Complex Regional Pain Syndrome in Emergency Medicine

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Overview

Background

Reflex sympathetic dystrophy syndrome (RSDS) has been recognized since the Civil War when it was called causalgia, a name chosen to describe intense, burning extremity pain after an injury. Since then, RSDS has had a number of name changes. Bonica coined the term reflex sympathetic dystrophy in 1953. The American Association of Hand Surgery proposed changing the name to sympathetic maintained pain syndrome. A consensus expert panel recommended a change to complex regional pain syndrome (CRPS). However, although many clinicians still use the term RSDS, the terms currently in favor are complex regional pain syndrome I (the equivalent of RSD) and complex regional pain syndrome II, also known as causalgia.

CRPS/RSDS has readily identifiable signs and symptoms and is treatable if recognized early; however, the syndrome may become disabling if unrecognized.[1] Emergency physicians are frequently in a position to identify the problem and may play a significant role in minimizing impact of this common entity.

Pathophysiology

No single hypothesis explains all features of reflex sympathetic dystrophy syndrome (RSDS). Schwartzman stated that a common mechanism may be injury to central or peripheral neural tissue.[2] Roberts proposed that sympathetic pain results from tonic activity in myelinated mechanoreceptor afferents. Input causes tonic firing in neurons that are part of a nociceptive pathway. Campbell et al propose a hypothesis that places the primary abnormality in the peripheral nervous system.[3] More recent articles agree that the cause is still unknown.[4] Recent interest has focused on an immune-mediated mechanism.[5]

Most authors now agree that complex regional pain syndrome (CRPS) is a neurologic disorder affecting central and peripheral nervous systems.[6, 7] Mechanisms include peripheral and central sensitization, inflammation, altered sympathetic and catecholaminergic function, altered somatosensory representation in the brain, genetic factors, and psychophysiologic interactions.[7, 8]

Other etiologic possibilities have been suggested. German research has noted the association between elevated levels of soluble tumor necrosis factor receptor 1 (sTNF-R1) and enhanced tumor necrosis factor-alpha activity in patients with polyneuropathy with allodynia.[9] Other German researchers have described autoantibodies in patients with CRPS, especially CRPS type 2.[10]

Harvard researchers Oaklander and Fields have proposed that distal degeneration of small-diameter peripheral axons may be responsible for the pain, vasomotor instability, edema, osteopenia, and skin hypersensitivity of CRPS-1.[11]

The recent association between the use of ACE inhibitors and CRPS has caused some to consider a neuroinflammatory pathogenesis.[12]

Recent research has demonstrated cortical changes, suggesting a possible role in pathophysiology.[13]

All agree that, regardless of the mechanism, the patient experiences intense, burning pain in one or more extremities.
Epidemiology

Frequency

United States

CRPS occurs in approximately 1-15% of peripheral nerve injury cases. Schwartzman states that CRPS usually occurs secondary to fractures, sprains, and trivial soft tissue injury.[2] The incidence after fractures and contusions ranges from 10-30%. While some cases are associated with an identifiable nerve injury, many are not. Even "microtrauma" as might occur with an immunization may be responsible. The upper extremities are more likely to be involved than the lower. Entities that have led to RSDS include the following:

- Head injury
- Stroke
- Polio
- Amyotrophic lateral sclerosis (ALS)
- Myocardial infarction
- Polymyalgia rheumatica
- Operative procedures (eg, carpal tunnel release)
- Brachial plexopathy
- Cast/splint immobilization
- Minor extremity injury
- Prolonged bedrest

Mortality/Morbidity

In and of itself, the disease is not fatal. Morbidity of RSDS is associated with disease progress through a series of stages (see Physical).

Schwartzman et al recently reviewed questionnaires from 656 patients with CRPS. Once patients had experienced symptoms for more than one year, the majority of signs and symptoms were developed. No one reported spontaneous remission of symptoms.[14]

Race

The 2009 questionnaire review by Schwartzman et al showed that, in the population he studied, the overwhelming majority (96%) were white and 80% were female.[14]

Sex

Stanton-Hicks and others note that women predominate in a range of 60-80% of cases.[15]

Age

Persons of all ages are affected. Stanton-Hicks reports that in contrast to adults, 90% of pediatric cases occur in female children aged 8-16 years, with the youngest being 3 years. That author and others report that CRPS is treated most effectively in pediatric patients, with a remission rate of 97%.[16, 17]

An Israeli group suggested that CRPS in children and adolescents is underdiagnosed. They emphasize the importance of early recognition and multidisciplinary treatment.[18]
Several have looked into the possibility that there may be an increased risk of CRPS development in siblings. de Rooij et al showed that, although the overall risk is not increased, the risk in siblings younger than 50 years is significantly increased.[19, 20]

