

CHAPTER 2

Diagnostic criteria for CRPS 1: differences between patient profiles using three different diagnostic sets

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Abstract

Complex Regional Pain Syndrome type 1 (CRPS 1) is an illness which usually occurs due to major or minor tissue injury to the extremities. Because a unique pathophysiological mechanism for CRPS 1 has not yet been established, the diagnosis is based on observation and measurement of clinical symptoms and signs. In this study, a comparison was made between three sets of diagnostic criteria (the IASP, Bruehl et al. and Veldman et al.) based on patient reports and physicians' assessments of signs and symptoms associated with CRPS 1, in 372 outpatients suspected of having CRPS 1. Agreement between CRPS 1 diagnosis among the three sets was poor (k-range: 0.29-0.42), leading to positive CRPS 1 diagnoses according to Veldman et al.'s criteria in 218 cases (59%), according to the IASP in 268 cases (72%), and according to Bruehl et al. in 129 cases (35%). Significant differences in patient profiles were found between the diagnostic sets for the number of patients reporting continuing disproportionate pain, larger area affected than the initial trauma (both $p < 0.001$), increase of symptoms due to exercise ($p = 0.009$), edema ($p = 0.015$), temperature asymmetry ($p = 0.015$), hyperesthesia, allodynia (both $p < 0.001$) and hyperalgesia ($p = 0.036$). Similarly, significant differences emerged for physicians' observations of hyperesthesia and allodynia (both $p < 0.001$). Highest combined values of sensitivity (SE) and specificity (SP) for the strongest cases of presence ($n = 108$) or absence ($n = 62$) of CRPS 1 were found for reported hyperesthesia (SE+SP:165%), allodynia (160%), observed color asymmetry (162%), hyperesthesia (157%), temperature asymmetry (154%) and edema (152%). The lack of agreement between the different diagnostic sets for CRPS 1 and the different clinical profiles that result from it may lead to different therapeutic and study populations, hampering adequate treatment and scientific development for this illness. We propose explicit reference to diagnostic criteria used in studies, and registration in trials of a broad variety of CRPS 1 features, as used in this study, to make subgroup phenotyping and post hoc analyses based on different diagnostic criteria possible.

Introduction

Complex Regional Pain Syndrome type 1 (CRPS 1) is characterized by a variety of sensory and autonomic disturbances of an extremity, usually as a consequence of trauma. Clinical evaluation and diagnosis of CRPS 1 is based on clinical assessment of signs and symptoms, according to predetermined sets of diagnostic criteria. Although recent efforts have been made to unify the diagnostic process for CRPS 1 (1;2), several sets of diagnostic criteria have been or are currently used to distinguish CRPS 1 from other complaints (3-8). The most recent sets used are those proposed by Veldman et al. (7) (1993), the IASP (1994) (6) and Bruehl et al. (3;9) (1999). The sets vary in their scope and the way in which the criteria are determined or measured. Veldman et al.'s criteria were derived from a cross-sectional cohort study of 829 patients, and include the observation of a limited number of signs of inflammation, in combination with two criteria describing the disproportionate character of the complaint. Veldman et al.'s criteria were initially developed for the description of CRPS 1 in the acute phase of the disease (7). The consensus based IASP (6) criteria further include sensory and sudomotor signs/symptoms, and provide specific reference to the absence of other conditions that could account for the degree of pain and dysfunction. Bruehl et al.'s criteria (3;9) are a further specification of the IASP criteria, in which an explicit distinction is made between features of sensory, vasomotor, sudomotor-edema and motor-trophic nature reported by the patient (symptoms), and those observed by the physician (signs). The latter criteria were derived from the evaluation of 117 IASP-CRPS patients and 43 patients with neuropathic pain of other origin. Both the internal (9) and external validity (3) of the Bruehl et al. criteria have been addressed. Only the IASP criteria set is officially recognized by the IASP to be used for formal diagnosis of CRPS 1; Veldman et al.'s and Bruehl et al.'s criteria set are considered experimental. However, as the latter two are empirically derived, they can be considered more clinically valid than the IASP criteria.

