Complex regional pain syndrome underdiagnosed

CRPS type 1 is an under-recognized problem in limbs recovering from fracture or immobilized post-stroke

Practice recommendations

- Complex regional pain syndrome (CRPS) type 1 may be diagnosed by history and physical exam with no further testing (B). Several different diagnostic criteria have undergone validity testing: the 1993 IASP criteria, Bruehl’s criteria, and Veldman’s criteria; there is no compelling reason to recommend 1 set of criteria over the others (C).

- Some cases of CRPS type 1 may be preventable. Some cases of CRPS type 1 in post-stroke upper extremity hemiplegia (also known as shoulder-hand syndrome) may be prevented by early inpatient rehabilitation (C) and avoidance of shoulder trauma to the affected arm (B). Some cases of post-fracture CRPS type 1 may be prevented with 500 mg vitamin C daily started upon diagnosis of fracture and continued through healing (B).

Do you have a patient recovering from a limb fracture who is complaining of pain and tenderness long after most patients with a similar injury would be symptom free? The problem may be an under-recognized one—complex regional pain syndrome (CRPS) type 1, also known as reflex sympathetic dystrophy. The problem is also encountered in immobilized limbs of post-stroke patients.

Persons with persistent post-traumatic pain eventually diagnosed with CRPS type 1 often undergo unnecessary testing resulting in inappropriate or delayed treatment. Signs and symptoms typical of CRPS type 1 can also occur transiently with a normally recovering immobilized limb, so diagnosis of CRPS type 1 is based on increasing severity and duration of signs and symptoms (level of evidence [LOE]: 3; consensus guidelines):

- pain
- hyperalgesia/allodynia (pain or exaggerated response resulting from a normally painless or only slightly painful stimulus)
- joint stiffness
- swelling
- autonomic abnormalities (often sweating and temperature differences compared with the unaffected limb).

Diagnosis: Watch recovery course over first 9 weeks

Clinicians face a number of challenges in diagnosing CRPS type 1. No psychological or personality traits appear to predispose to CRPS type 1 (LOE: 2, lower-quality literature review). Fracture types and severity of injury among persons who develop CRPS type 1 are not significantly different from persons who recover normally (LOE: 2, case control studies). The key is to remain alert to deviation from the normal course of recovery.

Studies have shown that 9 weeks post-
### Diagnostic criteria for CRPS type 1*

<table>
<thead>
<tr>
<th>NAME</th>
<th>CRITERIA</th>
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</table>
| IASP 1994 consensus criteria | Criteria 2, 3 and 4 are necessary for a diagnosis of CRPS type 1.  
1) Type 1 is a syndrome that develops after an initiating noxious event.  
2) Spontaneous occurrence of pain in the absence of an external stimulus, allodynia (pain due to a mechanical or thermal stimulus that normally does not provoke pain), or hyperalgesia (exaggerated response to a stimulus that is normally painful) that 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 (sweating) 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. |
| Bruehl's criteria: IASP-family | 1) Continuing pain disproportionate to any inciting event.  
2) Patient must report at least 1 symptom in each of the 4 following categories:  
   a) sensory: reports of hyperesthesia  
   b) vasomotor: reports of temperature asymmetry or skin color changes or skin color asymmetry  
   c) sudomotor/edema: reports of edema or sweating changes or sweating asymmetry  
   d) motor/trophic: reports of decreased range of motion or motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin)  
3) Must display at least 1 sign in 2 or more of the following categories:  
   e) sensory: evidence of hyperalgesia (to pinprick) or allodynia (to light touch)  
   f) vasomotor: evidence of temperature asymmetry or skin color changes or asymmetry  
   g) sudomotor/edema: evidence of edema or sweating changes or sweating asymmetry  
   h) motor/trophic: evidence of decreased range of motion or motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin) |
| Veldman's criteria | 1) Presence of 4 out of 5 symptoms:  
   a) Diffuse pain during exercise  
   b) Temperature differences between affected and unaffected extremity  
   c) Color differences between affected and unaffected extremity  
   d) Volume differences between affected and unaffected extremity  
   e) Limitations in active range of movement of the affected extremity  
2) Occurrence or increase of symptoms during or after use  
3) Symptoms in an area larger than the area of the primary injury |

*IASP definition of CRPS 1: A variety of painful conditions following injury which appears regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event and often resulting in significant impairment of motor function, and showing variable progression over time. (All 3 criteria sets use this definition.)

