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Complex Regional Pain Syndrome, Current Concepts and Treatment Options

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Abstract

Purpose of Review Complex regional pain syndrome (CRPS) refers to a chronic pain condition that is characterized by progressively worsening spontaneous regional pain without dermatomal distribution. The symptomatology includes pain out of proportion in time and severity to the inciting event. The purpose of this review is to present the most current information concerning epidemiology, diagnosis, pathophysiology, and therapy for CRPS.
Recent Findings In recent years, discovery of pathophysiologic mechanisms of CRPS has led to significant strides in the understanding of the disease process.
Summary Continued elucidation of the underlying pathophysiological mechanisms will allow for the development of more targeted and effective evidence-based therapy protocols. Further large clinical trials are needed to investigate mechanisms and treatment of the disorder.

Keywords Complex regional pain syndrome · CRPS-1 · Disproportionate pain · Allodynia · Hyperalgesia · Budapest criteria · Spinal cord stimulation

Introduction

Complex regional pain syndrome (CRPS) refers to a chronic pain condition that is characterized by progressively worsening spontaneous regional pain without dermatomal distribution. The pain experienced is out of proportion in time and severity to the inciting event and accompanied by symptoms that vary in severity including skin changes, autonomic dysfunction, abnormal sensory and motor changes, and trophic changes [1]. CRPS may develop after major trauma, surgery, or minor injury, and progresses with a variable course that ranges from self-limiting, mild symptomatology to chronic disease. In many cases, disease progression is debilitating and severely limits patients' quality of life, creating a tremendous burden to patients and their families [2]. While early recognition and treatment may improve disease course and limit progression, an incomplete understanding of the pathophysiology of the disease renders diagnosis challenging. Physicians must rely on clinical findings to diagnose CRPS, as no specific diagnostic test currently exists. The purpose of this review is to present the most up-to-date information concerning epidemiology, diagnosis, pathophysiology, and therapy for CRPS.

Definition/Diagnosis

Over time, CRPS has been defined and redefined. CRPS develops after an inciting noxious stimulus to an affected limb. The disease can be further divided into CRPS-1 and CRPS-2, differentiated by the absence or presence of peripheral nerve damage, respectively, as demonstrated by electrodiagnostic or physical evidence [3, 4]. CRPS-1, previously named reflex sympathetic dystrophy, is characterized by nociceptive pain while CRPS-2, previously named

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causalgia, is characterized by neuropathic pain [5]. An additional subtype, CRPS-NOS (CRPS not otherwise specified), has been identified as CRPS which partially meets criteria but is not better explained by other conditions [6].

In 1994, the International Association for the Study of Pain published a set of diagnostic criteria for CRPS [3]. These criteria included the following: (1) presence of an inciting event; (2) continuation of disproportionate pain, allodynia, and hyperalgesia; (3) skin changes, edema, and abnormal sudomotor activity; and (4) absence of other conditions that may account for the pain and dysfunction. While these criteria proved to identify most cases of CRPS, they demonstrated poor specificity and led to overdiagnosis [7].

From these original International Association for the Study of Pain (IASP) criteria, Harden et al. developed the Budapest Criteria (Table 1). This defined CRPS as a progressive array of painful conditions characterized by regional pain disproportionate to the inciting event in time and degree; a distal predominance of sensory, motor, sudomotor, vasomotor, and/or trophic findings; and an inability to better explain pathology by alternative diagnoses. These redefined criteria were intended to decrease clinical misdiagnosis and to improve research via enhancement of subject homogeneity. Validation of the criteria in diagnosing CRPS demonstrated a specificity of 0.79, in comparison to the original IASP criteria's specificity of 0.41 [8••].

