Complex Regional Pain Syndrome

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KEYWORDS

• Complex regional pain • CRPS • Causalgia • RSD

KEY POINTS

- Complex regional pain syndrome (CRPS) has been described as pain a patient feels that is disproportionate to the inciting event.
- The diagnosis and treatment of CRPS is challenged by the dynamic nature of its presentation and progression.
- The management that requires therapy and pain modulation is reviewed.

Complex regional pain syndrome (CRPS) has been described as pain a patient feels that is disproportionate to the inciting event. CRPS is, however, much more than pain because it is also associated with autonomic dysfunction, swelling, dystrophic skin changes, stiffness, functional impairment, and eventual atrophy. CRPS has a myriad of other synonyms, including but not limited to reflex sympathetic dystrophy, algoneurodystrophy, chronic traumatic edema, causalgia, neurodystrophy, and Sudeck atrophy. This hyperalgesic disease affects musculoskeletal, neural, and vascular structures more commonly in the upper extremity than the lower extremity.[1,2] The diagnosis and treatment of CRPS is challenged by the dynamic nature of its presentation and progression. The initial presentation may be confused with extraordinary postoperative pain and swelling. In a recent survey of 260 health professionals, half of respondents expressed difficulty in recognizing the symptoms of CRPS.[3] Acute presentation of CRPS pain can present as focal sympathetically maintained pain versus sympathetically independent pain (SMP vs SIP). Although patients with SMP may find initial relief with sympathetic blocks or medication, they may develop into SIP, thereby challenging treatment regimens.[4,5]

Early lack of consensus in diagnostic criteria for CRPS was clarified by the Budapest criteria in 2003. CRPS presentation was clarified as continuing pain, allodynia, or hyperalgesia, changes in skin perfusion, or abnormal sudomotor activity (edema and/or sweating) in the region of pain. These symptoms present with either an inciting noxious event to the nerve, CRPS type 1, or caused by other trauma, CRPS type 2. In 2007, given a tendency for overdiagnosis of CRPS, the Budapest criteria were refined to include the patient's report of at least 1 symptom in 3 of the 4 categories in their history, and display of at least 1 physical examination finding in 2 or more of the following categories: sensory, vasomotor, sudomotor/edema, or motor/trophic (**Table 1**).[6] Since 2007, the literature has recommended that additional efforts be made toward raising awareness surrounding the Budapest diagnostic criteria.[3] In 2010, Harden and colleagues[7] developed a CRPS severity score based on 17 different symptoms valued at 1 point each, which was validated most recently in 2017.

Patients with CRPS commonly describe hyperalgesia with characteristics of burning, searing, shooting, or aching pain. As expected, patients usually present with a greater physical disability

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Table 1
Budapest criteria for complex regional pain syndrome

All of the following statements must be met:
- The patient has continuing pain disproportionate to any inciting event.
- The patient has 1 physical examination sign in 2 of the categories below.
- The patient reports 1 symptom in 3 of the categories below AND 1 sign in 2 of the categories below.
- No other diagnosis better explains the patient's presentation.

Category	Signs/Symptoms
Sensory	Symptoms: hyperesthesias and/or allodynia Signs: evidence of allodynia to light touch, deep pressure, or joint movement and/or hyperalgesia to pinprick
Vasomotor	Symptoms: reported temperature asymmetry and/or skin color changes and/or skin color asymmetry Signs: Evidence of the above symptoms
Sudomotor/Edema	Symptoms: reports of edema and/or sweating changes and/or sweating asymmetry Signs: Evidence of the above symptoms
Motor/Trophic	Symptoms: Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) Signs: Evidence of the above symptoms

Adapted from Harden RN, Bruehl S, Stanton-Hicks M, et al: Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007; 8: pp. 326-331.

and have significantly more intense phenotype when compared with neuropathic pain of the extremities.[8] Innocuous stimuli frequently trigger allodynia caused by central pain sensitization of the neurons. Motor changes can include decreased range of motion, joint stiffness, weakness, tremor, and dystonia.