Injury, persons with persistent pain, tenderness, swelling, joint stiffness (fingers and wrist), and sweating or temperature changes in the injured limb may have CRPS type 1 (LOE: 2, case series and case control studies). In a prospective case series (n=10), no new cases of CRPS type 1 developed beyond 9 weeks (LOE: 2, case series).

**Diagnostic criteria: No consensus**

No one test identifies all persons with CRPS type 1. There is no objective gold standard for diagnosis.* Instead, researchers and clinicians must rely on clinically derived diagnostic criteria. Unfortunately, despite the development of diagnostic criteria by the IASP in 1994 (TABLE 1), experts have not reached consensus on the best method of diagnosis, and several different sets of diagnostic criteria are used.**

**Initial IASP criteria.** Of these, the 1994 IASP consensus-based diagnostic criteria appear to be most widely used in the literature. These criteria were intended as a start-
CRPS underdiagnosed

The diagnosis of CRPS type 1 is often missed,\textsuperscript{1,26,30} so it is likely that the diagnosis rate per population of 0.02% reported in a recent population based study is an underestimate of the actual prevalence.\textsuperscript{31} After distal radial fracture, rates of CRPS type I have varied widely in reports, from 0.9\%\textsuperscript{29} to 15\%\textsuperscript{26} to 28\%.\textsuperscript{34} After tibial shaft fracture, Sarangi et al\textsuperscript{29} reported that 30\% of persons developed CRPS type I.

In cases of post-stroke hemiplegia, CRPS type I has been reported in the paralyzed arm at rates between 25\%\textsuperscript{26} and 40\%.\textsuperscript{37} However, in a more recent study among stroke patients in the US who underwent early inpatient rehabilitation, Petchkrua et al reported a lower incidence of about 2\%.\textsuperscript{38} Impairment can be severe among persons with persistent CRPS type 1. A prospective study revealed that activities of daily living were significantly impaired in 62\% of persons with chronic CRPS type 1.\textsuperscript{39}

Criteria refinements. Derived from 1 of these studies, Buhr's criteria were subsequently developed to improve the IASP criteria (TABLE 1).\textsuperscript{11} Several other sets of diagnostic criteria exist, but only Veldman's criteria (TABLE 1),\textsuperscript{33} which have been adopted as the standard in the Netherlands, have undergone further study.\textsuperscript{14} Studies of Buhr's and IASP criteria have measured specificity and sensitivity, and along with Veldman's criteria, interobserver reliability (TABLE 2).\textsuperscript{11,32,49} However, these numbers must be interpreted with care due to the absence of an objective and independent gold standard.

The absence of an objective gold standard does not mean CRPS type 1 is not a "real" disorder.\textsuperscript{2} In developing diagnostic criteria for CRPS, the IASP turned to models developed for other conditions without objectively measurable findings: the International Headache Society (IHS) classification and the Diagnostic and Statistical Manual of Mental Disorders (DSM). These descriptive systems are based largely on history and self-reported symptoms rather than on clinical signs and laboratory tests. The accuracy of these types of diagnostic criteria is refined over time, through repeated, controlled validation studies using the best means available.\textsuperscript{31}

Specificity of criteria. Specificity has been tested using controls with neuropathic conditions.\textsuperscript{11,12} In these studies, nonblinded clinicians applied CRPS type 1 diagnostic criteria, except the exclusion criterion, to patients who had either CRPS type 1 or neuropathic pain from other causes. Many persons with peripheral neuropathy met criteria for CRPS type 1. However, as stated in the IASP criteria, the diagnosis of CRPS type 1 is not considered until common causes of neuropathic pain and post-traumatic limb pain have been excluded.\textsuperscript{4} As long as the primary care provider considers and rules out other causes of pain, the clinically relevant specificity of these criteria is likely much higher.