All three sets have been subjected to methodological assessment (3;9-14), and have been used in studies evaluating treatment effect of CRPS 1 (15;16).

However, it is still unclear whether the choice for a particular diagnostic set could lead to differences in the number of patients being diagnosed, and whether differences between them could lead to different patient profiles. If so, this could pose a problem for the comparability of studies that have been performed in the past (17-21), and therefore for the interpretation of their results for specific clinical CRPS 1 populations diagnosed according to one of the criteria sets.

A further point of consideration is the fact that no gold standard for the diagnosis of CRPS 1 has been established, because a single pathophysiological mechanism explaining the variety of features observed in CRPS 1 is lacking. In essence, therefore, the choice for the set of diagnostic criteria with which to diagnose CRPS 1 is arbitrary: If we are unable to determine (in a pathophysiological sense) what CRPS 1 is, claims made from the perspective of each set of criteria with respect to the presence or absence of CRPS 1 are equally valid. This ambiguity poses additional therapeutic problems for physicians with respect to possible under- and over-diagnosis of CRPS 1 (i.e. prevent false negative and false positive diagnostic decisions). This problem arises especially in cases where no other probable cause can explain the amount of pain and dysfunction (1). Evaluation of the most strong cases of absence or presence of CRPS 1 (within the constrictions of a lack of a gold standard and absent alternative hypothesis) could provide better directions as to the most indicative features for establishing the presence or absence of CRPS 1.

The aim of the present study is to evaluate the way in which the three most dominant sets for diagnosing CRPS 1 relate to one another and to derive clinically useful indications for diagnosing CRPS 1.

To that respect, we evaluated the presence of symptoms and signs of CRPS 1 according to the diagnostic criteria of Veldman et al.(7), the IASP (6), and proposed modifications by Bruehl et al. (3;9) in order to answer the following questions:

- What is the agreement between these three sets of criteria in diagnosing patients with CRPS 1?
- Which differences can be found in patient profiles between the three sets of diagnostic criteria?
- Taking the lack of a gold standard into account; which clinical directions can be followed to minimize the amount of false diagnoses?

Methods

Between 2001 and 2005, ambulatory patients suspected of having CRPS 1 referred to our outpatient clinic for first screening, were evaluated by a resident and consultant anesthesiologist on the presence of the following clinical symptoms and/or signs associated with CRPS 1: pain, limitation in active range of movement (AROM), edema, color and temperature asymmetries, sweating disturbances, hyperesthesia, allodynia, hyperalgesia, motor dysfunction (i.e. tremor, muscle weakness, dystonia) and trophic disturbances (i.e. of hair, nail and skin). Evaluations took place under

stable environmental conditions, and were performed according to a strict measurement protocol, whereby distinguishing symptoms reported by the patient and signs established by the physicians. Physicians' assessments of signs were performed in a clinical fashion (i.e. left-right comparisons, palpation, provocation tests). The features were registered as dichotomous variables (present/absent). Based on the observed or reported features, the presence of CRPS 1 was determined according to Veldman et al., the IASP and Bruehl et al. as described below:

Veldman et al. (7): 1. At least four out of five signs or symptoms: pain, difference in skin color, edema, difference in skin temperature and active range of motion; 2. Signs and symptoms present in an area larger than might be expected of the initial trauma; 3. Increase of signs and/or symptoms during or after exercise.

IASP (6): 1. Type 1 is a syndrome that develops after an initiating noxious event; 2. Spontaneous pain or allodynia/hyperalgesia occurs, is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event; 3. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event; 4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction. (For the diagnosis of CRPS 1, criteria 2-4 must be fulfilled)

Bruehl et al. (3;9): 1. Continuing pain disproportionate to any inciting event; 2. Presence of at least one symptom in each of the following categories: sensory, vasomotor, sudomotor/edema and motor/trophic nature, and 3. Two signs of sensory, vasomotor, sudomotor/edema and motor/trophic nature.

In order to identify the most strong cases for the presence or absence of CRPS 1 within our sample, patients fulfilling the diagnosis according to all criteria and patients meeting none of the three criteria were identified. These groups were used to determine the diagnostic value of the observed and reported features of CRPS 1.