**Presentation**

**History**

The most widely accepted criteria for the diagnosis were published by the International Association for the Study of Pain (IASP). It lists the diagnostic criteria for complex regional pain syndrome I (CRPS I) (RSDS) as follows[21] :[22]

1. The presence of an initiating noxious event or a cause of immobilization
2. Continuing pain, alldynia (perception of pain from a nonpainful stimulus), or hyperalgesia disproportionate to the inciting event
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the area of pain
4. The diagnosis is excluded by the existence of any condition that would otherwise account for the degree of pain and dysfunction.

According to the IASP, CRPS II (also known as causalgia) is diagnosed as follows:

1. The presence of continuing pain, alldynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve
2. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain
3. The diagnosis is excluded by the existence of any condition that would otherwise account for the degree of pain and dysfunction.

Several authors note that these diagnostic criteria show high sensitivity but low specificity.[23]

Note that the primary difference between type I and type II is the identification of a definable nerve injury.

Two other criteria sets are in common use for CRPS I, though the IASP only accepts the above criteria. While there is overlap, the differences have caused some difficulties in that authors may define their populations differently.[24]

Veldmen et al list the following[25] :

1. At least 4 out of 5 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 in signs and/or symptoms after exercise

Bruehl et al list the following[26] :

- Continuing pain disproportionate to any inciting event.
- Presence of at least one symptom in each of the following categories:
  - Sensory
  - Vasomotor
  - Sudomotor/edema
  - Motor/trophic
- Two signs of sensory, vasomotor, sudomotor/edema, and motor/trophic
Brunner et al performed a Delphi survey among international experts.[27] The survey asked those experts to list and grade diagnostic and follow-up parameters for CRPS I. Although there was some disagreement about weighting, the consensus follows.

The 3 diagnostic parameters, each with a subcategory, are listed below.

- **Pain**
  - Hyperesthesia
  - Hyperalgesia
  - Allodynia

- **Signs**
  - Edema
  - Color

- **Mobility**
  - Motor change
  - Range of motion
  - Strength

The one follow-up parameter is clinical course. The subcategories are as follows:

- Decrease in pain
- Decrease in hyperalgesia
- Decreased edema
- Improvement in motor function
- Improvement in strength

The experts from this survey also agreed that the diagnosis can and should be established without additional studies (radiography, scintigraphy).[27] Other authors believe likewise.[28] Much of the older RSDS literature notes a predisposing personality of depression. However, many other studies have demonstrated that, while most patients are depressed, they are depressed because of their pain. (See Causes below.)

Many patients with CRPS/RSDS will exhibit some type of movement disorder ranging from strength reduction (78%) to tremor (25-60%) to myoclonus and dystonia. Although some authors believe these are pain-induced findings, others believe they are primary abnormalities.[29]

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**Physical**

The physical findings have been listed as part of the "History" section because the criteria sets include both signs and symptoms. Three stages have been classified. Although a consensus panel recommended that staging be eliminated, it is important that the emergency physician has an awareness of potential disease progress. Disease progress is very variable.

- **Stage I or early RSDS:** Pain is more severe than would be expected from the injury, and it has a burning or aching quality. It may be increased by dependency of the limb, physical contact, or emotional upset. The affected area becomes edematous, may be hyperthermic or hypothermic, and shows increased nail and hair growth. Radiographs may show early bony changes. Duration is usually 3 months from onset of symptoms. Some patients remain in one stage or another for many months or even years. They may never progress or they may progress quickly to late stage. Remember that physical findings may be minimal, especially in those who remain in stage I or progress slowly.

- **Stage II or established RSDS:** Edematous tissue becomes indurated. Skin becomes cool and hyperhidrotic with livedo reticularis or cyanosis. Hair may be lost, and nails become ridged, cracked, and brittle. Hand dryness becomes
prominent, and atrophy of skin and subcutaneous tissues becomes noticeable. Pain remains the dominant feature. It usually is constant and is increased by any stimulus to the affected area. Stiffness develops at this stage. Radiographs may show diffuse osteoporosis. The 3-phase bone scan is usually positive. Duration is 3-12 months from onset.

- Stage III or late RSDS: Pain spreads proximally. Although it may diminish in intensity, pain remains a prominent feature. Flare-ups may occur spontaneously. Irreversible tissue damage occurs. Skin is thin and shiny. Edema is absent. Contractures may occur. Radiographs indicate marked demineralization.

