



Complex regional pain syndrome

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In 1994, publication of the 2nd edition, “Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms” by the IASP Press (Mersky H, Bogduk N) [1–3] introduced the new name Complex regional pain syndrome (CRPS) I for what was previously described by the term reflex sympathetic dystrophy. Causalgia was renamed CRPS II at the same time. The change in taxonomy was an attempt to remove from the old terminology any mechanistic connotation as the pathophysiology of this clinical entity still remains unclear. Essentially, the diagnosis of CRPS I includes sensory changes (allodynia, hyperalgesia, hypoalgesia) edema, abnormalities of temperature, and sweating. Generally, a history of some trauma or inciting event precedes the onset of these clinical features.

The distinction between CRPS I and II is the evidence of a definable nerve lesion. The signs and symptoms for both conditions, however, are clinically indistinguishable. The differential diagnosis of CRPS I and CRPS II is defined by the IASP criteria (Table 1). Other clinical conditions such as neuropathic pain syndromes, peripheral neuropathies, infectious or inflammatory disorders, and vasospastic disorders must be excluded as potential causes of pain. While the existing IASP criteria do not require evidence of a movement disorder, a recent study by Birklein, et al [4] make a strong argument for including motor signs, trophic changes, and increased sweating as diagnostic predictors.

Recent validation studies have suggested separating criteria for vasomotor signs and symptoms from those describing sudomotor function and grouping motor and trophic changes to improve the diagnostic criteria (Table 2) [5,6].

Clinic features and epidemiology

Women tend to predominate in a range of 60% to 80%, the mean age varying between 36 and 42 years [7–9]. The injury may be minor such as a sprain, or more severe such as a fracture or contusion, in which case an incidence of 10% to 30%

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Table 1

International association for the study of pain (IASP) diagnostic criteria for CRPS I and CRPS II

CRPS I (reflex sympathetic dystrophy) ^a	CRPS II (causalgia) ^b
1. The presence of an initiating noxious event, or a cause of immobilization.	1. The presence of continuing pain, allodynia or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve.
2. Continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event.	2. Evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain.
3. Evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain.	3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.	

^a NOTE: Criteria 2–4 must be satisfied.^b NOTE: All three criteria must be satisfied.

Adapted from Janig W, Stanton–Hicks M, editors. Reflex sympathetic dystrophy: a reappraisal. Progress in Pain Research and Management, Vol. 6. Seattle: IASP Press; 1996, with permission.

has been reported. However, the condition may arise without a known cause or it may arise after microscopic trauma, for example, after immunization. The upper extremity tends to be more frequently affected than the lower extremity in a ratio of approximately 55:45 [5,7,8].

Pain is the cardinal feature of CRPS and is defined as pain that is “out of the ordinary” and seemingly not compatible with the clinical signs. The pain is mostly described as burning, deep-seated, aching and occasionally shooting in nature. This is frequently associated with severe sensitivity—allodynia or hyperalgesia [10].

Table 2

Frequency of signs and symptoms among CRPS patients^a

Variables	Signs (%)	Symptoms (%)
“Burning” pain	NA	81.1
Hyperesthesia	NA	65.1
Temperature asymmetry	56.3	78.7
Color changes	66.4	86.9
Sweating changes	24.2	52.9
Edema	56.1	79.7
Nail changes	9.3	21.1
Hair changes	8.5	18.7
Skin changes	19.5	24.4
Weakness	56.1	74.6
Tremor	8.8	23.7
Dystonia	14.0	20.2
Decreased range of motion	70.3	80.3
Hyperalgesia	63.2	NA
Allodynia	74.0	NA

^a NA, not applicable. Items were assessed as objective sign or subjective symptoms only.

These evoked sensations are elicited by mechanical stimuli and more frequently by cold than heat [11,12] 33% of patients with CRPS have hemisensory impairment, decreased temperature, and pinprick sensation ipsilateral to their disease [13].

Autonomic features

Most patients present with edema of the affected extremity. This is exacerbated by evoked pain such as physical activity and extreme environmental changes in temperature [3,5]. Temperature asymmetry (between corresponding sides), originally described by Blumberg [14], generally exceeds 1°C, and sweating abnormalities are well documented by Low et al and Birklein, et al [15,16]. The incidence of sudomotor abnormalities in patients exceeds 94% of patients [17].