Sensitivity of criteria varies. The sensitivity in these studies is based on a non-independent reference standard. Patients with CRPS type 1 were chosen for these studies using clinical criteria, and these criteria were reapplied by study clinicians to determine sensitivity.\textsuperscript{11,12} This method does not allow any determination of whether cases of CRPS type 1 might be missed by the criteria. Sensitivity measured in this way more closely resembles interobserver reliability—the likelihood that different clinicians using the same diagnostic criteria will reach the same diagnosis—and it appears quite good, especially for IASP criteria, in these 2 studies.\textsuperscript{11,12}

However, when interobserver reliability has been directly studied, albeit in small studies of 3 and 6 observers, only Veldman's criteria achieve good reliability; IASP and Buhr's criteria appear unreliable (TABLE 3).\textsuperscript{15,16} However, IASP and Buhr's criteria do fall within the range of reliability of other clinical assessments including medical fitness for a job and shoulder disorders.\textsuperscript{15}
### TABLE 2

**Accuracy of diagnostic criteria for CRPS type 1**

<table>
<thead>
<tr>
<th>CRITERIA TESTED</th>
<th>STUDY OF ACCURACY</th>
<th>STUDY QUALITY</th>
<th>CONTROL GROUP</th>
<th>SN</th>
<th>SP</th>
<th>LR+</th>
<th>LR−</th>
<th>PV+</th>
<th>PV−</th>
</tr>
</thead>
<tbody>
<tr>
<td>IASP</td>
<td>Bruehl et al., 1999</td>
<td>3 (non-indep. ref. standard)</td>
<td>Patients with diabetic neuropathy, polyneuropathy, neuropathic pain, and radiculopathy</td>
<td>98%</td>
<td>36%</td>
<td>1.5</td>
<td>0.1</td>
<td>0.21</td>
<td>0.99</td>
</tr>
<tr>
<td>IASP</td>
<td>Galer et al., 1998</td>
<td>3 (non-indep. ref. standard)</td>
<td>Patients with diabetic neuropathy</td>
<td>100%</td>
<td>55%</td>
<td>2.2</td>
<td>0</td>
<td>0.28</td>
<td>1.0</td>
</tr>
<tr>
<td>Bruehl's</td>
<td>Bruehl et al., 1991</td>
<td>3 (non-indep. ref. standard)</td>
<td>Patients with diabetic neuropathy, polyneuropathy, neuropathic pain, and radiculopathy</td>
<td>70%</td>
<td>94%</td>
<td>12</td>
<td>0.3</td>
<td>0.67</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Sn, sensitivity; Sp, specificity; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PV+, positive predictive value (probability of disease given a positive test); PV−, negative predictive value (probability of disease given a negative test). PV+ and PV− assume baseline likelihood of disease of 15%.

### TABLE 3

**Interobserver reliability of diagnostic criteria for CRPS type 1**

<table>
<thead>
<tr>
<th>DIAGNOSTIC CRITERIA TESTED</th>
<th>STUDY QUALITY</th>
<th>STUDY SIZE</th>
<th>INTEROBSERVER RELIABILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>IASP</td>
<td>2 (small cohort study)</td>
<td>6 diagnosticians</td>
<td>Poor</td>
</tr>
<tr>
<td>Bruehl's</td>
<td>2 (small cohort study)</td>
<td>6 diagnosticians</td>
<td>Borderline moderate</td>
</tr>
<tr>
<td>Veldman's</td>
<td>2 (small cohort study)</td>
<td>3 diagnosticians</td>
<td>Good</td>
</tr>
</tbody>
</table>

**Factors undermining objective evaluation**

Despite clinically based diagnostic criteria, researchers and physicians continue to use office, laboratory, and radiographic tests to diagnose CRPS type 1, perhaps in an attempt to provide a more objective basis for the diagnosis. However, the evaluation of these methods has been plagued by difficulties.

First, because current clinical diagnostic criteria are not yet optimized or even standardized in the literature, there is no gold standard by which to measure the accuracy of these tests.

