of neuropathic pain diagnoses. It may have been ideal to compare efficiency of diagnostic discriminations between CRPS patients all experiencing the same initiating event and homogeneous non-CRPS pain patients experiencing the same type of initiating event. However, it was not possible to accrue a sufficiently large sample meeting these stringent criteria within a reasonable time frame. One potential benefit of the heterogeneous non-CRPS sample in this study was a reduced risk of results being biased by the unique clinical characteristics of a single non-CRPS condition. Also regarding sample characteristics, lower extremity pain location was significantly more common in the non-CRPS group than in the CRPS group. However, nearly half of the CRPS patients were experiencing lower extremity pain, and thus results are unlikely to simply reflect differences in the ability of various diagnostic criteria to distinguish between upper versus lower extremity neuropathic pain. Sample sizes of the CRPS and non-CRPS groups were also unequal. While diagnostic efficiency analyses were in theory insensitive to such differences, the relatively smaller sample size of the non-CRPS group did limit the statistical power for descriptive comparisons across groups. Additional significant differences in clinical characteristics between groups might have been found if a larger non-CRPS sample had been available. A final limitation relates to the multi-site nature of the study. It was not possible to control differences across sites in the severity or subtypes of CRPS patients presenting for referral, and such differences may have impacted on the results in unknown ways. Although attempts to standardize evaluation procedures as much as possible were made, slight differences in procedures (e.g., wind-up evaluation) across sites might have affected the study results as well.

In conclusion, the current study supports the validity of the Budapest diagnostic criteria for CRPS, and further highlights their superiority over current IASP criteria. These results did not strongly support the utility of separate Budapest Criteria decision rules for research purposes specifically. Results of this study provide support for proposals to adopt the Budapest Criteria as the standard for clinical CRPS diagnosis.

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## Table 1

Sample characteristics by diagnostic subgroup.

| Variable | Diagnosis | |
|---|---|---|
| | CRPS-I (*n* = 113) | Non-CRPS (*n* = 47) |
| Gender (female %)** | 68.1 | 44.7 |
| Age (years)** | 39.3 ± 15.47 | 53.8 ± 15.28 |
| Pain duration (median (IQR) in months)** | 14.2 (42.1) | 41.3 (117.99) |
| Affected extremity (% lower extremity)** | 47.7 | 74.4 |
| Affected side (% right) | 50.5 | 57.1 |
| VAS pain intensity (0–100) | 53.3 ± 25.83 | 49.4 ± 26.38 |
| Affected side cold perception threshold (°C)* | 28.4 ± 3.78 | 25.8 ± 5.19 |
| Affected side warmth perception threshold (°C)** | 36.7 ± 3.33 | 41.5 ± 3.61 |
| Affected side heat pain threshold (°C)** | 42.3 ± 3.99 | 46.1 ± 2.48 |
| Light touch sensitivity (% abnormal) | | |
| Face – affected side | 4.5 | 4.7 |
| Face – unaffected side* | 0.0 | 4.7 |
| Chest – affected side | 3.6 | 4.9 |
| Chest – unaffected side | 0.0 | 2.4 |
| Bicep – affected side | 14.2 | 9.5 |
| Bicep – unaffected side | 0.9 | 4.8 |
| Thigh – affected side | 17.0 | 26.2 |
| Thigh – unaffected side** | 0.9 | 11.9 |

*Note:* summary statistics are presented as percentages or mean ± SD. Abnormalities in light touch perception reflect either hypoesthetic or allodynic responses as judged by the clinician.

* $p < .05$.

** $p < .01$.

## Table 2

Diagnostic signs and symptoms by subgroup.

| Variable | Diagnosis | |
|---|---|---|
| | CRPS-I (*n* = 113) | Non-CRPS (*n* = 47) |
| *Self-reported symptoms (% yes)* | | |
| Hyperesthesia (allodynia, hyperpathia)** | 90.2 | 63.8 |
| Hypoesthesia (localized "numbness")** | 38.5 | 65.0 |
| Temperature asymmetry** | 86.6 | 38.3 |
| Skin color asymmetry** | 91.1 | 27.7 |
| Sweating asymmetry** | 62.5 | 15.2 |
| Asymmetric edema** | 89.2 | 40.4 |
| Trophic changes** | 75.0 | 38.3 |
| Motor changes** | 88.3 | 46.7 |
| *Signs observed on examination (% yes)* | | |
| Hyperalgesia to pinprick** | 81.5 | 43.5 |
| Hypoesthesia to light touch* | 57.7 | 77.5 |
| Allodynia (any stimulus)** | 70.5 | 29.8 |
| Allodynia to cold** | 63.6 | 10.5 |
| Allodynia to heat | 20.8 | 6.7 |
| Allodynia to light touch | 68.8 | 52.6 |
| Allodynia to vibration* | 40.0 | 10.5 |
| Allodynia to deep joint pressure** | 67.6 | 26.7 |
| Windup to series of 10 pinpricks (0–100) | 16.4 ± 16.88 | 13.9 ± 17.61 |
| Temperature asymmetry by palpation** | 69.4 | 14.9 |
| % Affected side colder | 62.3 | 85.7 |
| Mean asymmetry by IR thermometry (°C)* | −0.62 ± 1.97 | 0.11 ± 1.04 |
| Skin color asymmetry** | 83.9 | 36.2 |
| % Affected side red | 41.3 | 35.3 |
| % Affected side blue/pale | 43.5 | 29.4 |
| Sweating asymmetry** | 43.8 | 10.6 |
| % Affected side increased | 80.9 | 60.0 |
| Asymmetric edema** | 63.5 | 24.2 |
| Trophic changes (any)** | 68.5 | 29.8 |
| Nails | 42.9 | 27.8 |
| Hair | 54.5 | 66.7 |
| Skin | 45.5 | 66.7 |
| Motor changes (any)** | 79.3 | 40.0 |
| Weakness | 85.5 | 72.2 |