Trophic changes and movement disorder

Although some form of motor dysfunction in CRPS has been recognized since its original description, this has never been accepted as a primary movement disorder by neurophysiologists. Clinical terms like tremor, dystonia, myoclonus, and reduction in range of motion have all been used to describe the clinical features of patients. This sign has tended to be dismissed as pain induced, posturing, or resulting from psychosomatic attributes. Blumberg [18] has long felt that the motor dysfunction was a primary abnormality and not one secondary to pain. Zyluk [19] described a reduction of strength in 78% of patients. Tremor is reported in from 24% to 60% of patients [17,20]. Myoclonus and dystonia have also been documented [21–24]. Although trophic changes of the integument, such as thinning of the epidermis, a shiny patina and nail changes may occur early in the course of the disease, these may not become apparent until the disease has been present for 1 year or longer. Typical skin changes may be hyperkeratosis, glossy skin, and ulcer formation; changes not unlike those seen in severe arterial insufficiency or in the presence of severe venous engorgement [3]. Atrophy of muscles from disuse with associated tendon contractures generally occurs later in the disease (several months); they can, however, appear earlier in fulminant cases.

Pathophysiology

It is now generally accepted that CRPS is a neurologic disorder affecting both central and peripheral nervous systems. While an inflammatory component, well described by Sudeck in 1902 [24], is clinically evident, there is little agreement as to whether this is an epiphenomenon associated with the neuropathic disorder or whether this might play a primary role in disease causation. Mailis and Wade [25] have drawn an association between Class I and II HLA expression in patients with poor clinical outcome. They determined that HLA antigens were elevated in 90% of treatment resistant patients [25]. Similar genetic characteristics that determine the expression of neuropathic pain have been described in a Murine model [26].

Several studies have suggested a central nervous system hypothesis although the manner in which sympathetic dysfunction and clinical symptoms correlated has not been clarified [10,20,27].

Although a number of hypothetical mechanisms for CRPS have been suggested [28,29] recent experimental data suggest that sensitization of small diameter polymodal C and A delta afferent fibers to noxious stimuli may be the basis for the hyperalgesia that is seen with heat and algescic agents. In addition, central mechanisms may also play a role with sensitization of central neurons (wide dynamic range—[WDR] neurons) that occur after intense peripheral mechanical stimuli or continuous activity in nociceptors [30]. Altered activity in A-beta (low threshold mechanoreceptors) associated with central plasticity, and generally induced and sustained by a peripheral nociceptor activity, is a source of continuing hyperalgesia/allodynia. The role of alpha-1 adrenoceptors in sympathetic efferent or afferent coupling, either directly or indirectly through prostaglandin and alpha-2 adrenoceptor activity, are considered to be responsible for excitation and sensitization of nociceptor afferents [31–34]. The density of alpha-1 adrenoceptors is increased in hyperalgesic skin of CRPS patients [35]. The foregoing observations in the laboratory have tended to support sympathetic dysfunction, at least early in the course of the disease, and also tends to underscore a central hypothesis for this neurologic disease.

Clinical guidelines

In 1998 a group of basic scientists and clinicians met in an attempt to develop an integrated approach to the clinical management of patients with CRPS. The consensus reached was that in the context of a disease, the mechanism of which is not understood, treatment should be developed around functional restoration; perhaps the only modality that has repeatedly proven to be effective in the management of such patients. In fact, most patients will improve as long as sufficient analgesia and symptomatic control can be provided to support this exercise therapy. These guidelines were published in 1998 [36].

While a considerable improvement for the management of CRPS, these guidelines failed to emphasize at which point any particular modality should be used in response to a failure of improvement. In an attempt to address this, a revised guideline (clinical pathway) was published in 2002 [37]. Based on the former premise that rehabilitation is fundamental to the treatment of CRPS [11,38–43], the new algorithm is built around the same functional restoration pathway, but in contrast to the former guideline, it provides the treating physician with an “escape” at any particular step to use whatever modality seems most appropriate and, which when applied temporally, promotes continued improvement.