The Budapest Criteria is a useful diagnostic tool for CRPS, but neither provides information regarding symptom severity nor permits monitoring of disease progression. Based on an analysis of the data used to create the Budapest Criteria, Harden et al. designed a CRPS Severity Score (CSS) for continuous measurement of CRPS severity [9••]. To validate their CSS, the group conducted a prospective multicenter analysis to assess its sensitivity in tracking changes in CRPS patient's symptoms over time. They sought to analyze the sensitivity of their developed CSS to change in CRPS severity. This study included 156 patients who met the 2012 IASP criteria for CRPS and were either newly treated patients initiating treatment or established patients following a stable treatment protocol. They hypothesized that those patients who were initiating treatment would show greater changes in CSS than established patients. Results showed that compared to the stable CRPS group, patients in the New CRPS group displayed greater improvements on the CSS. This was found to be consistent with improvements in NRS ratings of pain intensity, CES depression scores, and Rand-36 Physical Functioning. In their analysis of the CSS, they found that larger changes on the CSS corresponded to greater changes in pain intensity, daily functioning, and overall well-being. The overall findings of the study support the validity of the CSS and its use in clinical practice.

Table 1 The Budapest Criteria. Diagnostic criteria for CRPS as defined by an international consensus meeting held in Budapest [4, 8••]

Budapest Criteria: clinical diagnostic criteria for CRPS

Continuing pain, which is disproportionate to any inciting event.

Must report at least 1 symptom in 3 of the 4 following categories:
- Sensory: reports of hyperalgesia and/or allodynia
- Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
- Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
- Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)

Must display at least 1 sign at time of evaluation in 2 or more of the following categories:
- Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
- Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry
- Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry
- Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)

There is no other diagnosis that better explains the signs and symptoms.
- A sign is counted only if it is observed at the time of diagnosis.
- Research criteria for CRPS are recommended that are more specific, but less sensitive than the clinical criteria; they require that 4 of the symptom categories and at least 2 sign categories be present.

Epidemiology—Population

Until recently, there have been limited studies on the epidemiological occurrence of CRPS. The first population-based study of CRPS was performed by Sandroni et al. in 2003 [10]. In a study population of Olmstead County, Minnesota, they found the overall incidence of CRPS1 to be 5.46 per 100,000 people, or 0.55%. Women were affected four times as often as men, with a median age of onset of 46 years. Upper extremities were involved twice as often as lower extremities. These findings have been supported by subsequent studies. Women have been shown to be affected as much as two to five times as often as men with the highest incidence in postmenopausal females [10, 11••, 12–14].

Elsharydah et al. conducted the largest to-date population-based study of CRPS, published in 2016. The group performed a retrospective analysis of the nationwide inpatient sample database from 2007 to 2011. Of the inpatient sample of 33,406,123 total patients, 22,533 patients were identified with a discharge diagnosis of CRPS1. Their findings were consistent with those previously demonstrated in literature. The estimated overall incidence of CRPS1 over the study period was 0.07% [11••]. They found that CRPS1 occurred more commonly in females (73%) and the peak age at onset was found to be 45–55 years. Other population variables

associated with CRPS included Caucasian race, higher median household income, depression, headache, and drug abuse. Diabetes, obesity, and hypothyroidism were associated with lower rates of CRPS1 [11••].

Fracture and Surgery

Extremity fracture is a common inciting event of CRPS1. Seven percent of patients who suffered a single fracture of the wrist, scaphoid, ankle, or metatarsal V developed CRPS1 [15]. In particular, ankle dislocation complicated by intraarticular fracture and immobilization has demonstrated a high association with disease onset [12, 16]. There is also an association between the development of CRPS and rheumatoid arthritis or other musculoskeletal comorbidities [15]. Following the inciting event, CRPS1 typically develops within 8 weeks. Though patients experience an initial improvement in symptoms within 3 months, symptoms are not significantly improved at 1 year [15, 17]. Patients who continue to experience persistent pain and swelling have an increased risk of developing CRPS1 [17, 18].

