Complex regional pain syndrome: A review

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ABSTRACT

Complex regional pain syndrome (CRPS) is a challenging neuropathic pain state, quite difficult to comprehend and treat. Its pathophysiological mechanisms are unclear and its treatment is difficult. Multiple factors play a role in the generation and maintenance of CRPS. A close interdisciplinary collaboration amongst the psychologist, physical and occupational therapists, neurologist and pain medicine consultants is necessary to achieve optimal treatment effects. The primary goals of managing patients with this syndrome are to: 1) perform a comprehensive diagnostic evaluation, 2) be prompt and aggressive in treatment interventions, 3) assess and reassess the patient’s clinical and psychological status, 4) be consistently supportive, and 5) strive for the maximal amount of pain relief and functional improvement. This article reviews the different aspects of CRPS including definition, classification, epidemiology and natural history, clinical presentation, pathophysiology and management.

KEY WORDS: Complex regional pain syndrome, Reflex sympathetic dystrophy, Hyperaesthesia, Visual Analogue Scale, Active range of motion

Pain is the most common symptom with which patients seek medical consultation and its management involves tremendous health care expenditure. Nociceptive pain is the pain that all normal human beings can experience as a result of the application of stimuli that produce or have the potential to produce injury or damage to the skin, subcutaneous tissue or internal tissues. Nociceptive pain is a normal sensory experience resulting from the excitation of peripheral sensory detectors, which activate the appropriate spinal cord pathways and their sensory nuclei. On the other hand, many of the pain syndromes are associated with mystifying pain symptoms well outside the range of the sensations produced by the normal nociceptive system, even after serious peripheral injury or inflammation. Such pains, called abnormal, neuropathic or pathological pains are experienced by only a minority of people, and are the consequence of neurological disease produced by damage to the peripheral nerves or to the central nervous system itself. Complex regional pain syndrome (CRPS), trigeminal neuralgia, post-herpatic neuralgia, phantom limb pain syndrome, coccygodynia, etc. are frequently seen neuropathic pain states.¹

Past terminology

The terminology and classification of these chronic pain syndromes was in a state of flux till recently. Syndromes with presumed autonomic dysfunction had been referred to by many names including reflex sympathetic dystrophy (RSD), causalgia, post-traumatic pain syndrome, Sudeck’s dystrophy, reflex neurovascular dystrophy, post-traumatic spreading neuralgia, sympathalgia, shoulder-hand syndrome, etc.²

The first description of chronic pain as causalgia appeared at the time of the American civil war when S. Weir Mitchell, one of the fathers of modern neurology, coined the term causalgia (from Greek) for burning pain.² Sudeck described Sudeck’s dystrophy in 1900.² In 1941, Homans described minor causalgia.³ The term RSD was introduced by Evans as early as 1946.⁴ The International Association for Study of Pain (IASP) had previously defined RSD as “continuous pain in a portion of an extremity after trauma etc.” CRPS is a regional pain syndrome of unclear pathophysiology typically affecting the hand or foot (but may either occur in or spread to other
Two types of CRPS have been recognized: CRPS I corresponds to RSD and occurs without a definable nerve lesion. CRPS II refers to a case where a definable nerve lesion is present and corresponds to the earlier terminology of causalgia (Table 1). The evolution of standardized, consensus-based diagnostic criteria for CRPS constitutes an important step forward in the diagnosis of these pain disorders. These standardized CRPS criteria published by IASP in 1994 are intended to improve the clinical recognition of the disorder. It would also facilitate the selection of an appropriate sample for studying treatment-outcome and spur basic science research in this field. Recent work by Bruehl S et al, raised concerns about the internal validity of IASP criteria for CRPS suggesting that although sensitivity was quite high, specificity was poor and a positive diagnosis of CRPS was likely to be correct in as few as 40% of the cases. They proposed modifications to the IASP criteria. These modified criteria (Table 2) may help improve external validity and differentiate between CRPS and non-CRPS groups. The efficiency of the diagnosis was optimised by the presence of at least one symptom in each of the four categories and one sign in two or more of the four categories.

Clinical experiences have shown that the sympathetic nervous system is linked to the maintenance of CRPS in a subset of patients. Roberts introduced the term ‘Sympathetically Maintained Pain (SMP)’ to describe that aspect of pain which is relieved by blockade of the efferent sympathetic nervous system. In contrast, ‘Sympathetic Independent Pain (SIP)’ refers to that aspect of pain which is unresponsive to sympathetic blockade.

