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# Complex Regional Pain Syndrome (CRPS), Reflex Sympathetic Dystrophy (RSD)

**Authors**

Kevin B. Guthmiller[1]; Matthew Varacallo[2].

**Affiliations**

[1] USC Keck School of Medicine
[2] Department of Orthopaedic Surgery, University of Kentucky School of Medicine

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## Introduction

Complex Regional Pain Syndrome (CRPS) is a neuropathic pain disorder defined by the presence of distinct clinical features including allodynia, hyperalgesia, sudomotor and vasomotor abnormalities, and trophic changes. The pain experienced is disproportionate to the degree of tissue injury and persists beyond the normal expected time for tissue healing. The pathophysiology is multifactorial and involves pain dysregulation in both the sympathetic and central nervous systems, with likely genetic, inflammatory and psychological contributions.

There are two subtypes: type I, formerly known as reflex sympathetic dystrophy, and type II, formerly known as causalgia. Type I occurs in the absence of nerve trauma, while type II occurs in the setting of known nerve trauma. Clinically they are indistinguishable and follow a regional rather than a dermatomal or peripheral nerve distribution and favor the distal extremities, though spread outside of the initially affected area commonly occurs to the proximal or contralateral limb.  CRPS is further subdivided into "warm" versus "cold," and sympathetically-maintained (SMP) versus sympathetically-independent (SIP), which may affect prognosis and treatment options.[1]

## Etiology

CRPS occurs as a result of varying degrees or types of tissue trauma but has even been documented in the absence of injury or due to periods of prolonged immobilization. The most common injury associated with developing CRPS is a fracture which occurs in > 40% of CRPS cases. Other common inciting injuries or insults include sprains, contusions, crush injuries, and surgery. CPRS even has been reported to arise after seemingly innocuous interventions such as intravenous line placement. Increased psychological distress experienced during the physical injury associated with the onset of CRPS may affect its severity and prognosis.

## Epidemiology

Using the 1994 International Association for the Study of Pain (IASP) diagnostic criteria, the incidence of CRPS in the United States was noted to be 5.46 per 100,000 person-years for CRPS type I and 0.82 per 100,000 person-years for CRPS type II, with CRPS to be three to four times more common in women than in men, more common in the upper limbs, and with a peak incidence at 50-70 years of age. Of note, the modification of the IASP diagnostic criteria for CRPS in 2012 has been shown to reduce diagnostic rates by 50%.[1]

## Pathophysiology

The underlying mechanism is multifactorial and involves at least abnormal neuronal transmission, autonomic

dysregulation, and central sensitization. This contributes to the variation in clinical presentation. At the site of injury, there is a proinflammatory and immunological response which includes B-cell activation and increased production of interleukins, bradykinin, substance P, and osteoprotegerin (an osteoclastogenesis inhibitory factor). Peripheral sensitization ensues which results in persistent noxious primary afferent traffic into the dorsal horn leading to "wind up" and central sensitization. This, in turn, may result in eventual remodeling in the spinal cord and somatosensory cortex.  There is an alteration of the sympathetic nervous system; sympatho-afferent coupling occurs, and there is an increased expression of adrenergic receptors on nociceptive fibers, which during times of sympathetic activation may explain the presence of autonomic features. The genetic and immune-related factors are subjects of ongoing research.

## History and Physical

Patients may endorse allodynia, hyperalgesia, vasomotor dysfunction, and sudomotor dysfunction. The vasomotor and sudomotor dysfunctions manifest as alterations in sweating, skin color, and temperature and trophic changes in the skin, hair, or nails. There may also be weakness or decreased range of motion in the affected extremity. A systematic review by Lohnberg et al examined psychosocial factors associated with CRPS and concluded there is no support in the literature for specific personality or psychopathology predictors of CRPS.[2]  However, patients with a significant comorbid psychological burden and/or poor coping mechanisms may demonstrate pain-related behavior and catastrophic thinking.  CRPS has been associated with systemic medical issues as well as described by Schwartzman (Schwartzman RJ. Systemic complications of complex regional pain syndrome. *Neurosci Med*. 2012;3:225-242). Systemic complications of complex regional pain syndrome. *Neurosci Med*. 2012;3:225-242 -- PMID not available), including neuropsychological deficits (executive functioning, memory, word retrieval), constitutional symptoms (lethargy, weakness, disruptions in sleep architecture), cardiopulmonary involvement (neurocardiogenic syncope, atypical chest pain, chest wall muscle dystonia leading to shortness of breath), endocrinopathies (impaired hypothalamo-pituitary-adrenal axis with low serum cortisol, hypothyroidism), urologic dysfunction (increased urinary frequency and urgency, urinary incontinence), and gastrointestinal dysmotility (nausea, vomiting, diarrhea, constipation, indigestion).