CRPS1 may develop following surgery of the extremities, as 4.36% of patients develop postoperative CRPS after elective foot and/or ankle surgery [13]. In a study of patients undergoing closed reduction and casting of a distal radius fracture, 32.2% of patients developed CRPS1, with an average onset of 21 days after cast removal [14]. In contrast, only 8.8% of patients with a distal radius fracture developed CRPS postoperatively [19]. The incidence of CRPS in patients undergoing carpal tunnel release surgery was 8.3%. Of note, there was no association between anesthetic technique and CRPS1 incidence [20].

Pathophysiology

The underlying pathophysiology of CRPS remains unclear and controversial. There is no consensus on primary versus secondary mediators of the changes observed in CRPS, nor whether all cases of CRPS share the same underlying pathophysiology. Though there have been many advances in the understanding of CRPS, the exact mechanism of disease onset and progression remains unknown [21]. CRPS appears to be multifactorial with evidence in literature pointing to components of inflammation, autoimmune factors, neuronal plasticity, and autonomic dysregulation [21].

Inflammation

Inflammation following trauma and surgery is a normal and expected component of the healing process. This inflammatory process appears to be exaggerated in CRPS. Many typical signs of inflammation manifest as elevated skin temperature, skin color changes, edema of the limb, and inexplicable pain [22].

Neurogenic inflammation is a healthy response, elicited by the release of proinflammatory modulators from peripheral nerve endings involved in nociception [23]. The released neuropeptides influence blood vessels, local immune cells, and neural structures which leads to surrounding tissue erythema, flushing at the site of injury, and plasma extravasation. In CRPS, tissue injury with or without nerve injury seems to lead to an exaggerated neuroinflammatory response including the release of proinflammatory neuropeptides. In a process termed peripheral sensitization, proinflammatory mediators lead to nociceptor activation and the subsequent allodynia and hyperalgesia characteristic of CRPS [24, 25].

A recently published review outlines the literature describing CRPS as a predominantly proinflammatory state [26]. While the results of the study demonstrated a significantly elevated state of inflammation in patients with CRPS, they were unable to deduce whether this was more indicative of a state of chronic pain rather than of a primary mediator of CRPS. Moreover, the study failed to find evidence of a higher level of inflammatory factors in the affected limb compared to the unaffected limb. Whether inflammation plays a causal role in CRPS remains unclear.

Sympathetic Component

The increased release of neuroinflammatory modulators may lead to an overactivation of sympathetic nervous activity, resulting in catecholamine-induced nociceptive activation. Patients with CRPS characteristically exhibit cool skin and diaphoresis. Autonomic abnormalities present as skin vasomotor abnormalities including changes in skin color, edema, abnormal sweating, osteopenia, and extremity coolness, which may be explained by pathologic changes of unmyelinated peripheral nerve fibers [27–29]. Increased noradrenergic receptor density and sensitivity in the affected region may be responsible for sympathetically driven symptoms [30]. The autonomic dysfunction in CRPS, including increased heart rate, decreased heart rate variability, and a decreased orthostatic response in cardiac output, is likely a result of the contribution of degenerative neuronal changes and resulting hypersensitivity of denervated tissue [27, 31] Moreover, these changes in hemodynamics correlate with disease duration. Patients with CRPS1 demonstrate significantly lower sympathetic sweat response and skin vasomotor reflex in the affected extremity, consistent with findings of abnormalities in sympathetic postganglionic fibers [32].

Some treatment modalities that target the sympathetic nervous system have been effective in treating CRPS, providing further evidence of its role in the disorder. Local anesthetic sympathetic blockade is often employed for treatment of CRPS symptoms, though there is limited evidence to support

its long-term effectiveness [33•]. To enhance the short-term effects of a single-shot sympathetic block, continuous thoracic sympathetic block using a catheter has been performed with success. More invasive techniques such as pulsed radiofrequency treatment have been safely performed and with effective relief of symptoms for a mean of 31 days [32].