For treatment of CRPS to be successful three basic measures are required: (1) pain management, (2) rehabilitation, and (3) psychological therapy. Treatment of pain requires great flexibility and a constant application of non-interventional and interventional measures. Standard pharmacologic therapies used for the man-

agement of neuropathic pain are used to treat CRPS, namely, anti-depressants, anti-epileptics, and steroids. Many of these agents that are efficacious such as amitriptyline, gabapentin, and steroids have satisfied randomized controlled prospective trials. Other agents include alpha-1 adrenoceptor antagonists—Terazosin and phenoxybenzamine; alpha-2 adrenoceptor agonists—Clonidine; NMDA receptor antagonists—Ketamine, dextramethorphan and calcitonin have, either individually or in combination, shown promise in the management of symptoms [44–52].

Interventional management

Regional anesthetic procedures such as blocks of the sympathetic trunks or intravenous regional anesthesia and somatic blocks are used to provide pain relief or determine whether a particular patient has sympathetically maintained pain (SMP). This latter symptom, when present, might respond to the use of an alpha-1 adrenoceptor blocking agent, such as Terazosin or phenoxybenzamine for its long-term treatment. Patients with mixed pain or sympathetically independent pain (SIP) might do better with continuous brachial plexus or epidural infusions. It is generally impractical to use single injection techniques for the long-term support of physical and occupational therapy for many of these patients.

More invasive interventions are required when therapy has reached a standstill. Such methods are the use of tunneled epidural catheters and neuro-augmentation [7,22,53–55]. Spinal cord stimulation is used for the treatment of CRPS I and II. Although pain, by definition, in CRPS II occurs outside of the injured nerve territory, treatment by peripheral nerve stimulation can be very successful [8,56–59]. Intrathecal therapy may be required in those cases in which symptoms have not responded to all modalities, including neurostimulation [22].

It should be noted that neurostimulation may not only provide analgesia, particularly from evoked stimuli—allodynia or hyperalgesia, but it may also reduce the level of burning dysesthesia of which many patients complain. Neurostimulation also improves circulation to the affected extremity by (1) block of the sympathetic efferent pathways, and (2) the antidromic release of peptides (eg, calcitonin gene related peptide [CGRP]) in the affected region. Another as yet unexplained response to neurostimulation is the improvement of motor function in the affected limb.

In some patients who have become refractory to all therapies it may be necessary to undertake palliative surgery. Sympathectomy, although controversial, may be useful when an improvement in the microcirculation can be demonstrated by sympathetic block to the affected region, and amputation of the affected limb notwithstanding the almost inevitable development of post amputation pain and phantom limb, may be mandated by the development of osteomyelitis and other severe tissue breakdown in the affected extremity [53].

Psychologic therapy, particularly in children, is essential to assist in the general rehabilitation of patients. Helping the patient with relaxation techniques, imagery, biofeedback, and auto hypnosis coupled with stress management and cognitive

behavioral therapy (CBT) are integral to the overall rehabilitation of patients with CRPS [60–62].

Should Axis I co-morbid disorders like somatoform disease or Schizophrenia be found in a patient with CRPS, these must be treated with appropriate pharmacologic and psychotropic (CBT) therapy. The use of thermal and surface EMG biofeedback techniques may prove equally useful [63,64].

Rehabilitation

Functional restoration involves a multiplicity of modalities, most of which are physical in nature. The manner in which these physical modalities are employed in patients with CRPS is quite different from the rehabilitation measures that are used for the treatment of fractures, sprains, and other sports injuries. In 1987, a specific form of therapy that came to be known as “stress loading” together with “isometric” techniques is especially beneficial for patients with CRPS [39,41–45]. The underlying principle in “stress loading” can be defined as active exercise requiring stressful use of the affected extremity with minimal joint motion. Two exercises are routinely used, scrubbing and carrying—essentially loading the limb with a force directed proximal to the shoulder or hip girdle and distraction or stretching the limb distally. The intensity and duration of these exercises are related directly to the individual patient’s tolerance. Early in the treatment of patients, range of motion is contraindicated. This is to prevent the large A-beta fibers type I and II mechanoreceptors from being activated. Similarly, passive motion exercises are absolutely contraindicated.