### Epidemiology and natural history

The epidemiology and natural history of CRPS are poorly understood due to the diversity of clinical presentation. The mean age of CRPS patients ranges from 36-46 years with women predominating (60-81%). Although unusual, it has also been reported in the paediatric age-group. The upper extremity is involved in 44-61% of cases and the lower extremity in 39-51%. The aetiology is typically an injury (often minor), fracture in 16-46%, strain or sprain in 10-29%, post-surgery in 3-24%, and contusion or crush injury in 8-18%. The aetiology remains undetermined in 2-17% of cases.

The review of CRPS treatment strategies suggests that the reported outcome regarding pain relief, functional capacity and disease remission is suboptimal. A retrospective study of 146 patients found that although 64% of patients had a good outcome, only 29% were pain-free and only 15% had grip strength >15% of normal. In one series of patients with CRPS, 64% of cases with severe pain lasting over 12 months had severe impairment and rated their pain ‘7’ on a 10-point visual analogue scale. Results from a self-report questionnaire of 31 patients showed that CRPS continued to interfere significantly with general activity, normal work, mood and recreational and social activities.

### Clinical presentation

#### Sensory signs and symptoms

Excruciating pain and hyperaesthesia are the predominant sensory symptoms encountered. In most patients, the pain is of burning, aching, pricking or shooting type and is localized deep to the somatic tissue. Evoked abnormal sensations of hyperalgesia, predominantly to mechanical stimuli or upon joint movements or exposure to cold and allodynia (pain from
innocuous tactile stimuli) are frequently present. A cooling stimulus such as a drop of alcohol or acetone in the painful region, may be perceived as painful especially in the subset of patients with predominant SMP. Sensory deficits are common. Rommel and colleagues observed that 33% patients had decreased temperature and pinprick sensations in the affected limb. Thimmimeur et al found trigeminal hypesthesia in 49% of patients who had CRPS with involvement of upper extremity. The corresponding figure in normal subjects and in 49% of patients who had CRPS with involvement of upper extremity. The corresponding figure in normal subjects and other patients is less than 10%. 

**Autonomic signs and symptoms**

Autonomic signs and symptoms present in the form of vasomotor or sudomotor changes. They present as swelling, colour and temperature changes, and sweating abnormalities. Oedema of the affected limb is present in the majority of patients, which gets aggravated by physical load, painful stimuli, temperature changes and hydrostatic pressure. Temperature asymmetry between the affected and unaffected side exceeds 1°C. Sweating abnormalities were observed in 59% of patients with increased production in 94% of these patients. The skin colour of the affected area may be blue, purple or pale.

**Motor and dystrophic signs and symptoms**

Motor dysfunctions in CRPS include weakness, decreased range of motion (ROM), tremor, dystonia and myoclonus. Muscular strength is often decreased. Zyluk observed that 78% of patients had significantly reduced grip strength. ROM is decreased by joint effusion early in the disease and by contractures and fibrosis late in the disease course. Tremors have been reported in 24-60% of patients. Dystonic posturing and myoclonic jerks can also be present in patients with CRPS. Dystrophic manifestations are seen in the form of increased or decreased nail and hair growth in the affected extremity, hyperkeratosis and thin glossy skin.

**Myofascial dysfunction**

Myofascial dysfunction is present in the majority of cases (56 to 61%). It is more prevalent when the upper extremity is affected and is also related to the duration of disease. The pathophysiology of CRPS is not completely understood as yet. Multiple mechanisms are considered to play a role in the generation and maintenance of CRPS. These include neurogenic inflammation, immunological mechanisms, and plastic changes in the sympathetic and central nervous system.

Birklein et al tested the contribution of neurogenic inflammation and neuropeptide release to the pathophysiology of CRPS. They found elevated levels of calcitonin gene related peptide (CGRP) in patients with CRPS. They concluded that increased systemic CRGP levels in patients with acute CRPS suggest neurogenic inflammation as the pathological mechanism contributing to oedema, vasodilatation and increased sweating. However, pain and hyperalgesia in the chronic stage were independent of increased neuropeptide concentration. Immunological mechanisms (such as altered expression of HLA, substance P, cytokines, interleukins etc.) may play a role. Mails et al examined the correlation of Class I and II HLA expressions in 15 patients with poor outcome and found elevated levels of both HLA antigens in 50% of treatment-resistant patients. A retrospective analysis by van der Laan in 1006 patients demonstrated that immunologically-mediated (i.e., infection, oedema) factors were associated with severe complications.