Central Nervous System Involvement

In addition to peripheral mechanisms, the central nervous system is implicated in the pathogenesis of CRPS [22]. While damage to peripheral tissues and subsequent proinflammatory state appear in early clinical stages, progressively worsening signs of impaired recognition, neglect, and motor dysfunction point to an important role of the CNS [34]. Symptoms associated with CRPS commonly mimic those of movement disorders; tremors, dystonia, and the basal ganglia have been implicated in the development of CRPS symptoms [35]. In patients performing action of observation, CRPS patients showed an abnormal response via fMRI; video stimuli elicited a greater unpleasant stimulus in patients with CRPS than in healthy patients, suggesting that central sensory circuitry which processes painful stimuli may contribute to pain and disability [36].

Numerous studies assert that functional reorganization of the primary somatosensory cortex leads to the development and progression of CRPS [37, 38]. A recent systematic review aimed to determine differences in activity and spatial representation within affected regions of primary somatosensory cortex in patients with CRPS [39•]. Interestingly, the study reported that affected body parts display smaller representation versus control in the primary somatosensory cortex, although no differences in latency and activation strength were reported. As evidenced by the lack of differences in latency between hemispheres of the affected limb and control, signal transmission is unlikely to be solely responsible for observed changes in cortical function.

Autoimmune

CRPS has been described as an autoimmune disease, in which immunological aspects play an important role in disease development and progression [40]. IgG autoantibodies with agonism directed to the β2 adrenergic receptor and the muscarinic-2 receptor have been demonstrated [41].

Transfer of serum from wild-type fracture mice to B cell-deficient mice displayed pronociceptive effects. Mice receiving fracture mouse immunoglobulin developed increased paw allodynia consistent with chronic pain behavioral patterns. Moreover, the duration of symptoms was consistent with the half-life of the transferred immunoglobulin [42]. Results of this study support that fracture with immobilization can induce regional expression of pronociceptive antigens.

Ultimately, this process may trigger B cell expression of IgM autoantibodies and confer an autoimmune nociceptive response.

Abnormal alpha noradrenergic signaling has also been implicated in CRPS pathogenesis. Patients with long-standing CRPS exhibit serum antibodies directed against the alpha-1a receptor [43]. Furthermore, low-dose intravenous immunoglobulin may improve symptoms in patients with long-standing CRPS [44–46].

Findings supporting an immunological component of CRPS pathophysiology have led to the IRAM hypothesis: "injury-triggered, regionally-restricted autoantibody-mediated autoimmune disorder with minimally-destructive course." Goebel et al. describe the etiology of CRPS as the development of pathogenic autoimmune features in preexisting circulating antibodies with exposure to specific antigens following regional trauma [40].

Psychological Factors

Psychological factors have been linked to the severity and progression of CRPS. Patients with lower baseline anxiety, pain-related fear, and perception of disability have an improved disease course. Patients who exhibit a greater degree of anxiety and kinesophobia are more disabled by their symptoms [47]. The fear avoidance model describes the process by which pain-related fear leads to further disuse and more pain in patients with chronic musculoskeletal pain. As such, coping with pain by resting further contributes to limitations experienced by CRPS patients [48].

Conversely, a large multicenter prospective study failed to show psychological factors, i.e., agoraphobia, depression, and somatization, as predictive of CRPS development [49]. There remains much dispute regarding the psychological component of CRPS disease progression and the role that psychological factors exert on the onset and maintenance of CRPS [50].

Treatment

Although symptoms of CRPS may spontaneously improve, aggressive treatment should not be delayed as progressive worsening of symptoms is associated with poor prognosis. Treatment of CRPS is often challenging and involves a multimodal approach of psychiatric therapy, physical therapy, medical management, and interventional procedures. CRPS is a phenotypically variable disease and a multitude of therapies are utilized to address the variety of physical manifestations. However, because of the heterogeneous nature of the disease, it is difficult to monitor clinical changes in patients undergoing treatment (Table 2).

