# Complex Regional Pain Syndrome

# 23

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**Key Concepts**

- Complex regional pain syndrome (CRPS) was formerly called reflex sympathetic dystrophy (RSD), "causalgia," or reflex neurovascular dystrophy (RND). As a result of a special consensus workshop in 1993, the term CRPS was adopted to describe a chronic systemic disease characterized by severe pain, swelling, and changes in the skin. This term does not imply any understanding of its mechanism.
- A large population-based study showed that the estimated overall incidence of CRPS was 26.2 per 100,000 person-years. Females were affected at least three times more often than males. The highest incidence occurred in females in the age group of 61–70 years. The upper extremity was affected more frequently than the lower extremity, and a fracture was the most common precipitating event even though it could occur after any type of injury, or even spontaneously.
- CRPS can be described as a painful inflammatory condition that occurs in most cases after trivial trauma to an extremity. The sympathetic nervous system is in some way involved with its pathophysiology. Neuropeptides, substance P, and CGRP, antidromically released from sensory terminals in the skin, evoke dilatation and protein extravasation in the tissue. The resulting signs – reddening, warming, and edema – are termed *neurogenic inflammation*.
- The diagnosis is essentially based on four different diagnostic categories – *sensory* (hyperesthesia, hyperalgesia, allodynia), *vasomotor* (temperature asymmetry and/or skin color changes and/or skin color asymmetry), *sudomotor/edema* (edema and/or sweating changes and/or sweating asymmetry), and *motor/trophic* (motor dysfunction and/or trophic changes). However, not all categories have to be met for each patient.
- The principals of therapy as currently recommended cover standard medical treatment used for neuropathic syndromes and other interventions directed at the current pathophysiology that may be necessary.

The original term to describe this syndrome reflex sympathetic dystrophy (RSD) was proposed by Evans in 1946. It was thought at the time that sympathetic hyperactivity underlies the signs and symptoms of the condition. However, many patients do not respond to sympathetic blocks; there is no evidence for a reflex mechanism, and dystrophy only occurs in a very small subgroup of patients. In 1993, as a result of a

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special consensus workshop, the name of the syndrome was changed to complex regional pain syndrome (CRPS), a term that did not imply any understanding of its mechanism. Because some patients respond to block of the sympathetic nervous system to the affected extremity, the relief of pain that follows is termed sympathetically maintained pain (SMP). If no relief of pain occurs, the term sympathetically independent pain (SIP) is used. It is however understood that both SMP and SIP to a varying degree may coexist in the same patient. See Fig. 23.1.

## Epidemiology

The largest study of 100,000 persons was undertaken in the Netherlands where a peak incidence of 61–70 years of age was found. The higher age range was most likely due to the occurrence of fractures at an older age which, together with sprain, is the most common cause of CRPS. The most recent study done in 2012 found that 7% of patients develop CRPS Type 1 after their injury and that none of these patients were free of symptoms 1 year later: 596 patients comprised this series. Two recent studies have found there to be no psychological factors or personality traits that predispose an individual to the development of CRPS Type 1.

## Pathophysiology

CRPS can be described as a painful inflammatory condition that occurs in most cases after sprain or fracture and in a few cases after trivial trauma to an extremity. Our current understanding is that the sympathetic nervous system is in some way involved with its pathophysiology. The expression of α1-adrenoceptor mRNA was upregulated in DRG neurons after peripheral nerve injury or inflammation typical with that seen in CRPS Type 1. An increase in α1-adrenoceptors was seen in hyperalgesic skin of patients with CRPS Type 1. Inflammation is normally marked by a typical response of immune cells such as lymphocytes, phagocytes, and mast cells. These secrete proinflammatory cytokines. CRPS patients are associated with an increase in proinflammatory cytokines, TNF-α, IL-1β, IL-2, and IL-6, in local blister fluid, circulating plasma, and cerebral spinal fluid (CSF). Proinflammatory cytokines excite nociceptors and can induce long-term peripheral sensitization. Also found is an increase of calcitonin gene-related peptide (CGRP).