Data were registered using standardized diagnostic forms, and recorded and analyzed using SPSS 11.0 software. Agreement between diagnostic tests was established by calculating the percentage of agreement and Cohen's Kappa (k) (22). Differences between occurrence of signs and symptoms between the three sets of diagnostic criteria were calculated using Chi-square tests, Kruskal-Wallis tests (with Bonferroni corrections) and Mann-Whitney-U tests as appropriate. Diagnostic value of individual signs and symptoms was expressed by means of the sensitivity and specificity for patients meeting all or none of the three criteria. Significance levels were set at 5%.

In total, 372 patients (table 1) were evaluated on the presence or absence of criteria and signs and symptoms (missing data max. 5.6%). The relatively high percentages of missing data for duration of the complaints (16%) and initial trauma type (33%) were predominantly due to later addition of these variables in the initial phase of the study. No significant differences were found between patients diagnosed according to the three sets of criteria with respect to gender (Chi-square; $p = 1.000$), age (Kruskal-Wallis; $p = 1.000$), duration of the complaint (Kruskal-Wallis; $p = 0.903$), affected extremity (Chi-square; $p = .768$), affected side (Chi-square; $p = .762$), and initial trauma (Chi-square; $p = 1.000$).

Table 1: Patient characteristics

		percentage	% missing
Gender male / female *	86 / 286	23 / 77	0
Affected extr. arm / leg / both *	196 / 169 / 4	53 / 46 / 1	1
Affected side left / right / both *	196 / 162 / 11	53 / 44 / 3	0
Initial trauma *			33
- Fracture	129	52	
- Strain/sprain	48	19	
- operation	30	12	
- other	34	13	
- spontaneous	6	2	
Age (years) **	49,1 (16,6)		3
Duration of complaints (weeks) ***	18, 7 (11,2-82.3)		16

* = counts; ** = mean (SD); *** = median (interquartile range)

Results

Table 2 shows the presence of symptoms and signs in the total sample, categorized according to patients meeting the three sets of diagnostic criteria. In the total sample, pain, limited active range of motion, motor dysfunction, edema, color and temperature asymmetries were present in the majority of patients. Most patients experienced increase of signs and symptoms due to exercise.

CRPS 1 diagnosis according to Veldman et al.'s criteria was ascertained in 218 cases (59%), according to the IASP in 268 cases (72%), and according to Bruehl et al.'s in 129 cases (35%). The percentage of agreement (for positive and negative diagnoses) between Veldman et al. and IASP was 74%, between Veldman et al. and Bruehl et al. 63%, and between IASP and Bruehl et al. 61%. Corrected for chance, the agreement between the diagnostic sets for above mentioned combinations is $k = 0.42$, $k = 0.31$ and $k = 0.29$, respectively.

Significant differences (see table 2) between the three diagnostic criteria sets were found for the number of patients reporting continuing disproportionate pain, affected area larger than the initial trauma (both $p < 0.001$), increase of symptoms due to exercise ($p = 0.009$), edema ($p = 0.015$), temperature asymmetry ($p = 0.015$), hyperesthesia, allodynia (both $p < 0.001$) and hyperalgesia ($p = 0.036$) (all chi-square test).

Higher proportions of reports of temperature asymmetry (compared to the IASP), hyperesthesia, allodynia and hyperalgesia (compared to Veldman et al. and IASP) in the group of patients fulfilling Bruehl et al.'s criteria accounted for the significant differences found between the three groups.

Significant differences (see table 2) between diagnostic sets were also found for physicians' observations of hyperesthesia and allodynia (both $p < 0.001$) (chi-square test), which were explained by higher proportions of these signs in the group fulfilling Bruehl et al.'s criteria.