Extensive changes are present in the muscles of patients with long-standing disease.[30]

**Causes**

Many hypotheses exist, but a definite cause has not been identified. (See Pathophysiology).

Older literature suggested that development of complex regional pain syndrome (CRPS) required a triad of conditions: an injury, an abnormal sympathetic response, and a predisposing personality. Most current literature disputes the need for an underlying personality disorder. In August 2000, Schwartzman stated, "There is no evidence that affected patients have a personality disorder, but the severity of pain and the disruption of the patient's life can lead to anxiety and depression."[31] Beerthuizen et al reviewed 31 articles that addressed an association between psychiatric illness and CRPS-1. Almost all the studies showed no causal relationship.[32]

Peterlin et al suggested that migraine may be a risk factor for the development of CRPS, but theirs is the only paper of its type.[33]

ACE inhibitors have been suggested as a possible cause for the development of CRPS.[12, 34]

Evidence now shows that CRPS may have a genetic predisposition.[7, 8]

**DDx**

**Differential Diagnoses**

- Deep Venous Thrombosis and Thrombophlebitis
- Thoracic Outlet Syndrome Imaging

**Workup**

**Laboratory Studies**

See the list below:

- A single, reliable, sensitive, and specific diagnostic test for reflex sympathetic dystrophy syndrome (RSDS) is not available.

- Quantitative sensory testing and quantitative sudomotor axon reflex test (QSART) may be performed to look for sensory and sweating abnormalities.[35]

- And as noted above, experts agree that diagnostic studies are not necessary to make the diagnosis.[27, 28]
Imaging Studies

Although not required for diagnosis, these studies have been advocated for a variety of reasons.

- Three-phase bone scan and gadolinium magnetic resonance imaging (MRI) have been used to diagnose and stage the disease.
- Standard radiographic findings are normal in as many as 30% of patients. However, they may show osteoporosis as soon as 3-5 weeks of onset.
- Laser Doppler flow studies have been used to monitor background vasomotor control.
- A cold pressor test performed in conjunction with thermographic imaging observes vasoconstrictor response.
- Functional MRI (fMRI) has been used to demonstrate that allodynic stimulation produces objective findings.[35]

Procedures

See the list below:

- Some authors believe that the best diagnostic approach involves use of differential neural blockade. In those with sympathetically mediated pain (as opposed to those whose pain is sympathetically independent), response to neural blockade may help guide medical therapy.
  - For cases involving an upper extremity, a stellate ganglion block may aid the diagnostic process and may be therapeutic. However, failure to relieve pain does not eliminate the diagnosis.[2, 31]
  - Differential blockade has been performed using Bier blocks with a variety of agents, including local anesthetics, bretylium, steroids, ketorolac, reserpine, and guanethidine and clonidine.[31, 36]
  - The rationale for selective neural blockade is to interrupt stimulation to the sympathetic nervous system. Again, this is effective only in those whose pain is sympathetically dependent.[31]

Treatment

Prehospital Care

There is nothing for prehospital providers to do except transport. Most state guidelines do not include chronic pain syndromes as an indication for narcotic administration.

Emergency Department Care

Definitive care is really beyond the purview of the ED physician. An emergency physician's primary role with patients who have complex regional pain syndrome (CPRS)/reflex sympathetic dystrophy syndrome (RSDS) is to recognize the possibility of the diagnosis and refer such patients to colleagues who are capable of using available therapies. Breaking through the pain cycle early increases the likelihood of a better outcome.

The 3 basic modes of therapy include pain management, rehabilitation (including physical therapy), and psychological therapy.[37]
Once the diagnosis is established, a number of treatment modalities that have been proven helpful are available. The most effective treatment involves differential neural blockade. Children may also benefit from neural blockade.\[36\]

CRPS experts and researchers have looked at many treatment possibilities. Some have proven beneficial, others less so. The list below includes most of the possibilities that have been considered. Some of the oral medications may be prescribed in the ED after discussion with the primary care physician or pain specialist. Although none of the other modalities will be used in the ED, the clinician should have an overview of the available options.