Of utmost importance to a stress loading program is the active functional use of the extremity that uses basic principles of exercise physiology: adaptation of the body in response to demand; increased demand on cardiovascular system; increase in musculoskeletal, neural and metabolic systems, all of which are impacted by the pathophysiology of CRPS. While care must be taken not to induce severe pain, any progress in rehabilitation will be limited by the success of analgesic methods. The afferent input associated with loading of the musculoskeletal and neurovascular systems with stress loading exercises may, in part, override the mechanoreceptor activity from types I and II receptors [65].

The vasomotor changes that occur during physical therapy in patients with CRPS may initially in vasoconstriction and regional edema. The response to physical therapy in patients with CRPS has been evaluated by Rosen, et al [66]. The use of video photometric capillaroscopy and laser Doppler flowmetry has been used for this purpose [10]. It has been suggested that the demand of stress loading in patients with CRPS may act primarily on local auto regulatory mechanism or secondary to an effect on the sympathetic nervous system.

The beneficial effect of stress loading on the trophic and other degenerative changes that occur in patients with CRPS can be demonstrated by bone density measurements [67]. In the early stages of CRPS, occupational and physical therapies are essential to facilitate progression along the clinical pathway [68].

At all stages, a therapist can assess the patient's motivation, set goals and request whatever increased analgesia or behavioral support may be necessary to facilitate for progress. Sequential or concurrent application of particular physical modalities, desensitization, progress from isometric exercises to gradual resisted range of motion, and stress loading can be applied to the upper and lower extremities.

Increasing a patient's flexibility by the foregoing measures and focusing on the muscle dysfunction that is an inevitable accompaniment of CRPS is a fundamental goal of treatment. The associated myofascial pain syndrome (MFPS) tends to first affect the distal muscles and with the progression of time, also proximal muscles; in particular, the shoulder or pelvic girdle (depending on whether the upper or lower extremity is involved). Modalities required are trigger point injections, stretch and spray techniques, and the use of electrical stimulation and muscle relaxants. The control of edema may require elevation, massage, JOBST compression pump, the use of diuretics, and in some cases, sympathetic blocks or alpha adrenoceptor blocking agents. In accompaniment with stress loading techniques, general aerobic conditioning and postural normalization is paramount [69]. A team approach is essential to coordinate all of the measures that will be used in the clinical pathway. Patients must be kept motivated and engaged [70–72], and it may be necessary to modify a home or workplace; particularly in respect to the ergonomics and postural requirements, in an effort to achieve the maximum restoration of function. Recreational and vocational therapy should, where indicated, be used concurrently. As stressed earlier in this report, any failure to progress in rehabilitation may require different medications, stronger analgesics behavioral help, or the use of interventional techniques such as regional anesthesia or neurostimulation.

The updated clinical pathway for CRPS is shown in Fig. 1. As described earlier, and can be seen from the Fig. 1, it exemplifies the three principle domains of management, namely, rehabilitation, pain management, and psychologic treatment. Emphasized is the fact that the approach to treatment of CRPS should be interdisciplinary, incorporating the various treatment options that are discussed here. None of the domains can be treated individually, rather all must be addressed simultaneously and in accordance with a patient's particular response to treatment. In no way is there intended to be a particular emphasis in respect to the measures shown in different "boxes", the relative contribution of any particular modality should be determined by a patient's progress or response.

Most patients with CRPS respond well to conservative measures. It is only those patients who prove refractory to conservative treatment or who develop unforeseen and rapid temporal changes that require ongoing assessment and who demand a flexible therapeutic response to keep them engaged in their rehabilitation. Such changes may apply to their rehabilitation, pain control, or psychologic management. For example, when in certain cases, because of the fulminant course the disease takes, and treatment comes to a standstill, neurostimulation, either SCS or PNS should be an immediate consideration to arrest the disease and allow the patient to resume their therapy.