What is now known is that neuropeptides, substance P and CGRP, antidromically released from sensory terminals in the skin evoke dilatation and protein extravasation in the tissue. The resulting signs – reddening, warming, and

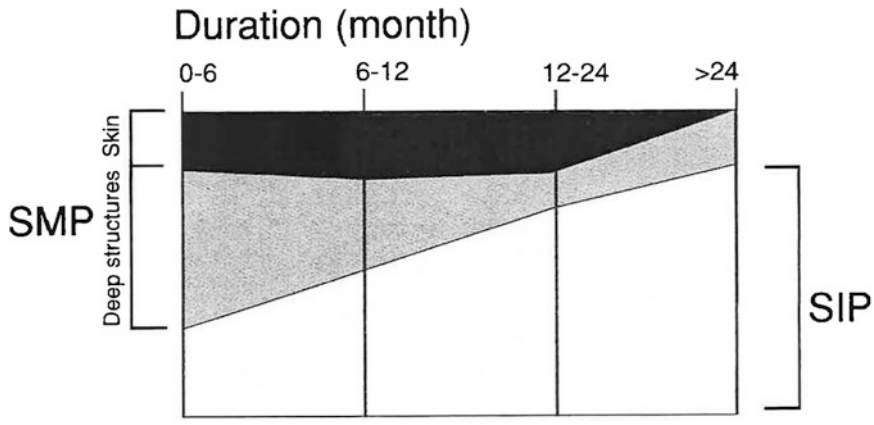


**Fig. 23.1** The relationship between sympathetically maintained pain (SMP) and sympathetically independent pain (SIP) during the course of the CRPS. Also shown, the components of deep somatic sympathetic innervation (deep SMP) and superficial SMP (With permission: Wolters Kluwer Health, Inc., Jörn Schattschneider, Andreas Binder, Dieter Siebrecht, et al., Complex regional pain syndromes: the influence of cutaneous and deep somatic sympathetic innervation on pain. *Clin J Pain*. 2006;22(3):242, Fig. 1)

edema – are termed *neurogenic inflammation*. The importance of neuropeptides in CRPS pathophysiology is the recent association with the antihypertensive medication angiotensin converting enzyme (ACE) inhibitor therapy. ACE is responsible for metabolizing bradykinin and substance P to the inactive form and its inhibition leads to higher tissue levels of both neuropeptides and a possible increased risk for CRPS. The recent studies on lenalidomide and thalidomide emphasize the contribution of inflammation to the metabolic process of CRPS.

The production of free radicals in the affected limb is possibly responsible for the endothelial dysfunction observed in CRPS patients. The impaired endothelial function is a major factor in the pathogenesis of the trophic changes that are found in both superficial and deep tissues. Tissue acidosis is invariably followed by sensitization and activation of nociceptive afferents and therefore spontaneous pain sensation. Increased nociceptive activity will trigger central sensitization which in turn is responsible for allodynia and hyperalgesia. The increased CNS neuronal hyperactivity due to the nociceptive barrage particularly in the dorsal horn is one factor responsible for the pathogenesis of chronic pain in CRPS. Furthermore, temporal summation is significantly greater in CRPS patients because of repeated nociception from thermal and mechanical stimuli in the affected limb.

N-Methyl-D-aspartate (NMDA) receptors also contribute to central sensitization and are the reason why ketamine is used to reduce the associated pain. Another factor in central sensitization is glial activity particularly microglia and astrocytes. These are immunocompetent cells in the CNS which can help to drive and maintain allodynia and hyperalgesia. Glia are responsible for releasing a number of proinflammatory cytokines, nitric oxide (NO), excitatory amino acids, prostaglandins, and ATP. Elevated proinflammatory cytokines (IL-6, IL-β), glial fibrillary acidic protein (GFAP), MCPL, NO metabolites, glutamate, and calcium are found in increasing quantities in the CSF of patients with CRPS. The sensory, somatomotor, and autonomic changes observed in CRPS patients are likely the result of disordered CNS processing. Imaging studies of the somatosensory cortex (S1) have demonstrated reorganization that is related to the severity of pain, particularly the mechanical hyperalgesia found in CRPS. Other cortical changes associated with the motor system are also found in CRPS Type 1 and occur particularly in the primary motor and supplementary motor cortices which are related to the extent of motor dysfunction.