Thermoregulatory dysfunction seen in CRPS presents with distinct vascular dysregulation patterns. The body part in question has series of color and temperature changes. The skin can appear erythematous, hyperemic, blue, purple, pale, or mottled all within minutes of each other. Digit and hand swelling is accompanied with joint stiffness and disuse. Trophic skin and nail changes, including an increase or decrease in hair and nail growth with associated hyperkeratosis, are often seen within 10 days of onset in 30% of CRPS type 1 presentations.[9] In the first 6 months of the acute phase, patients will experience an increase in perfusion consistent with a warm regulation pattern. As the pathology continues to progress, patients may experience a cold regulation pattern, with intermittent changes of intermediate dysregulation throughout the course of disease.[10] Heat and cold aggravate the pain. Other trophic changes of the skin may be significant for discoloration, abnormal sweating, or thermoregulatory dysfunction.[11] The physical examination of a patient with concern for CRPS is often significant for extensive sensory dysfunction, variable in both temporal progression and severity of symptoms.[11] Although focused examination may occasionally identify the etiology of an underlying disorder such as a compression neuropathy, the patients' presentations have many manifestations, which mask potential focal etiology. It is crucial to evaluate for compression neuropathies from cervical nerve compression and thoracic outlet syndrome to more distal peripheral nerve compression. In a recent review of sensory abnormalities using quantitative sensory testing methods, light touch correlated with pain outcomes in CRPS.[11] The Budapest criteria has actually published a template with a rating scale of 0 (not severe) to 4 (very severe) to aptly capture each clinical symptom as described by the patient, and physical examination findings as identified by the provider.[7]

Unfortunately, to date there are no serum markers or standard laboratory findings to help with the diagnosis of CRPS despite best attempts, which have included identifying experimental microRNA signatures that are significantly elevated in patients with CRPS.[1,12] Thermography is the most common imaging modality, although large thermal differences in measurement do not appear to correlate with the severity of pain.[13] Sudeck atrophy is a known historical description of plain film radiographic findings consistent with

CRPS that include diffuse osteopenia with juxtacortical demineralization, and subchondral cystic changes that are actually determined to be commonly seen with any trauma.[14,15] Ultrasound has been used to characterize radiographic differences in muscle tissue and identify key areas of distortion in patients with CRPS. Ultrasound can identify focal or generalized muscle edema or dystrophic changes seen in CRPS. These findings are not present in neuropathic pain syndromes or in the normal resting muscle tone in asymptomatic patients.[16]

Although CRPS can occur following a variety of inciting events, fractures overall were the most common inciting event leading to CRPS type 1, specifically those of the distal radius and ulna.[2,17] Application of tight casts was also determined to be a secondary cause of type 2 CRPS.[18] Common hand and arm injuries or routine surgeries with no apparent complication can incite CRPS. CRPS affects female individuals at least 3 times more frequently than male individuals.[2] In the pediatric population, CRPS is most common in girls around the age of 12, and was found to be more frequently found in the lower extremity.[19] Any nerve irritation or injury can incite CRPS. The more common nerve injuries causing CRPS identified include injury to the palmar cutaneous branch of the median nerve during carpal tunnel release, injury to the superficial branch of the radial nerve during surgical approaches to the first and second extensor compartments, and trauma to the dorsal cutaneous branch of the ulnar nerve when approaching the distal ulna for fracture fixation.[20]

Although the etiology behind the pathophysiology of CRPS is unknown, the pain pathway extending from peripheral nociception to central nervous system modulation of stimuli is highly sensitized and overactive, disrupting the surrounding autonomic response.[21] Following an inciting disruption of the peripheral nervous system, it is hypothesized that neuropeptides, substance P, and calcitonin gene-related peptide, among other chemical modulators, evoke surrounding neurogenic inflammation and catecholamine sensitization.[10,22] Following the persistent hyperactivation of the peripheral nervous system, it has been demonstrated in animal models that central nervous system sensitization decreases the threshold for response to stimuli.[21,23]

Although transient pain following any trauma or an inciting event is expected, the persistent and prolonged nature of the presentation of CRPS is abnormal.[24] An essential component of this particular pathogenesis is due to autonomic features of the sympathetic nerve system in which alterations of receptors, specifically an upregulation of adrenoceptors and reduced cutaneous nerve fiber density, appear to contribute to sympathetic maintained pain.[25] More extensive discussions of the physiology of pain are covered in Greg I. Lee and Michael W. Neumeister's article, "Pain: Pathways and Physiology," in this issue. It is important to note that there is not a distinct psychological component to CRPS, or associated personality disorder, and patients' symptoms should be addressed and worked up accordingly; however, the debilitating nature of the disease can lead to psychological comorbidities and significant psychological burden.