Time is of the essence in the management of patients with CRPS. It was felt reasonable when developing the new clinical pathway to limit the duration of

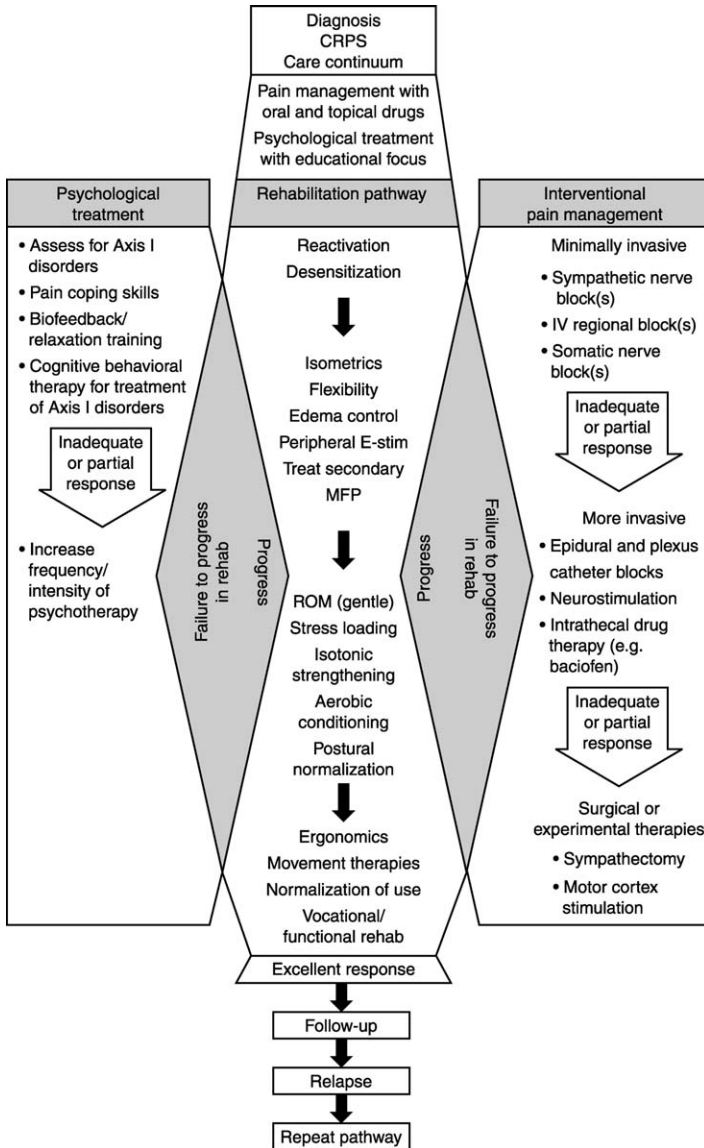


Fig. 1. Clinical Pathway for CRPS.

conservative measures to 12 to 16 weeks as dictated by the clinical state discussed earlier. There is literature in support of the foregoing time frame, but because of the evanescent nature of CRPS and at times completely unpredictable severity that it may assume, some cases will require more invasive interventions [7,22,59,70].

Summary

As suggested by this article, considerable advances in clinical management and research have taken place during the past 20 years. Although mechanisms underlying the pain syndrome CRPS I and CRPS II remain far from one's understanding, glimpses of the pathophysiology are beginning to take shape. There is now strong evidence that these syndromes exemplify a complex neurologic disease involving the brain at several integrated levels. The changes that occur in CRPS I patients involve somatosensory, sympathetic, and somatomotor systems. The diagnostic criteria have helped to focus on aspects of these foregoing systems and whereas there is no specific laboratory test for CRPS, enough is now known about the pathophysiology to use the following tests: quantitative sensory testing (QST), autonomic testing that include quantitative sudomotor axon reflex test (QSART) for sweating abnormalities, the cold pressor test in conjunction with thermographic imaging to observe the vasoconstrictor response, and laser Doppler flowmetry to monitor background vasomotor control. Recognition of a motor disorder requires accurate documentation and may be a component of the diagnostic criteria in the future.

Until a better understanding of mechanistic overtones that would help to put in place mechanism-based therapeutic strategies, current management is built around a rehabilitation model. For this to be successful, as described in the foregoing pages, different non-interventional and interventional modalities are applied in a time-restricted manner to facilitate those modalities that favor progress in the treatment algorithm. As has been described, it is important when using physiotherapeutic maneuvers to minimize joint movement in the affected region to reduce the mechanoreceptor barrage and its increase in perceived pain to encourage and maintain a patient's compliance with their rehabilitation. Finally, of greater significance is the understanding that sympatholysis per se is not a "diagnostic" test for CRPS, but rather a useful procedure that may facilitate treatment for pain that is sympathetically maintained.

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