## Interesting Clinical Aspects

The classical description of CRPS that included successive stages has been replaced by three clinical findings (see Table 23.1, Bruehl et al.). Pain however is always disproportional in intensity to what would be expected by the inciting event. Three distinct vascular dysregulation patterns are described:

- Patients with a *warm* type of regulation – generally the acute stage or less than 6 months. There is an associated increase in perfusion of the affected limb in comparison with the contralateral side.
- Patients with a *cold* type of regulation – chronic stage has lower skin temperatures and perfusion values than the unaffected side.
- Patients with an *intermediate* type in which the temperature and perfusion are either high or low depending on the degree of sympathetic dysfunction.

Edema is common in acute CRPS. It has been demonstrated that edema in CRPS Type 1 patients disappeared after spinal anesthesia, suggesting that sympathetic activity may maintain the edema

**Table 23.1** Clinical findings

| | |
|---|---|
| 1. | Vasomotor and motor/trophic changes |
| 2. | Pain and sensory abnormalities<br>Particularly allodynia/hyperalgesia |
| 3. | Florid or all aspects of syndrome<br>Pain may be SMP or SIP<br>Frequently both coexist in a variable manner |

Adapted: Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? *Pain* 2002; 95:119–124.

although the mechanism is unknown. Sympathetic afferent coupling is responsible for the release of peptides from peptidergic afferent neurons with unmyelinated fibers that cause vasodilatation and plasma extravasation.

Motor dysfunction is found in 97% of CRPS patients who were evaluated prospectively. Motor disorders include tremors, weakness, decreased range of motion, dystonia, and incoordination. Dystonia of the lower extremity typically is seen as an equinus foot deformity. In the upper limb it presents as finger flexion.

Patients with extensive hypoesthesia have increased thresholds for mechanical, cold, warm, and noxious heat stimuli. These phenomena are due to CNS changes. Half of CRPS patients can demonstrate these sensory changes in the ipsilateral quadrant or in a hemicorporeal distribution.

Maleki describes three patterns of spread in CRPS Type 1 – contiguous, independent, and noncontiguous such as mirror image spread. Van der Laan et al. described 7% out of 1006 patients developed severe complications of the lower extremity that included ulcers, edema, myoclonus, and dystonia.

## Diagnosis

The standard IASP criteria which were published in 1994 have now been revised to include the following: four different diagnostic categories – *sensory* (hyperesthesia, hyperalgesia, allodynia), *vasomotor* (temperature asymmetry and/or skin color changes and /or skin color asymmetry), *sudomotor/edema* (edema and/or sweating changes and/or sweating asymmetry), and *motor/trophic* (motor dysfunction and/or trophic changes) (Table 23.2). If one sign is observed in two or more of these categories and at least one symptom is described in three of four categories, the resulting diagnosis of CRPS has a sensitivity of 0.85 and a specificity of 0.69. These modified diagnostic criteria (Budapest Criteria) have now been validated. The Committee for Classification of Chronic Pain Terms of the IASP has accepted these criteria for clinical and research diagnosis (Table 23.1). Additional diagnostic tests may be helpful to support the foregoing clinical diagnostic criteria. Because sweating abnormalities are relatively common (24%), they can be assessed by clinical examination. Table 23.3 lists some laboratory tests which may be useful to document the pathophysiological disturbances which occur in CRPS.

## Management Approaches to CRPS

Without a definitive mechanism to address, treatment should follow an interdisciplinary approach that uses whichever modalities that are appropriate to treat the pathophysiology and achieve a restoration of function. Traditional measures that have been determined either by evidence or from experience should be applied in the management of CRPS. However, there is a paucity of evidence-based treatments. Many treatments are taken from experience gained from management of other neuropathic pain syndromes such as postherpetic neuralgia and diabetic neuropathy. The three greatest impediments to treatment that use physical modalities are allodynia, hyperalgesia, and the movement disorder.