The treatment of patients with CRPS should be proactive in nature, patients should be seen frequently, and a multidisciplinary approach should be applied to the patient's management.[3] The management should be multidisciplinary, to include the involvement of physical and occupational therapists, pain clinic, primary care provider, psychological therapists, and case workers. Manual therapy has been shown to reduce oxidative stress and pain behavior in a murine model.[26] Acupuncture[27] and biofeedback[28] also may be useful to reduce pain, increase mobility, and ultimately improve functionality of the extremity. A Cochrane review in 2016 identified the greatest rehabilitation benefit from mirror therapy and graded motor imagery, which both significantly improved the patient's pain and quality of life.[29]

The treatment methodology can be divided into acute and chronic stages of CRPS (**Fig. 1**). Before the development of atrophy and contracture, acute treatment protocols should focus on alleviating pain, managing edema, and correcting any compressive or neuropathic abnormalities. Pain control should be prioritized starting with a focus on the peripheral nature of the disease, including local anesthetic blocks.[30,31] At early onset of symptoms, high-dose steroids coupled with a rapid taper have been shown to have good success; as an alternative for those not in the acute phase, a long-term low-dose course of steroids have also been considered beneficial.[32] Tramadol has been proven, given its dual action on mu opioid receptors and serotonin/norepinephrine reuptake.[33] Neuropathic medications, such as gabapentin, have shown evidence of pain reduction in patients with CRPS.[34,35] Medications commonly used in chronic pain management include antidepressants, such as selective serotonin reuptake inhibitors and tricyclic antidepressants.[36] In addition, ketamine gel application may play a role in pain relief. Similar to the treatment of chronic pain, management with intravenous ketamine has been associated with pain relief and