- The anesthesia literature provides good evidence that spinal stimulation is effective.\[38, 39\]
- Most patients, especially children, can benefit from physical therapy.\[16, 40, 41, 42\] A new physical modality—graded motor imagery—has recently received a great deal of attention.\[43, 44\]
- Tricyclic antidepressants have been used to decrease burning. Gabapentin (Neurontin) and systemic steroids have also been used with varying degrees of success. Other agents include the alpha-1 adrenoreceptor antagonists terazosin and phenoxybenzamine; the alpha-2 adrenoreceptor agonist clonidine; and the NDMA receptor antagonists ketamine, dextromethorphan, and calcitonin. When treatment reaches a plateau, invasive interventions to be considered include tunneled epidural catheters and neuroaugmentation.
- Dadure et al recently described a series of pediatric patients with recurrent CRPS who benefited from continuous peripheral nerve blocks given at home.\[36\]
- Acupuncture has been reported to have some value, especially in children.\[45\]
- Topical and intravenous lidocaine have been reported to be effective in some cases.\[46\] Most of the literature appeared several years ago, but the group at Drexel University College of Medicine in Philadelphia reported favorable results for a 5-day lidocaine infusion.\[47\]
- Eckmann et al performed a randomized, controlled trial that looked at several parameters with the use of IV regional block with ketorolac and lidocaine for treating CRPS. This small study of 10 patients with lower extremity CRPS type I showed short-term (1 week) pain relief. No improvement was shown in the primary outcome of overall pain numeric rating scale or secondary outcomes of pain in motion, allodynia, joint pain score, edema, range of ankle motion, and skin temperature.\[48\]
- A Turkish group performed a randomized controlled trial using a Bier block containing methylprednisolone and lidocaine in patients with CRPS type I patients. The group concluded that the therapy did not provide long-term benefit, and the short-term benefit was no better than with placebo.\[49\]
- Case reports and small number studies have reported good efficacy for topical and IV infusion of ketamine. As a dissociative anesthetic, the logic is to try to "erase the memory" of the pain stimulation.\[50, 51, 52\] Several more recent studies also discuss the value of this therapy.\[53, 54, 55\]
- A group in the Netherlands reported significant pain decrease in 8 patients treated with an IV infusion of magnesium.\[56\]
- Work that is looking at the efficacy of bisphosphonates has begun.\[8, 57\]
- Intravenous immunoglobulin has been studied.\[5\]
- Case reports describe some promise for the injection of botulinum toxin.\[58, 59\]
- For patients who cannot be seen in the ED or cannot be treated in an expeditious fashion with neural blockade, the primary care physician who knows the patient best should arrange for narcotic analgesia, recognizing that neuropathic pain may be very resistant to standard analgesics, even potent ones. Patients who fail neural blockade very well may have disease that has progressed to the sympathetic-independent stage, and they are likely to have a lifelong problem. In this group, treatment by specialists in pain management, who have access to more sophisticated and experimental therapies, is mandatory.
- In the ED, narcotics often are required to provide temporary relief while waiting for definitive treatment to begin. Patients with refractory disease may present to the ED with flare-ups that require narcotics. Although distinguishing between those who are truly in pain and those who are malingering is very difficult, the clinician must not assume that all who present without an obvious painful problem are drug seekers. Those with CRPS/RSDS may have a paucity of objective findings. Many are under the care of a knowledgeable pain expert and do not allow themselves to run out of analgesia.
- The Reflex Sympathetic Dystrophy Syndrome Association has produced a very user-friendly guideline document that may be helpful to both clinician and patient.\[6\]
Consultations

See the list below:

- Consider consultation with an anesthesiologist or other qualified pain management specialist regarding management.
- Consider consultation with physical medicine personnel regarding rehabilitation.
- Consider consultation with a hand surgeon.

Medication

Medication Summary

Specialists in pain management (usually an anesthesiologist or physiatrist) commonly perform neural blockade. Use of pain modifying agents, such as cyclic antidepressants and gabapentin, usually is left to the primary care physician or pain management team.

The ED physician's primary responsibilities are to recognize the disease and refer patients to an appropriate specialist. However, these patients experience severe pain and should be given sufficient analgesia to provide relief. Narcotics usually are required.

Discussion of available agents has been limited to morphine and hydromorphone. ED physicians choose the agent with which they are most familiar and comfortable. Clinicians who choose to use meperidine should remember that it provides some euphoria and also has an active metabolite that may accumulate.

Agents with a short duration of action (eg, fentanyl) are not usually appropriate.

Some pain specialists prefer methadone for its long duration of action and mechanism of action benefit. This agent is an NMDA antagonist and may therefore be more effective in neuropathic pain syndromes. Conversion from other opioids to methadone should be done by a qualified pain management professional.[60] Other long-acting agents include sustained-release forms of oxycodone and morphine.

Analgesics

Class Summary

Pain relief should be a high priority. Pain control is essential to quality patient care. Analgesics ensure patient comfort, promote pulmonary toilet, and have sedating properties. Note that controversy exists among authors about the appropriateness of chronic narcotic analgesia. Some are opposed. Others note that, when more specific measures fail, patients must have pain relief in order to live their lives. The latter believe that patients with CRPS have a true chronic pain syndrome.