Figure 23.2 illustrates the emphasis on rehabilitation, which is the core treatment for CRPS. Essentially the idea is that reactivation of the impacted tissue with desensitization and satisfactory pain management will begin the process of functional return. Because of induced pain resulting from pathological movement and mechanoreceptor dysfunction, it may be necessary to use isometric exercises before any attempt is made to move (range) the affected joint(s). Once early movement is achieved, this should be gradually increased against resistance (rROM). Passive movement is probably counterproductive to return of function. Sometimes it may be necessary to use mirror box treatment and mirror visual feedback (MV1). This has been found successful for both upper and lower extremity movement with laterality training and imaging of the movements by the patient. The premotor cortex may become active without involving other motor cortical areas. Sometimes it may be necessary to couple this with graded

**Table 23.2** *Budapest criteria*. At least one symptom in three of four categories and one sign in two or more categories (SENS. 0.99: SPEC 0.68)

| Category | Symptom | Sign |
|---|---|---|
| Sensory | Hyperesthesia, allodynia | Hyperalgesia (PP) allodynia – Mech./thermal/deep |
| Vasomotor | Δ Skin/color<br>Δ Temperature | >1 °C/Δ skin/color |
| Sudomotor<br>Edema | Δ Sweating/edema | Δ Sweating/edema |
| Motor<br>Trophic | Motor dysfunction<br>↓ROM<br>Δ Trophic | Motor function<br>↓ROM (weak, dystonia, tremor)/trophic |

Adapted: Harden et al. *Pain* (2010);150: 268–274

**Table 23.3** Supplementary tests for CRPS

| Tests | Sensitivity | Specificity | Helpful |
|---|---|---|---|
| 1. Plain x-rays (late in disease)<br>Gradl et al. (2003) | 73 | 57 | No |
| 2. 3-phase bone scan (early disease)<br>Wuppenhorst et al. (2010) | 97 | 86 | Possibly |
| 3. Temperature side differences<br>Wasner et al. (2002) | 76 | 93 | Yes, during sympathetic stimulation |
| 4. Quantitative sensory testing<br>Rommel et al. (2001) | High | Low | Impractical except research |
| 5. Laser Doppler scintigraphy | High | High | Practical if equipment available |
| 6. Quantitative sudomotor axon reflex test (QSART) | High | Fair | Requires special laboratory |
| 7. Magnetic resonance imaging MRI<br>Koch et al. (1991) | 91 | 17 | Impractical |
| 8. FMRI cortical reorganization<br>Maihofner et al. (2007) | Under investigation | | |
| 9. Magnetoencephalography<br>Pahapill et al. (2013) | Under investigation | | |

motor imagery (GMI). It may be necessary to use (GMI) over a period of 6 weeks. The theoretical basis for these programs is still evolving.

CRPS management should be in an interdisciplinary setting where psychological approaches are frequently required to assist patients with their treatment. The use of cognitive behavioral therapy (CBT) is often necessary in the early stages of treatment. The combination of behavioral therapy with CBT and GMI together accelerated the return of function in children. The three principles that should be followed are:

- Education regarding the nature of disease for patients and families.
- Patients whose condition has exceeded 2 months should be psychologically evaluated with or without CBT.
- Any psychiatric comorbidity or other live stressors should also be addressed.

## Pharmacological Management

Any medications that are used for the treatment of patients with CRPS should be given on a symptomatic basis or for the treatment of known pathophysiology. These medications should be