Table 2 Summary of conclusions from recent systematic reviews regarding efficacy of treatment modalities

Therapy	Evidence-based conclusions on therapeutic utility
Vitamin C	No benefit in preventing CRPS after distal radius fractures [51]
Ketamine	Weak evidence suggests subanesthetic dosing may be safe and efficacious [52].
Physiotherapy	Low-quality evidence suggests benefit with a multimodal approach [53•].
Immunomodulation	Very poor quality studies yield inconclusive evidence [54].
Bisphosphonates	May be safe and effective and safe in reducing pain [55•]
Sympathectomy	Limited data suggests sympathectomy is not effective for reducing pain [33•, 56].
Spinal cord stimulation	High-level evidence supports the role of SCS in improving pain relief, pain score, and quality of life [57].

Physiotherapy

Physical therapy and occupational therapy reduce pain and improve mobility in patients with CRPS, with increased benefits when combined [58–60]. However, physical therapy that is too aggressive may cause pain and lead to increased inflammatory and sympathetic symptoms of CRPS [61].

A 2016 Cochrane review studied 18 RCTs on physiotherapy-based interventions and found that all were of "very low" or "low" quality and at either "high" or "unclear" risk of bias, as per the Grading of Recommendations Assessment, Development and Evaluation approach [53•]. Specifically, the examined trials included studies of graded motor imagery, multimodal physiotherapy, mirror therapy, tactile discrimination training, stellate ganglion block via ultrasound and pulses electromagnetic field therapy, and manual lymphatic drainage. Higher-quality RCTs are needed to determine the impact of physiotherapy-based interventions in patients with CRPS1 and CRPS2.

Spinal Cord Stimulation

When other more conservative therapeutic modalities fail to provide adequate relief and improve quality of life, it has become common practice to use spinal cord stimulation (SCS) for the treatment of CRPS. After treatment, angiogenic growth factors including VEGF decrease in the affected extremity, suggesting improvement in tissue hypoxia [62]. In one study, 95% (19/20) of patients were satisfied with their SCS treatment after 5 years [63].

A retrospective study evaluating the long-term effects of SCS on patients over a mean follow-up period of 88 months found that SCS was most effective within the first year of disease onset and in patients under 40 years of age [64]. Many patients decreased their usage of anticonvulsants, antidepressants, and/or NSAIDs by at least 25% and reported improvements in pain, quality of life, and functional status [64]. However, treatment did not prevent progression and all patients experienced contiguous spread with progressive enlargement of the initial affected area [64, 65].

A recent review of SCS therapy for CRPS, conducted by Visnjevac et al., evaluated the outcome specific efficacy of SCS, focusing on perceived pain relief, resolution of clinical manifestations, and improvement in quality of life [57••]. The group conducted a review, including all randomized control trials, prospective observational studies, cohort studies, and case reports in their analysis. A total of 19 studies were identified, spanning from 1989 to 2015. Effectiveness of the treatment on improving each outcome measure was scored from 1A+ to 2C−. Ultimately, they found SCS therapy to have a positive effect on patients' perception of pain relief (1B+), quality of life (1B+), and overall satisfaction (2C+).

Ketamine

Ketamine is an N-methyl-D-aspartic acid receptor antagonist involved with central sensitization and nociceptive pain, and has been used to treat chronic pain syndromes including CRPS, postural orthostatic tachycardia syndrome, and cancer [66–69]. Ketamine treatment imparts analgesic benefit and can decrease opioid requirements [70, 71]. However, ketamine may have neurologic, cognitive, and psychiatric effects [72, 73]. In addition, administering ketamine may induce mania, as described in two case reports. Notably, the patients in both reports had a history of depression and opioid use; potential interactions of ketamine with opioids and antidepressants must be considered [74, 75].

Connolly et al. conducted a 2015 review of ketamine for CRPS and concluded that there is weak evidence for the role of ketamine in CRPS treatment and that higher-quality randomized control studies should be conducted [52]. Furthermore, a 2016 study found that initial improvements in pain only lasted 1.5–2.5 months before returning to baseline [76].