There is considerable evidence supporting the hypothesis that the sympathetic nervous system plays a role in the pathogenesis of CRPS. Up-regulation of α-adrenergic receptors, super-sensitivity of adrenergic receptors, and functional coupling between sympathetic efferent and sensory afferent fibres have been shown to occur. Clinically, patients with Type I CRPS have significant impairment in the sympathetic nervous system function characterized by decreased sympathetic outflow and increased adrenergic responsiveness in target tissues. This alteration of sympathetic function can be generalised. Patients with CRPS have been shown to have an increased density of α1-adrenoceptor in hyperalgesic skin.

There are also data supporting a central mechanism. Rommel et al prospectively studied 24 patients with CRPS I and concluded that functional alteration in central processing might result in motor/sensory impairment in CRPS patients. Mailhofner et al assessed possible cortical reorganization in the primary somatosensory cortex (S I) of patients with CRPS. They found a significant shrinkage of cortical hand representation for the side affected with CRPS. The cortical reorganization correlated with the amount of mechanical hyperalgesia. Schwenkreis et al assessed excitability changes in the motor cortex in patients with CRPS I and showed a bilateral disinhibition of the motor cortex.

**Measurements**

**Pain assessment**

For CRPS, pain assessment is a crucial measurement. In most of the clinical studies on CRPS, single pain rating using Visual Analogue Scale (VAS) is used as primary outcome measure (under the assumption that this is equivalent to multiple rating). The pain intensity changes over time and even during the course of the day. Jensen et al have shown that in patients with chronic pain a single pain intensity rating was the least reliable, whereas three measures of pain intensity per day over the course of four days show excellent internal consistency and validity. But as multiple assessments are impractical both in clinical and research settings, Dworkin et al suggested that patients may be able to assess their own average pain asking them to rate their pain “on average” at a single point in time. Forouzanfar et al compared the multiple and single pain ratings in patients with CRPS and showed that both measurements correlate with each other and have excellent agreement. Both ratings demonstrate significant pain reduction after treatment; “recalled average” pain, however, re-
flects greater change in pain intensity.45

**Skin temperature assessment**

Schurmann et al measured skin temperature with infrared thermo-camera after 15 minutes of acclimatization in a temperature-controlled room (21-23°C). The temperature of each fingertip compared with the contralateral limb and the mean of systematic difference was calculated.36 Systematic temperature differences (≥1°C) between the affected and unaffected limbs were seen in only 42% of CRPS I patients. Their findings support the assumption that systematic temperature difference in a thermoneutral environment might be present in CRPS I but could not be taken as a diagnostic criterion, since it is non-specific.36

**Motor assessment**

The active range of motion (AROM) has been classified in four categories (normal, impaired, severely impaired and abolished).36 Electromyogram and nerve conduction studies have also been used for testing motor function.23

**Autonomic function assessment**

Autonomic changes have been assessed by oedema on a 5-point scale (no oedema, localized oedema, localized severe oedema, generalized oedema, generalized severe oedema), by skin temperature, skin colour changes and by increased sweating.36 Sudomotor function can be assessed by the sweat test. The capacity to produce sweat can be assessed quantitatively and qualitatively. The quantitative sudomotor axon reflex test (QSART) is a measure of regional autonomic function mediated by acetylcholine-induced sweating. The thermoregulatory sweat test (TST) is a qualitative measure of regional sweat production in response to elevation of body temperature. A significantly greater sweating response to both the methods of sudomotor stimulus has been reported.27

**Management**

CRPS is a challenging neuropathic pain state that is quite difficult to treat as the mechanisms of pain are not well understood. A close collaboration amongst professionals of multiple disciplines i.e. psychologist, physical and occupational therapists, oncologist, neurologist and pain medicine consultants is helpful in achieving optimal treatment effects. The treatment goal is pain relief, functional recovery and psychological improvement. No one therapeutic modality achieves this goal in all patients, and a scientifically proven cure does not exist. There are several reviews on treatment modalities. They all demonstrate that there is limited to no evidence for the efficacy of any one treatment modality.46-49

Many treatment modalities have been proposed and found to be useful to varying degrees. Results of two meta-analyses have shown that most of them lack scientific basis.46,47 Studies on the role of different strategies for CRPS are difficult to compare because of the heterogeneous inclusion criteria employed, use of inappropriate controls or total absence of control subjects, studies that lack adequate power because of the small sample size employed and lack of blinding or randomisation. In addition, long-term follow-up studies are scarce.

**Guidelines**

The proposed modified guidelines called CRPS clinical pathway, illustrated in Figure 1, centre around the same three domains as in the original: rehabilitation, pain management, and psychological treatment. However, it has been updated to encourage an interdisciplinary, time-contingent guidance that incorporates more recently published treatment options.49 These should be addressed simultaneously, with advanced approaches in each area applied according to the patient’s response to the treatment. The relative contribution of each modality will be determined by the patient’s response and progress.