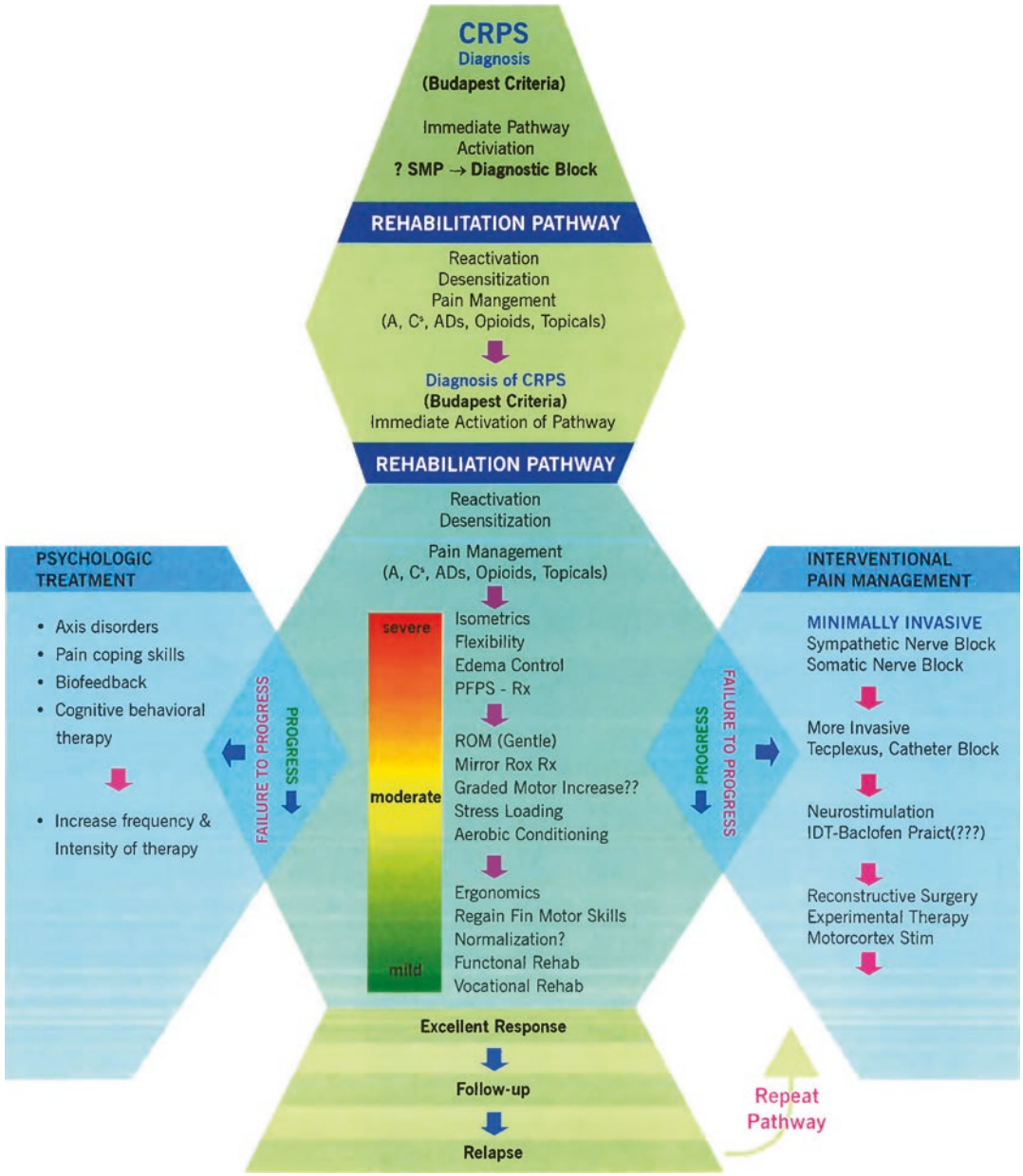


**Fig. 23.2** Modified multidisciplinary care continuum for CRPS. The various treatment modalities are woven into the rehabilitation sequence; these are introduced in a time-contingent fashion. The severity gauge is a guide to the degree with which it may be necessary to introduce the different functional modalities throughout the course of functional restoration (With permission: John Wiley and Sons, Michael D. StantonHicks, Allen W. Burton, Stephen P. Bruehl, Daniel B. Carr, R. Norman Harden, Samuel J. Hassenbusch, Timothy R. Lubenow, John C. Oakley, Gabor B. Racz, P. Prithvi Raj, Richard L. Rauck, Ali R. Rezai. An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. *Pain Practice*. 2002;1–16, Fig. 1)

considered facilitators whereby they assist the patient to undergo physical therapy. It should be understood that there are no FDA approved medications for CRPS. As already stated, many of the drugs used to treat CRPS are those already shown to be effective for other neuropathic pain. The

following medications will be classified under their levels of evidence (Table 23.4).