Intrathecal Baclofen

Intrathecal baclofen (ITB) has been used successfully to treat patients with intractable CRPS [77]. Baclofen, most potent when injected intrathecally, stimulates the gamma-

aminobutyric-acid B receptor on primary afferent fibers and acts on dorsal horn nociception units to inhibit neuronal transmission [78, 79]. ITB reduces pain as well as improves dystonia and quality of life [80, 81]. A combination of ITB with SCS may decrease pain and improve dystonia in patients with CRPS refractory to conservative treatment [82]. However, a study of 36 patients in 2009 resulted in a complication rate of 38.9%, including nausea and headache as well as more serious adverse events such as baclofen intoxication, psychosis, and depression [80].

Bisphosphonates

Bisphosphonates are commonly used to treat pain related to abnormal bone metabolism in conditions such as osteoporosis, Paget's disease, and metastatic disease. In recent years, a role for the use of bisphosphonates in the treatment of CRPS has been proposed, though enhanced osteoclastic activity in CRPS1 has not been demonstrated [83]. The therapeutic mechanism by which bisphosphates reduce pain remains unclear. Theories by which bisphosphonates impart an antalgic effect include modulation of inflammatory mediators in CRPS1, inhibition of growth and migration of bone marrow cells, and reduction of proton concentration in the bone microenvironment [55•, 84]. In a rat model of CRPS, bisphosphonates effectively inhibited pain, osteoclast activity, and bone loss, leading to a reduction in inflammatory mediators including tumor necrosis factor, IL-1, IL-6, and nerve growth factor [85]. Human clinical trials have similarly demonstrated that the use of bisphosphonates reduces pain in patients with CRPS, though a Cochrane literature review conjectured only low quality of evidence of efficacy in comparison to placebo [33•, 55•].

Immunoglobulin Therapy

In light of evidence of an immunomodulatory-based mechanism behind CRPS, immunoglobulin therapy has been employed as a treatment modality. Several small trials have demonstrated benefit of immunoglobulin therapy in CRPS [44, 86]. Subsequent large randomized controlled trials demonstrated no benefit with immunoglobulin therapy [46, 87, 88]. The LIPS trial, a randomized placebo-controlled study, assessed the efficacy of low-dose IVIG therapy in patients with long-standing CRPS. Results concluded that IVIG therapy is not an effective analgesic regimen for CRPS. [88]

Vitamin C

Preventative supplementation of high-dose vitamin C may decrease the incidence of CRPS1 following extremity trauma and surgery [89–93]. The mechanism by which vitamin C mitigates disease progression may occur through reduction of oxidative stress via free radicals. In an animal model of CRPS, administration of vitamin C reduced oxidative stress via the upregulation of antioxidants and decreased CRPS symptomatology [94]. A recent meta-analysis demonstrated that the use of vitamin C decreased the incidence of CRPS1 in patients with distal radius fractures. [92]

Amputation

The extensive myriad of treatment modalities for CRPS1 often fail to achieve a cure. CRPS1 may lead to debilitating pain, contractures, and life-threatening infections. After exhaustion of less-invasive therapy, certain instances leave limb amputation as a last-resort option. Compared to nonamputees, patients who undergo amputation exhibit better pain scores, less disability, improved quality of life, and less depression [95]. The decision to undergo amputation for CRPS1 is controversial, as there is insufficient evidence to support significant benefit of the procedure [4].

Conclusion

Complex regional pain syndrome is an intriguing and challenging disease that is yet to be fully understood. In recent years, discovery of pathophysiologic mechanisms has led to significant strides in the understanding of the disease process. Continued elucidation of the underlying pathophysiological mechanisms will allow for the development of more targeted and effective evidence-based therapy protocols. The development of and improvement upon a classification system will help guide accurate clinical diagnosis. More importantly, more precise classification in the research setting will allow for standardization and homogeneity in research literature. Though advances have been made in improving treatment for patients with CRPS, the condition remains devastating to those afflicted. Further large clinical trials are needed to investigate mechanisms and treatment of the disorder.

Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:
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