Second, patients in different studies have been diagnosed with CRPS type 1 by varying criteria.

Third, CRPS type 1 presents differently in different people, and symptoms and signs vary over time in the same person. As a result, the sets of diagnostic criteria have been designed with various clinical findings, and CRPS patients may meet only a few at any one time.

For example, if a group of CRPS type 1 patients were tested for sweating abnormalities, only 24% at best might be expected to test positive (see TABLE 4 for representative frequency of symptoms and signs), resulting in an apparent sensitivity of 24% for sweating abnormalities. This is why it is important for clinicians to consider patients' report of typical signs even when these signs are not present on examination.

**FAST TRACK**

It is important to consider patients' report of typical signs even when these signs are not present on examination.
**TABLE 4:**

**Frequency of symptoms and clinically observed signs in CRPS type 1**

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>SIGNS (%)</th>
<th>SYMPTOMS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allodynia</td>
<td>74</td>
<td>—</td>
</tr>
<tr>
<td>Decreased range of motion</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>Color changes</td>
<td>66</td>
<td>87</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>63</td>
<td>—</td>
</tr>
<tr>
<td>Temperature asymmetry</td>
<td>56</td>
<td>79</td>
</tr>
<tr>
<td>Edema</td>
<td>56</td>
<td>80</td>
</tr>
<tr>
<td>Weakness</td>
<td>56</td>
<td>75</td>
</tr>
<tr>
<td>Sweating changes</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>Skin changes</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Dystonia</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Nail changes</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Hair changes</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Tremor</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Hyperesthesia</td>
<td>—</td>
<td>65</td>
</tr>
<tr>
<td>“Burning” pain</td>
<td>—</td>
<td>81</td>
</tr>
</tbody>
</table>

By exam or report in patients meeting IASP criteria for CRPS, adapted from Harden et al, 1999.11

**Diagnostic instrumentation adds little**

Some investigators have tried using instruments to measure the clinically apparent signs included in diagnostic criteria—volumetry to measure edema, thermometry to measure skin temperature differences, and resting sweat output (RSO) to measure sweating.

**Confounding nature of CRPS 1.** The value of these tests is limited by factors such as the duration of CRPS type 1, time of day, relaxation of the subject, ambient temperature, body temperature, and exact placement of the measuring device,10,19 so it is not clear that objective measurement is practical or adds precision. In fact, in a study comparing testing to clinical diagnosis, instrumentation added little to the overall accuracy of diagnosing CRPS type 1 (LOE: 2, prospective cohort study).14

**Sympathetic nerve block unhelpful.** Other investigators have focused on testing to improve or replace clinical diagnostic criteria. Although at one time a response to sympathetic block was considered diagnostic for CRPS type 1,4 subsequent studies have demonstrated there is a significant placebo response to sympathetic block, that many persons with CRPS type 1 do not respond, and that some persons with other neuropathic pain conditions do respond. A negative or positive response to sympathetic block cannot rule CRPS type 1 in or out (LOE: 2, systematic reviews with only a few high-quality studies).20-22

**Radiographic findings add nothing.** Bone scanning (scintigraphy) and radiography have been used frequently in the diagnosis of CRPS type 1. Although 3-phase scintigraphy looking for different uptake of radioisotope between affected and unaffected limbs has been touted as an objective and definitive test for CRPS type 1,21 this method also suffers from the subjective interpretation of the radiologist and poor interobserver reliability.24 Researchers disagree on whether the typical appearance on scintigraphy is periarticular cuffing25,26 or diffuse uptake of radioisotope,27 and about whether delayed phase scintigraphy is adequate25 or whether 3-phase scintigraphy is necessary.27

To make the interpretation of these scans more objective, quantitative analysis of bone scans has been undertaken; however, subjective interpretation was required to decide where to measure the uptake and what degree of difference between affected and unaffected limbs was considered positive for CRPS type 1.25

In 1 study, without mention of whether the radiologist was blinded but using an appropriate post-traumatic control group, sensitivity of 80% and specificity of 80% were reported (LOE: 2, case-control design).27 In a cohort of persons with upper extremity pain, also without mention of blinding, sensitivity of 73% and specificity of 86% were reported
Pathophysiology unclear

Researchers have been unable to identify the underlying pathophysiology for CRPS type 1, perhaps in part because patients with different pathophysiology may present with similar clinical findings. Recent discovery of an HLA linkage suggests that there may be a genetic predisposition to CRPS type 1.6

By definition, in CRPS type 1 no major nerve damage can be detected, but there may be damage to nerve fibers too small to detect on electromyograph.