Also in table 2, the proportions of symptoms and signs for patients meeting all three sets of criteria ($n = 108$), and those meeting none of the criteria sets ($n = 62$) are displayed. The features continuing disproportionate pain, larger area affected than the initial trauma and increase of symptoms due to exercise, and patient reports of hyperesthesia occur in all patients meeting all three sets of criteria, because they are obligatory items for one or more sets. As might be expected, a significantly higher proportion of all reported and observed features of CRPS 1 was found for the patients meeting all criteria compared to those meeting none (Chi-square; p range $< 0.001 - 0.002$).

Significant differences were also found when comparing patients meeting individual criteria sets with patients meeting none of these sets.

Patients meeting Veldman et al.'s criteria showed a significantly higher occurrence of all reported and observed features compared to the group meeting none of the criteria (Chi-square; p range $< 0.001 - 0.002$), except for patient reports of motor disturbances (Chi square; $p = 0.175$). Patients meeting the IASP criteria differed from the none-group on all observed and reported features (Chi-square; p range $< 0.001 - 0.043$), except for patient reports of motor disturbances (Chi square; $p = 0.232$) and sweating disturbances (Chi square; $p = 0.059$). Both patient groups meeting Veldman et al.'s and the IASP criteria showed a significantly shorter median duration of the complaints compared to patients fulfilling none of the criteria sets (Mann-Whitney-U: $p = 0.001$ and $p = 0.006$ respectively; Veldman: 15.7 (IQR: 10.3-58.2); IASP: 18.7 (IQR: 10.3-88.9); none: 42.0 (IQR: 14.4-195.5) weeks.

Patients meeting Bruehl et al.'s criteria showed significantly higher proportion of all

Table 2: Criteria, symptoms (reported) and signs (observed by physician)

	Total = 372			Veldman = 218			IASP = 268			Bruehl = 129			Patients meeting all three sets = 108			Patients meeting none of the sets = 62								
	Symptom	Sign	N	Symptom	Sign	N	Symptom	Sign	N	Symptom	Sign	N	Symptom	Sign	N	Symptom	Sign	N						
Continuing disproportional pain	286	77	-	184	84	-	252	94	-	129	100	-	108	100	-	31	50	-						
Larger area affected	303	86	-	218	100	-	239	89	-	119	92	-	108	100	-	31	50	-						
Increase complaints with exercise	332	93	-	218	100	-	254	95	-	127	98	-	108	100	-	41	66	-						
Pain	345	93	-	212	97	-	265	99	-	129	100	-	108	100	-	47	76	-						
Limited AROM	308	83	269	72	195	89	187	86	227	85	213	79	119	92	111	86	101	94	95	88	47	76	31	50
Color asymmetry	260	70	249	67	179	82	187	86	197	74	203	76	108	84	102	79	94	87	94	87	32	52	16	26
Temperature asymmetry	304	81	257	69	196	89	184	84	229	85	212	79	124	96	104	81	105	97	91	84	43	69	19	31
Edema	253	68	221	59	174	80	170	78	191	71	180	67	109	84	91	71	94	87	80	74	30	48	14	23
Hyperesthesia	194	52	121	33	127	58	90	41	158	59	109	41	129	100	89	69	108	100	74	69	22	35	7	11
Hyperalgesia	172	46	91	24	112	51	66	30	140	52	98	37	86	67	56	43	72	68	46	43	19	31	6	10
Allodynia	174	47	108	29	120	55	81	37	154	57	82	31	102	79	74	57	87	81	63	58	13	21	8	13
Trophic disturbances	168	45	126	34	110	50	92	42	131	49	105	39	77	60	60	47	63	59	51	47	17	27	5	8
Sweating disturbances	165	44	86	23	109	50	62	28	127	47	69	26	73	57	43	33	64	59	37	34	21	34	7	11
Motoric disturbances	264	71	209	56	164	75	152	70	200	75	185	69	107	83	94	73	91	85	82	76	43	69	24	39

reported and observed features compared to the none-group (Chi-square; p range <0.001 – 0.016). However, no significant difference was found in duration of the complaints between both groups (Mann-Whitney-U: p = 0.054).