## Evaluation

The diagnosis of CRPS is largely clinical and one of exclusion.  The differential diagnosis includes small or large fiber sensorimotor neuropathy, cellulitis, erythromelalgia, vasculitis, vascular insufficiency, lymphedema, deep vein thrombosis, and Reynaud's phenomenon.

The  Budapest consensus panel implemented a set of decision rules for proposed clinical criteria (sensitivity 0.85, specificity 0.7). In addition to continuing pain which is disproportionate to the inciting event, they must demonstrate the following symptoms and signs.

**They should report at least one symptom in three of the four following categories:**

1. *Sensory*: Reports of hyperalgesia and/or allodynia,
2. *Vasomotor*: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry,
3. *Sudomotor/edema*: Reports of edema and/or sweating changes and/or sweating asymmetry,
4. *Motor/trophic*: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, skin, nails).

**Additionally, they must display at least one sign at the time of evaluation in two or more of the following categories:**

1. *Sensory*: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch or deep somatic pressure),
2. *Vasomotor*: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry,
3. *Sudomotor/edema*: Edema and/or sweating changes and/or sweating asymmetry,
4. *Motor/trophic*: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, skin, nails).

**Finally, there is no other diagnosis that better explains the signs and symptoms.**

Various objective testing measures have been utilized to include thermography, triple phase bone scan, and the quantitative sudomotor axon reflex test. While these studies provide further data, they are not necessary to make the diagnosis of CRPS.

## Treatment / Management

Although there is a possibility that patients with CRPS may spontaneously improve, considering the debilitating nature of this syndrome, it is prudent to institute aggressive management as soon as possible as a delay may result in an unfavorable outcome. Comprehensive treatment involves a multidisciplinary strategy with a rehabilitation program at the forefront, so referral to a pain management clinic with these capabilities is ideal.[3]

Physical and occupational therapy including mirror therapy is imperative in the treatment of CRPS.

Drug treatments considered standard therapeutic options include oral corticosteroids (for warm CRPS), anticonvulsants (ie, gabapentin), analgesic antidepressants (ie, duloxetine), transdermal lidocaine, and opioids. A multimodal pharmacologic regimen that combines several different classes may be superior.

The 2013 Cochrane Review of Interventions for CRPS concluded that although a broad range of therapeutic approaches have been proposed for the treatment of CRPS pain and disability, there is a critical lack of high-quality evidence evaluating the effectiveness of most of these therapies.[4] Despite this, procedural interventions may be helpful when timed correctly and utilized in a multidisciplinary setting. Serial sympathetic ganglion blocks, either with local anesthetic or chemical/thermal neurolysis, are often utilized to provide relief; yet, despite their widespread use and several case reports and series touting their benefit, when reviewed systematically they have not been shown to provide significant long-term improvement.  Still, when timed very early on in the course of CPRS they might convey substantial benefit, such as demonstrated by Gungor et al.[5]  Sympathetic and perineural blockade with or without a catheter may enable patients to tolerate PT and OT if administered beforehand. Neuromodulation usually is considered after sympathetic nerve blockade has been attempted. While the literature overall reflects positively on spinal cord stimulation (SCS) for CRPS, especially in CRPS with an SMP component, an RCT comparing SCS to physical therapy found that the SCS group performed no better than physical therapy alone 5 years after implantation. Intrathecal drug delivery systems are typically considered salvage therapy. Intravenous regional sympatholytic blocks with guanethidine and reserpine have not been supported by RCTs, and there is moderate quality evidence that intravenous regional blockade with guanethidine is not effective.  With respect to intravenous infusions in particular, a 2016 review concluded that while there is evidence to support infusions of ketamine, lidocaine, bisphosphonates, and immunoglobulin as being efficacious, the authors noted that most of the included studies were pre- Budapest Criteria and several were not of high quality.[6]

Because of the association with comorbid psychiatric disorders such as depression and anxiety, cognitive behavioral therapy is considered a necessary component in treating CRPS, although there are no available studies to provide evidence to support the use of this treatment approach. Still, the treating clinician should appreciate that suboptimal management of psychological comorbidities serves as a barrier to improvement for any chronic pain

condition.

Additional treatment options include topical capsaicin, free radical scavengers (topical dimethylsulfoxide, oral vitamin C), and surgical sympathectomy.

Patients with the SIP variant may have a worse prognosis.

## Enhancing Healthcare Team Outcomes

A team approach to this problem is required to maximize recovery. Social service,pharmacology nursing and physical therapy along with early advanced pain management are key to improved outcomes.

## Questions

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