Research suggests that injured peripheral C-fibers and A-delta pain fibers immediately flood the central nervous system (CNS) with neurochemicals via the dorsal root ganglion and central pain projecting neurons of the CNS. The CNS is pathologically altered and sends signals to the injured area that serve to maintain the clinical signs and symptoms of CRPS type 1: peripheral pain and sensory changes, local sympathetic changes in blood vessels and sweat glands, and local motor changes. Abnormal sympathetic activity can be clearly demonstrated, but there is no evidence to suggest that this is the cause of CRPS type 1.11

Applying the evidence in practice

CRPS type 1 is often relegated to specialists. But, in fact, no special equipment or testing is required for the diagnosis of CRPS type 1, and the best treatments appear to be non-invasive and completely within the realm of family medicine.

With more attention to deviations from the normal course of recovery from trauma, the family physician will begin to recognize more cases of CRPS type 1 and can have full confidence that the treatments prescribed and monitored are in fact the treatments of choice.

Preventing CRPS 1

For persons with hemiplegia, and of course early inpatient rehabilitation of post-stroke patients with upper extremity hemiplegia. Give 500 mg of vitamin C daily to post-fracture patients in the hope of preventing CRPS type 1 (SOR: B).

Fast Track

Give 500 mg of vitamin C daily to post-fracture patients in the hope of preventing CRPS type 1
**FAST TRACK**

Plain radiography or bone scanning may identify a poorly healed fracture or bony lesions; WBC may identify infection or autoimmune disorders.

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**Diagnosing CRPS type 1**

At 9 weeks following injury to a limb, your patient still complains of pain and sensitivity. Examine the injured limb for signs not seen in the unaffected limb (swelling, diminished use, cold/hot skin, sweating). Also, rely on a patient's report of sweating, even if it is absent during the exam.

Apply any set of diagnostic criteria for CRPS type 1 (see Table 1) (SOR: B). Consider a combined set of criteria using aspects of all 3 (SOR: C—this author's opinion).

Is there further evidence of such underlying pathology as non-union of a fracture, osteomyelitis, neoplasm, thrombophlebitis, peripheral neuropathy, bursitis, rotator cuff tear, etc?

Yes

Treat as appropriate.

No

1) Symptoms/signs occur out-side the territory of a single peripheral nerve and involve a greater area than the original injury.

2) Persistent pain: spontaneous (occurring at rest), induced by use or exercise or hyperalgesia (exaggerated response to mildly painful stimulus such as pinprick); allodynia (pain in response to normally non-painful stimuli such as light touch).

3) Evidence of autonomic or motor dysfunction by report and on examination:
   - color differences between affected and unaffected extremities
   - swelling of affected extremity
   - temperature differences between extremities
   - sweating differences between extremities
   - motor dysfunction of the affected extremity (weakness, tremor, decreased active range of motion, dystonia)
   - increased or decreased hair, skin or nail growth on the affected extremity

Refer for further evaluation.

Are the diagnostic criteria met?

No

Yes

Treat as appropriate.

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**Using the diagnostic criteria.** Once other disorders have been ruled out, evidence does support the diagnosis of CRPS type 1 based on history and physical exam without further testing (SOR: B). In the absence of clear evidence supporting 1 set of criteria over the others, clinicians may use IASP, Bruehl's, or Veldman's clinical criteria for diagnosis (SOR: C). While the IASP criteria are nonspecific and possibly not as reproducible as Bruehl's or Veldman's criteria, they are cited more widely in the literature.
including treatment trials. The criteria (FIGURE) can also be combined to encompass their complementary aspects (SOR: C, this author's opinion).

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES


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