Table 3 shows the diagnostic value of individual reported and observed features of CRPS 1 using patients fulfilling all criteria and those meeting none as reference standard. Highest values for sensitivity were found for obligatory features of the criteria sets (i.e. continuing disproportionate pain, larger area affected than the initial trauma, increase of symptoms due to exercise, pain and reported hyperesthesia; all 100%). For non obligatory features, patient reports of temperature asymmetry, limited AROM, color asymmetry, edema and allodynia sensitivity values above 80% were found. Physicians' observations of limited AROM, color and temperature asymmetry yielded sensitivity values between 80 and 90%.

Overall, lower specificity values were found. None of the reported features reached a specificity value above 80%. Observed trophic disturbances, hyperalgesia, hyperesthesia, allodynia and hyperhidrosis reached specificity values over 80%.

Highest combined values of sensitivity and specificity were found for reported hyperesthesia (165%) and allodynia (160%), and observed color asymmetry (162%), hyperesthesia (157%), temperature asymmetry (154%) and edema (152%).

Table 3: Sensitivity and specificity of signs and symptoms features of CRPS 1

	Symptoms			Signs		
	SE	SP	Comb	SE	SP	Comb
Continuing disproportional pain	100	50	150	-	-	-
Larger area affected	100	45	145	-	-	-
Increase complaints with exercise	100	24	124	-	-	-
Pain	100	25	125	-	-	-
Limited AROM	94	27	121	88	52	140
Color asymmetry	87	49	136	87	75	162
Temperature asymmetry	97	33	130	84	70	154
Edema	87	49	136	74	78	152
Hyperesthesia	100	65	165	68	89	157
Hyperalgesia	68	68	136	43	90	133
Allodynia	81	79	160	59	87	136
Trophic disturbances	59	73	132	48	91	139
Sweating disturbances	60	66	122	35	89	124
Motoric disturbances	85	33	118	77	63	140

SE = sensitivity; SP = Specificity; Comb: addition of sensitivity and specificity

Discussion

Diagnosing CRPS 1 remains a difficult process in the absence of a discriminatory test and/or a universally accepted gold standard for diagnosis. Although the possible consequences of this issue have been discussed in various contexts, the effects of using different diagnostic sets for the clinical patient profile have not yet been described previously. The lack of agreement between the different diagnostic sets for CRPS 1 and the differences in clinical appearance between patients meeting the different criteria sets found in this study show that using different diagnostic sets may have profound consequences for the clinical profile of study populations. Furthermore, the diagnostic criteria used in this study did not apply for a large proportion (35-72%, depending upon the diagnostic set used) of the patients initially referred to our clinic suspected of having CRPS 1. This may be an indication of uncertainty among physicians concerning the way to diagnose CRPS 1, and stresses the necessity for undisputed uniform diagnostic criteria for CRPS 1.

Although the percentage of agreement between sets for positive and negative diagnoses (61-74%) appears to be reasonable at first sight, it does also mean that 26%-39% of patients may be misdiagnosed depending upon the point of reference. The chance corrected agreement between criteria sets is even poorer still, indicating a potential overestimation of the amount of agreement. In general, for symptoms reported by the patients, the patients fulfilling Bruehl et al.'s criteria report the highest proportion of all CRPS characteristics, with significant differences for sensory symptoms compared to both other sets. Patients meeting the IASP criteria in general reported less CRPS features compared to the other two sets. For observed features, patients meeting Veldman et al.'s criteria showed a higher occurrence of inflammatory signs, and patients meeting Bruehl et al.'s criteria show a higher occurrence of sensory signs. Again, the IASP patients showed the least proportion of observed CRPS characteristics. Furthermore, the patients meeting Veldman et al.'s and the IASP criteria had a significantly shorter disease duration compared to patients meeting none of the criteria sets, whereas this difference was not statistically different for the group meeting Bruehl et al.'s criteria. Although some of these differences might be expected due to the scope of the different criteria sets, they do show that using different diagnostic sets is not without consequences. These differences could lead to dissimilar numbers of patients diagnosed or receiving treatment, and problems with translation of effects found in various studies using different diagnostic sets as inclusion criteria. Problems with the interpretation of research results will occur especially for studies with unclear or lacking description of the diagnostic criteria used for patient inclusion. The latter methodological flaw has been shown substantially