Morphine sulphate (Duramorph, MS Contin)

DOC for analgesia because of reliable and predictable effects, safety profile, and ease of reversibility with naloxone.

Initial dose dependent on whether patient already is taking narcotic analgesics. For patients not using long-term agents, as little as 2 mg IV/SC may be sufficient, though higher doses are often needed. Larger doses may be required in patients taking long-term narcotic analgesics.

Also available in oral form in immediate-release and timed-release preparations. Long-acting form usually is administered q12h, but many believe that it loses much of its effect after 8 h; immediate-release form may be needed for periods of pain "breakthrough," dose dependent on previous use. ED physician should begin at lowest available dose in newly diagnosed patients.
No intrinsic limit to the amount that can be given exists, as long as patient is observed for signs of adverse effects, especially respiratory depression. Various IV doses are used, commonly titrated until desired effect obtained.

**Hydromorphone (Dilaudid)**

Used to manage moderate to severe pain. Available IV and PO.

**Follow-up**

**Further Outpatient Care**

It is in the best interest of patients with complex regional pain syndrome (CRPS) to have a physician knowledgeable about this entity orchestrate all care. Appropriate referral is important.

**Further Inpatient Care**

Although not FDA approved in the United States, in some countries, patients with complex regional pain syndrome are hospitalized and placed on continuous intravenous infusions of medications such as lidocaine or ketamine. As a dissociative anesthetic, the latter is intended to "erase" the memory of dysfuctioning neurons. Results have been variable.

**Deterrence/Prevention**

It has been well documented that those with complex regional pain syndrome who are diagnosed earliest do the best. Once the disease is well established, it probably cannot be reversed.

**Complications**

Once refractory to neural blockade, pain is probably lifelong and may be severe enough to be debilitating.

**Prognosis**

Prognosis of complex regional pain syndrome depends largely on timely diagnosis and use of early aggressive therapy.

**Patient Education**

Patients should be encouraged to seek out CRPS support groups.
Questions & Answers

Overview
What is complex regional pain syndrome (CRPS)?
What is the pathophysiology of complex regional pain syndrome (CRPS)?
What is the prevalence of complex regional pain syndrome (CRPS) in the US?
What is the mortality and morbidity of complex regional pain syndrome (CRPS)?
What are the racial predilections of complex regional pain syndrome (CRPS)?
What are the sexual predilections of complex regional pain syndrome (CRPS)?
Which age groups have the highest prevalence of complex regional pain syndrome (CRPS)?

Presentation
What are the IASP diagnostic criteria for complex regional pain syndrome I (CRPS I)?
What are the IASP diagnostic criteria for complex regional pain syndrome II (CRPS II)?
What are the Veldmen diagnostic criteria for complex regional pain syndrome (CRPS)?
What are the Bruehl diagnostic criteria for complex regional pain syndrome (CRPS)?
What are the Brunner diagnostic criteria for complex regional pain syndrome (CRPS)?
What is the prevalence of movement disorders in complex regional pain syndrome (CRPS)?
Which physical findings are characteristic of complex regional pain syndrome (CRPS)?
What causes complex regional pain syndrome (CRPS)?

DDX
What are the differential diagnoses for Complex Regional Pain Syndrome in Emergency Medicine?

Workup
Which lab tests are performed in the workup of complex regional pain syndrome (CRPS)?
What is the role of imaging studies in the workup of complex regional pain syndrome (CRPS)?
What is the role of a differential neural blockade in the workup of complex regional pain syndrome (CRPS)?

Treatment
What is included in the prehospital care for complex regional pain syndrome (CRPS)?
How is complex regional pain syndrome (CRPS) treated in the emergency department (ED)?
How is complex regional pain syndrome (CRPS) treated?
Which specialist consultations are beneficial to patients with complex regional pain syndrome (CRPS)?

Medications
Which medications are used in the treatment of complex regional pain syndrome (CRPS)?
Which medications in the drug class Analgesics are used in the treatment of Complex Regional Pain Syndrome in Emergency Medicine?

Follow-up
Where should a patient with complex regional pain syndrome (CRPS) be referred for ongoing care?

What is included in the inpatient care of complex regional pain syndrome (CRPS)?

How is complex regional pain syndrome (CRPS) prevented?

What are the possible complications of complex regional pain syndrome (CRPS)?

What is the prognosis of complex regional pain syndrome (CRPS)?

What is included in patient education about complex regional pain syndrome (CRPS)?