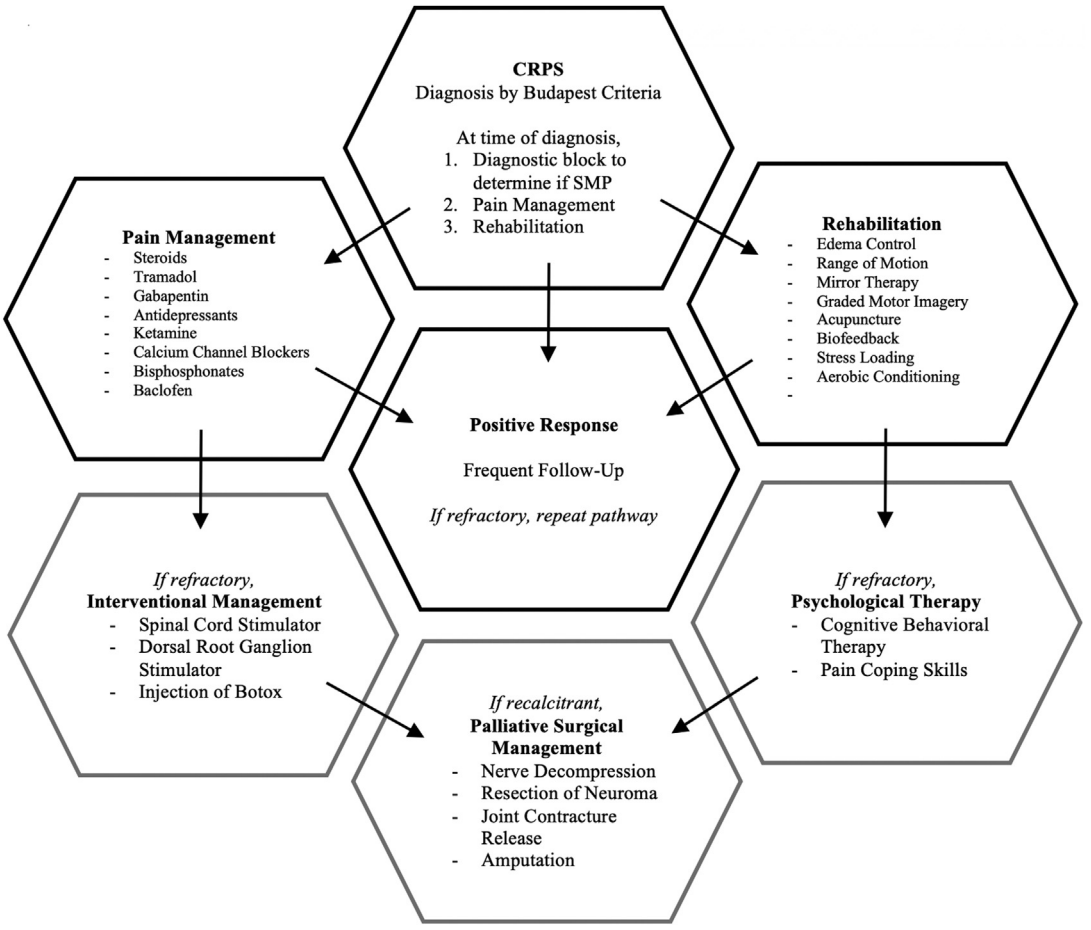

Fig. 1. Flow diagram of CRPS therapy guideline.

improvement of autonomic symptoms while under guidance of professionals.[37]

Other pain regimens directed at limiting the autonomic aspect of CRPS are commonly prescribed off-label. Adrenergics, such as phentolamine, have been shown to decrease pain for patients[38]; when patients experience relief after intravenous administration of phentolamine, it is pathognomonic for SMP.[4] In patients with edema and hyperalgesia, clonidine may provide patients with significant improvement.[39] Anticonvulsants, such as Dilantin, have been used to treat CRPS given their ability to stabilize hyperexcitable neurons.[34] Calcium channel blockers blockade of the sarcoplasmic reticulum and thus calcium, may also decrease sympathetic tone by stabilizing the cell membrane, which can result in pain relief.[39] Bisphosphonates may be used to prevent bone resorption and long-term effects of stiffness.[33,40] If patients experience significant autonomic effects, such as dystonia, baclofen may provide symptomatic relief.[41]

Interventional pain control has come to play a significant role in the management of CRPS. Sympathetic blockades, despite their short-term alleviation of symptoms, have been used as a diagnostic modality to determine whether CRPS is SMP or SIP (if it works, SMP) defined by temperature measurement or laser Doppler.[41] Spinal cord and dorsal root ganglion stimulators have been used and shown to provide some promise in the relief of pain.[42] Most recommendations suggest that stimulators should be considered earlier in the pain armamentarium.[43] As expected, further research must be performed to determine the safety and efficacy of use in the pregnant population.[44] One intriguing area of research includes proximal injection of Botox for patients with CRPS caused by myofascial pain syndromes.[45,46] Although most evidence in support of Botox are limited in levels of evidence, a recent study in a sample of 20 patients proved Botox effective in reducing self-assessed pain in refractory CRPS, and may be a promising new alternative for treatment.[47,48]

Following the late presentation of atrophy and contracture, a palliative approach may be tailored to the patient's needs for surgical correction of the contracture or deformity. Surgical intervention has historically been avoided unless clear indications such as mechanical or regenerative nerve pathology is identified. Examples of nerve-related pathology that may benefit from surgical intervention include resection of symptomatic neuromas or compression neuropathies.[49] As a last resort, amputation of the extremity with CRPS may be considered given the refractory nature of the symptoms. Amputations in patients with CRPS are controversial, however, and patients must be counseled on the risks of persistent symptoms and recurrence at the stump, and potential for phantom limb pain.[50] Ultimately, patients with amputations have shown consistently better results when compared with those who have not undergone amputation, and it should be considered given the difficult nature of this disease.[51]

DISCLOSURE

Nothing to disclose.

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