in several meta-analyses (20;21) and systematic reviews (17-19) on treatment of CRPS 1. The necessity, therefore, for uniform and internationally accepted diagnostic criteria as expressed by different authors (1;9;11;23) is again underlined by the data of the present study. However, since a clear pathophysiological mechanism has not yet been established, the choice for any of the criteria sets used in a study remains arbitrary. Different authors (24-26) have understandably proposed the criteria by Bruehl et al. due to their combination of an acceptable sensitivity and high specificity. However, in daily practice this could lead to a great number of patients not fulfilling these criteria and therefore possibly not receiving proper treatment. Using the description 'CRPS not otherwise specified' for those patient not fulfilling the criteria but without another cause explaining their symptoms and signs, as proposed by Harden et al. (1), could be a way to overcome this problem. A way to define patients falling into this category could be to include in it those patients fulfilling Veldman et al.'s or the IASP criteria. In case of this study, this would lead to 181 (49%) CRPS-NOS patients. Another solution as suggested by Baron (27), might be to make distinctions between clinical and scientific use of the diagnostic criteria. As recently described by Jänig and Baron(28), the disproportionate character of the complaint and the generalized distribution of signs and symptoms are key characteristics of CRPS 1. Our findings indicate that the presence of a disproportionate character of complaints, exceeding the primary trauma in both reactivity and affected surface, reports of pain, limited active range of motion and temperature asymmetry would provide a good indication of having CRPS 1 with high sensitivity (94-100%). The combination of reported hyperesthesia and allodynia, and observed hyperesthesia, temperature asymmetry, color asymmetry and edema, should provide a good clinical indication of the presence of CRPS 1, whereby maintaining adequate values for sensitivity and specificity. These indications should be regarded with caution, however, as the sensitivity and specificity values point in different directions for individual features (i.e. color asymmetry more sensitive than specific, and hyperesthesia more specific than sensitive), and these values are derived from analyses based on the most strong cases of presence or absence of CRPS 1 only. It is unclear whether using this combination of signs and symptoms would lead to underdiagnosis of CRPS 1 (i.e. miss mild and moderate cases). The importance of more sensitive or more specific combinations of signs and symptoms depend on whether they will be used for scientific or clinical purposes.

The problem that should subsequently be addressed is the translation of research findings from a more specific population to a clinical population with possibly a different clinical profile.

With regard to the use of Bruehl et al.'s criteria, it is important to add that new adaptations have been formulated in a recent IASP consensus meeting held in Budapest (1). In the future, these modified criteria might be adopted as reference standard (for scientific use) in favor of the original Bruehl et al. criteria. These adaptations represent small but significant changes compared to the original Bruehl criteria, such as the addition of assessment of allodynia to deep somatic pressure and to joint movement. For these new items no sensitivity and specificity data have been calculated yet.

Furthermore, for clinical purposes it was recommended to reduce the diagnostic threshold to 3 or more symptom clusters and 2 sign clusters to prevent underdiagnosis (1). Bruehl et al.'s criteria were initially developed to improve the use of the IASP criteria for scientific purposes, with emphasis on high specificity. The fact that only a relatively small part of the patients met Bruehl et al.'s criteria might therefore be an expression of (deliberately) more stringent research diagnostic approach. A comparison between the more lenient clinical decision rule proposed at the Budapest conference and Veldman et al.'s and the IASP criteria might therefore provide more agreement between these three criteria sets. These newly formulated adaptations have not been evaluated in our study because the Budapest criteria were launched several years after the initiation of our study. In future studies, the diagnostic properties of the Budapest adaptations have to be evaluated.