- Corticosteroids should be tried early – a few weeks – following onset of CRPS. A 10-day tapering dose is frequently associated with immediate improvement of symptoms and well-being.
- Opioid use has not been studied in CRPS. These drugs are useful for treating acute pain and there have been a number of studies supporting their use in postherpetic neuralgia (PHN). Similarly, tramadol, morphine, oxycodone, and levorphanol have undergone blinded crossover studies in which they were found to be more effective than placebo in this indication (Level 2 evidence). There are however no long-term studies of opioid use in the treatment of neuropathic pain. If such drugs are used, they should only be a component of an interdisciplinary program.
- Calcitonin is normally used in the management of bone disorders associated with resorption or increased osteoclastic activity. It has been used to reduce pain in CRPS (Level 1 evidence in a systematic meta-analysis).
- Bisphosphonates have been found useful in providing some analgesia in early CRPS (Level 2 evidence). They are poorly tolerated due to side effects.
- Free radical scavengers (antioxidants) have been used for some 20 years. The basis for their use is damage caused by free radicals in both deep and superficial tissues. Dimethyl sulfoxide (DMSO) is compounded as a fatty cream and has been found effective in a small study of 32 patients.

**Table 23.4** Level of evidence

| Level | |
|---|---|
| 1 | Results of systemic review or meta-analysis |
| 2 | Reflects one or more well-powered randomized controlled clinical trials |
| 3 | Retrospective studies, open-label trials, pilot studies |
| 4 | Anecdotes, case reports, clinical experience |

- Prophylactic vitamin C was shown to reduce the incidence of CRPS in patients with Colles fracture.
- A number of α1-adrenoceptor antagonists have been described in several studies. Phenoxybenzamine (Dibenzyline) was efficacious in 40 patients.
- Antiepileptics have found greatest utility in the treatment of CRPS. Gabapentin and pregabalin are among the most commonly used. Topiramate is a useful alternative to gabapentin and pregabalin because it frequently reduces the weight gain incurred by the former two agents.
- Antidepressants – mainly tricyclic antidepressants (TCAs) – have been studied extensively in the treatment of various neuropathic pains, e.g., diabetic neuropathy (Level 2 evidence). Desipramine, a selective norepinephrine blocker, can reduce pain in PDN and PHN (Levels 1 and 2 evidence). However, no studies of TCAs or serotonin reuptake inhibitors (SSRI) have been studied in CRPS. Antidepressants have some synergy as adjuvant medications with antiepileptics as well as their sedative and antidepressant properties.
- γ-Aminobutyric acid (GABA) receptor agonists may be useful in the treatment of the movement disorder, particularly tremor or dystonia in patients with CRPS. Both benzodiazepines and baclofen (GABA-A and GABA-B agonists) are useful for the treatment of the movement disorder of patients with CRPS. Baclofen may not be efficacious unless delivered by the intrathecal route.
- NMDA receptor blocking agents can be effective in moderating symptoms in either CRPS Type 2 or CRPS Type1. Ketamine, dextromethorphan, and memantine are such agents that have been found useful in the treatment of diabetic neuropathy. There are no prospective studies of dextromethorphan being used for CRPS. Ketamine has been studied in subanesthetic and anesthetic concentrations with promising results.
- Clonidine has been used either via transdermal, epidural, or intrathecal routes and oral

forms. Level 3 evidence is available for the use of transdermal clonidine in a small cohort.
- Topical lidocaine is supported by Level 2 evidence in the treatment of PHN and PDN. These compounds have also been studied in patients with CRPS (Level 3 evidence).

## Interventional Measures

### Sympathetic Blockade

Sympathetic block of the cervical thoracic or lumbar sympathetic chains may achieve complete pain relief in almost 80% of patients. As stated earlier in this chapter, this is mainly a diagnostic procedure to determine whether a patient has SMP or SIP. It is also important to emphasize that a technically successful sympathetic block can only be determined by temperature measurement (a temperature rise to 34 °C+ at a finger or toe pulp) or laser Doppler scintigraphy. There is no support for the continuing use of sympathetic blocks in the treatment of CRPS. If however on receiving a sympathetic block a patient obtains 1 or more weeks of pain relief, it may be useful to undertake another block in order to initiate physical therapy. A successful sympathetic block – meaning the patient has SMP – is supported by studies with Level 2 evidence.