**Rehabilitation / physiotherapy**

Rehabilitation is the mainstay of CRPS treatment. The concurrent implementation of physiotherapy, pain management and psychological therapies is meant to facilitate a sequential progression through the steps of the rehabilitation pathway. In the early stages of CRPS treatment, occupational and physical therapies are crucial to a patient’s progress through specific areas of the clinical pathway. Adequate analgesia, encouragement, and education about the disease process are essential to ensure the successful application of physical modalities such as desensitisation and isometric exercises.50,51

The next step in the clinical pathway is to increase the patient’s flexibility, beginning with gentle active ROM. The almost inevitable myofascial pain syndrome (MFPS), associated with the affected region, requires the use of stretching, strengthening and postural correction, and may require trigger point injections (TPIs), electrical stimulation, and muscle relaxants. These measures are supported by anecdotal data, and have not been validated by randomised prospective trials. Oedema control may require elevation, retrograde massage and use of Jobst compression pump.

Successive steps in the pathway as stated above involve stress loading, scrubbing techniques, isotonic strengthening, general aerobic conditioning, and postural normalisation.52 Coordinated team intervention will usually be required to keep a patient motivated and engaged.53 The final steps of the pathway involve normalisation of use, assessment of ergonomics and posture, and implementation of the required modifications at home and workplace. Complementary recreation therapy and vocational rehabilitation will encourage ongoing and normalised use of the affected limb.

**Psychological therapy**

The recent consensus report of the IASP recommends that patients with pain that is less than 2 months in duration generally do not require formal psychological intervention.49 The panel of experts recommended that after 2 months, patients with CRPS should receive psychological evaluation, including psychometric testing, to identify and treat psychological dis-
orders, such as anxiety, depression, or personality disorders. All factors that contribute to patient disability should be determined. Counselling, behavioural modification, biofeedback, relaxation therapy, group therapy, and self-hypnosis should be considered. Therapies aimed at improving patient motivation and coping skills are necessary. Meta-analysis by Morley S et al concluded that published randomised control trials provide good evidence for the effectiveness of cognitive behavioural therapy and behaviour therapy for chronic pain in adults. It should be borne in mind that psychological treatment of chronic pain is complex and lengthy and provides variable results.

**Pain management**

Pain is the fundamental symptom of CRPS management. A plethora of pain management techniques are available, from the less invasive pharmacological management to the more invasive technique of neuro-stimulation.

**Pharmacological management**

A few placebo control trials have determined the therapeutic efficacy of different analgesics for patients with CRPS. Corticosteroids proved to be effective analgesics in several trials with early CRPS patients. Christensen et al showed that prednisolone (30mg/day for up to 12 weeks) was more effec-
tive than placebo in treating CRPS patients.63 Braus et al used methylprednisolone 32mg/day (for 2 weeks and then tapered over the next 2 weeks) in CRPS patients and the drug demonstrated decreased pain after 4 weeks.55

Calcitonin administered subcutaneously or by intra-nasal spray over 3-4 weeks had mixed results in early CRPS, with two studies finding no difference between calcitonin and controls56,57 and one study showing benefit after calcitonin treatment.38

Intravenous systemic phentolamine studies have had conflicting results. One trial found that 45% of patients had significant short-term relief69 but a much larger trial demonstrated that only 9% patients had significant relief.60

A randomised controlled trial has demonstrated that prophylactic use of ascorbic acid (vitamin C) produces a significant reduction in pain in CRPS after surgical correction of Colles’ fracture.61 Alpha-1 antagonists (terazosin62 or phenoxybenzamine63-64) have been reported to be effective in the treatment of SMP by regional anaesthetic block. However, a recent meta-analysis of medical therapies aimed at inhibiting sympathetic function failed to establish the utility of sympathetic blockade.65

Recently, intravenous infusion of alendronate (alendronate bisphosphonate in the dose of 7.5mg dissolved in 250ml of saline daily for 3 days), a powerful inhibitor of bone resumption, was shown to be effective in decreasing pain and swelling, and increasing ROM in patients with CRPS in a randomised controlled trial.66