A limitation of this study is that we did not step out of the boundaries provided by the different sets. A substantial study comparing CRPS and established non-CRPS patients should be performed in order to establish the diagnostic value of (new adaptations of) CRPS 1 criteria in relation to similar illnesses. Although Bruehl et al. (3) have compared an IASP-patient sample to a non-CRPS neuropathic pain sample, their study contained only a limited number of non-CRPS controls ($n = 43$). On the other hand, the fact remains that for the patients used in this study, other explanatory options have been ruled out, and therefore a strong suspicion of CRPS was present for these patients. In essence, the diagnostic criteria should be useful in these frequently occurring clinical situations, and one should be able to distinguish CRPS from non-CRPS in these cases as well. Under the present circumstances, however, it is not possible to make absolutely sure that a correct diagnosis is made. For this we depend on future studies evaluating the underlying mechanism(s) of CRPS.

Another limitation of this study is the subjective nature of the physician-based evaluations. Although allodynia and hyperesthesia were measured with a cotton bud and hyperalgesia with a pinprick, features such as temperature differences, and sweating changes were performed by palpation by both assessors. However, two

studies performed in our institution showed good interrater agreement (12) and good correspondence between measured symptoms and physicians assessment (29) for establishing the presence or absence of pain, temperature, volume and limitations in active range of motion. We do however recognize that use of objective measurement instruments would have added to the reliability of our results. Furthermore, this study was performed mono disciplinary in one single tertiary institution. As Van der Vusse et al. (14) have pointed out, the correspondence of diagnosis of CRPS may vary between disciplines, possibly leading to variable prevalence of CRPS 1. A larger study, involving multiple centers and multiple disciplines, is necessary to establish the influence of institutional or disciplinary viewpoints on diagnostic aspects of CRPS 1.

Another aspect to be considered, again in relation to the scope of the diagnostic criteria used, is that we possibly did not measure the whole scope of complaints associated with CRPS 1. In a recent systematic review, Marinus et al. have made plausible that a broader scope on CRPS should be warranted, whereby a focus on local as well as systemic signs and symptoms (bowel, bladder and sicca complaints) should be adopted for evaluation of CRPS 1 (30).

A hypothesis that cannot be ruled out is the possibility that CRPS 1 involves different subgroups with possibly different or differently dominating underlying mechanisms. The study by Bruehl et al. (10) in 113 CRPS 1 patients showed three statistically distinct CRPS-subtypes with 1) vasomotor signs prevailing, 2) neuropathic/sensory signs prevailing and 3) a florid form with high occurrences of all signs/symptoms. Statistical considerations usually prescribe that in factor analysis and cluster analysis the sample size should be very large to produce a stable factor solution. There are no generally accepted procedures to calculate the required sample size, but conservative estimates indicate that several hundred patients may be required (31). Preliminary cluster analyses performed on the 268 patients meeting the IASP criteria in this study, did not reveal a subtype with neuropathic/sensory signs prevailing, but did show a florid subtype and inflammatory/vasomotor subtype, similar to Bruehl et al.'s findings. This, taken with the reports from RCT's on pharmacological interventions showing different responses to drugs (29;32), suggests that differentiating patients according to sign/symptom phenotype could be a more useful way of categorizing patients for treatment. A more integrated approach to CRPS 1 research, combining data from epidemiological (phenotyping and genotyping), pathophysiological and pharmacological (proof of concept) studies should shed more light on this complex and interrelated problem called CRPS 1.

We conclude that distinct differences were found between three sets of diagnostic criteria for CRPS 1, leading to different clinical patient profiles. In absence of a pathophysiological mechanism, the choice for either set of criteria remains arbitrary. Within these restrictions, we suggest that explicit reference to the diagnostic criteria used for inclusion in a study should be provided in articles, and a broad variety of CRPS 1 associated features be registered in order to make post hoc subgroup analyses based on different diagnostic criteria possible.

For patients without an alternative explanation for the complaints, we suggest to use a more broad diagnostic approach in order to prevent under treatment of patients, whereby focusing on the disproportionate character of complaints, exceeding the primary trauma in both reactivity and affected surface, reports of pain, limited active range of motion and temperature asymmetry.

Based on the strongest cases of absence or presence of CRPS, the presence or absence of reported hyperesthesia and allodynia, and observed hyperesthesia, temperature asymmetry, color asymmetry and edema, should provide a good clinical indication for a positive or negative CRPS 1 diagnosis, with adequate values for sensitivity and specificity.

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