| Variable | Diagnosis | |
|---|---|---|
| | CRPS-I (*n* = 113) | Non-CRPS (*n* = 47) |
| Tremor* | 30.1 | 5.6 |
| Dystonia* | 26.5 | 5.6 |
| Decreased active range of motion** | 80.0 | 37.8 |
| Altered reflexes in affected area* | 50.8 | 86.7 |

*Note:* summary statistics are presented as percentages or mean ± SD. Percentages for specific types/direction of allodynia, sweating, temperature, trophic, and motor changes reflect percentage of those patients who were positive for this sign category. The negative thermometric asymmetry value for the CRPS group indicates that on average the affected side was colder.

* $p < .05$.

** $p < .01$.

**Table 3**

Comparison of diagnostic efficiency of IASP CRPS criteria versus proposed modified (Budapest) criteria for discriminating between CRPS-I and non-CRPS neuropathic pain.

| Diagnostic criteria | Sensitivity | Specificity | Assume 70% CRPS prevalence | | Assume 50% CRPS prevalence | |
|---|---|---|---|---|---|---|
| | | | PPP | NPP | PPP | NPP |
| IASP | 1.00 | 0.41 | 0.80 | 1.00 | 0.63 | 1.00 |
| Budapest clinical | 0.99 | 0.68 | 0.88 | 0.97 | 0.76 | 0.99 |
| Budapest research | 0.78 | 0.79 | 0.90 | 0.60 | 0.79 | 0.78 |

*Note:* positive predictive power (PPP) and negative predictive power (NPP) are dependent on the assumed prevalence of CRPS in the population being considered. For illustrative purposes, two scenarios are presented in which either 70% or 50% of patients referred to rule CRPS in or out actually have the disorder. IASP = diagnosis based on presence of CRPS signs or symptoms using the International Association for the Study of Pain criteria.

**Table 4**

Comparison of the diagnostic efficiency of individual Budapest Criteria diagnostic components versus the combination of all diagnostic components.

| Criterion | Sensitivity | Specificity |
|---|---|---|
| All sign/symptom factor scores | 0.95 | 0.81 |
| Sensory factor only | 0.83 | 0.57 |
| Vasomotor factor only | 0.94 | 0.68 |
| Sudomotor/edema factor only | 0.85 | 0.71 |
| Motor/trophic factor only | 0.86 | 0.67 |

## Appendix I

Participants at the August 2003 consensus workshop on taxonomy and algorithm for Complex Regional Pain Syndrome held in Budapest, Hungary

| | |
|---|---|
| Ralf Baron, Dr. Med. | Anne Louise Oaklander, M.D., Ph.D. |
| Frank Birklein, M.D., Ph.D. | Gunnar Olsson, M.D., Ph.D. |
| Helmut Blumberg, M.D. | Gabor Racz, M.D. |
| Nikolai Bogduk, M.D., Ph.D. | P. Prithvi Raj, M.D. |
| Stephen Bruehl, Ph.D. | Richard Rauck, M.D. |
| Allen Burton, M.D. | Oliver Rommel, Dr. Med. |
| Peter Drummond, Ph.D. | Paola Sandroni, M.D. |
| Jan Geertzen, M.D., Ph.D. | Mathias Schurmann, Dr. Med. |
| Heinz-Joachim Häbler, M.D. | Robert J. Schwartzman, M.D. |
| R. Norman Harden, M.D. | Michael Stanton-Hicks, M.B.B.S., Dr. Med. |
| Wilfrid Jänig, Dr. Med. | J.J. van Hilten, M.D. |
| John D. Loeser, M.D. | Gunnar Wasner, Dr. Med. |
| Timothy Lubenow, M.D. | Robert T. Wilder, M.D., Ph.D. |
| Harold Merskey, D.M. | |

## Appendix II

Budapest clinical diagnostic criteria for CRPS

**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 deep somatic pressure and/or joint movement)
- *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)

**4** There is no other diagnosis that better explains the signs and symptoms