**Minimally invasive techniques**

Interventions that interrupt sympathetic nervous system or adrenergic receptor functions like sympathetic block, intravenous regional block (IVRB) and somatic nerve block were advocated as treatment for CRPS with SMP. Despite popular opinion, there is little evidence-based information regarding the proper timing, number, necessity or appropriateness of nerve blocks for the diagnosis and treatment of CRPS. Nerve blocks are recommended primarily to reduce pain and facilitate physiotherapy and functional rehabilitation.61 Nevertheless a retrospective study showed that the prophylactic use of stellate ganglion blocks in patients with previous history of CRPS decreased the recurrence rate of disease from 72% to 10% after re-operation of affected extremity.67 In their reviews of various treatment modalities Kingery et al68 and Tanelian et al69 reported only limited support for intravenous regional anaesthesia, although investigators assessed numerous agents. Intravenous regional blocks (IVRB) with guanethidine are ineffective analgesics compared to placebo and no treatment.69, 70 Two trials with reserpine did not demonstrate any analgesia.71,72 IVRB with bretylium has been used in a few trials.74-77 Bretylium provides significant longer analgesia (20±18 days) than lidocaine (2.7±4 days).77 Analgesia has been reported to last for three weeks following several ketanserine blocks.77 Verification of these findings through larger randomised controlled trials is needed before definite conclusions can be drawn.

**Epidural drug administration**

If a patient fails to progress in a rehabilitation pathway, or has inadequate or partial pain relief, more invasive procedures should be used. Tunneled epidural catheters may be used for providing prolonged somatic or sympathetic blockade, if the patient has had a partial response to sympathetic nerve blocks. Epidural clonidine and ketamine have been reported to be beneficial in patients with CRPS.78-83

**Intra-thecal drug delivery**

Intra-thecal drug delivery is used in patients who have a significant component of dystonia, failed neuro-stimulation and longstanding disease or need palliative care. A recent study demonstrated the effectiveness of intra-thecal baiopen in the treatment of CRPS-associated dystonia.88 Kanoff, administering intra-spinal morphine to 15 patients with intractable and chronic pain (5 with CRPS), reported good to excellent pain relief in 11 patients with few complications.83 Validation of the foregoing data is needed.

**Neurostimulation**

Neural stimulations has been considered late in the treatment of CRPS, with both spinal cord stimulation (SCS) for CRPS Type I84,85 and peripheral nerve stimulation (PNS) for CRPS Type II.86,87 Forouzanfar et al investigated the long-term effects of cervical and lumbar SCS in patients with CRPS I in 56 patients. The pain intensity was reduced at six months, 1 and 2 years after implantation. There was no difference in pain relief and complications between cervical and lumbar SCS.86 Kemler et al performed a randomised trial with two years follow-up of 36 patients for the effect of SCS in patients with CRPS. They reported that SCS results in a long-term pain reduction and health-related quality of life improvement.87

Recent reports have indicated a more consistent response of SCS in CRPS. In one series, six patients with causalgia responded to SNS and SCS.88 Hasenbush and colleagues89 reported favourable results in a prospective trial of 32 patients with CRPS. The authors concluded that SCS provided good relief from pain that is limited to the distribution of a major peripheral nerve.

**Sympathectomy**

CRPS refractory to conventional measures may be considered for surgical or experimental therapies. Sympathectomy may be considered in patients with SMP who respond to sympathetic blockade via regional anaesthetic technique. The phenomenon of SMP in CRPS must be confirmed by regional anaesthetic procedures before sympathectomy can be considered in the treatment of CRPS.90,91 Radiofrequency sympathectomy has been used for the treatment of CRPS only in anecdotal reports.92,93 The role of sympathectomy in the treatment of CRPS is controversial. Few studies support its role with a satisfactory outcome.90,91 However, a potential risk of sympathectomy is the development of post-sympathetic neuralgia, which may represent denervation supersensitivity of adrenergic receptors.94-96 The role of sympathectomy in the treatment of CRPS needs to be determined by conducting large,
Experimental therapies (deep brain and motor cortex stimulation)
Motor cortex and deep brain stimulation (DBS) may be considered as experimental options. Brain stimulation involves stimulation of the thalamic sensory nucleus and/or peri-ventricular or peri-aqueductal grey. A review of DBS literature shows that 30-40% of patients with intractable neuropathic pain have been adequately controlled. However, there is no study specifically evaluating DBS for CRPS. A more recent brain stimulation technique involving motor cortex stimulation has provided early promising results for the treatment of neuropathic pain. Nguyen et al reported data from a prospective study of 32 patients with refractory central and neuropathic fascial pain who were treated with chronic stimulation of the motor cortex. Seventy per cent of patients with central pain and 75% with neuropathic fascial pain had substantial pain relief. More data and research are required for establishing the efficacy of brain stimulation. The epidural motor cortex, also being used for the treatment of central pain is safer, less invasive and easier to perform than DBS.

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