### Neurostimulation

Spinal cord stimulation can be effective in the treatment of neuropathic pain and has been used to treat pain of CRPS since 1987. SCS inhibits the release of dorsal horn excitatory amino acids, glutamate, and aspartate, via a local GABAergic mechanism. SCS also has a β fiber-mediated inhibition at the wide dynamic range (WDR) neurons. Also, antidromic activation of dorsal column fibers induces a presynaptic inhibition of WDR neurons. There are three RCTs and six long-term follow-up studies that support the use of SCS for CRPS.

- The most quoted study by Kemler et al. randomized 36 patients to receive SCS and physical therapy while the remaining 18 underwent physical therapy alone. The neurostimulator was implanted in those cases where the trial was successful. While no material change in function occurred, all patients had an improvement in the quality of life (QOL), and when the same patients were seen 2 years later, the SCS plus physical therapy group had a significant improvement in HQOL compared with the physical therapy group alone.
- In 2009, the health technology assessment under the auspices of the National Institute for Health and Care Excellence (NICE) in the UK published a report that determined the cost-effectiveness and clinical efficacy of SCS for use in treating neuropathic pain, CRPS Type I, and ischemic conditions. The results of SCS were superior to conservative medical management (CMM). A significant savings in cost were also reported.
- SCS has been used to facilitate exercise therapy in an interdisciplinary pediatric pain program. Because of severe allodynia that prevented the use of physical or occupational therapy, SCS as an extended trial for several weeks was used to help children to participate in the program.
- Peripheral nerve stimulation (PNS) has also been used as adjunct to the multidisciplinary treatment of patients with CRPS. In many cases, because SCS may not provide adequate regional analgesia, PNS should be a consideration for such applications.

### Intrathecal Drug Delivery (IDD)

The intrathecal route for drug delivery may be necessary when both CMM and neurostimulation has failed to achieve either remission or symptomatic improvement. The opioids morphine, hydromorphone, fentanyl, and sufentanil have been used either alone or in conjunction with a local anesthetic such as bupivacaine or ropivacaine. Baclofen may be a consideration when dystonia or severe movement disorder of the

upper extremity is associated with CRPS. One study found that baclofen was very successful in the treatment of dystonia in CRPS.

More recently, intrathecal ziconotide, an N-type calcium channel blocker, can be successful in treating neuropathic pain. While the side effect profile of ziconotide prevents many patients from using this drug, it can be successful in a small number of patients (about 35%) and lends support for a trial when other approaches have failed. Ziconotide can be trialed as either a bolus injection or through the use of a small intrathecal catheter over a period of 3 to 7 days.

## Hyperbaric Oxygen

When indolent edema, skin breakdown, and open blisters remain refractory to all treatment measures in the affected extremity of patients with CRPS, hyperbaric oxygen should be considered. The one published RCT demonstrated significant improvement in joint movement and pain reduction in all patients that were studied. This author has experienced the complete resolution of similar clinical features in an adult and child.

## Surgery

Surgery may be required in those patients who as a result of their disorder have developed tendon shortening, restricted ROM of joints, and dystrophic changes that prevent the therapist from achieving a full return of function. For example, the development of an equinus deformity of the foot may require tendon lengthening, and a similar approach may be necessary in the upper extremity. Amputation while not recommended in the treatment algorithm may be necessary for those cases in whom the pathological process is so florid that it is not possible to physically manage a patient or in those cases where osteomyelitis has supervened. These surgical procedures can be safely carried out under a regional anesthetic which from experience appears to prevent an exacerbation of the syndrome.

## Summary

The treatment of CRPS requires an interdisciplinary and multimodal approach as early as possible after the onset of the syndrome. Physical functional maintenance or recovery of physical function should be the primary object of treatment. This approach has been defined by the IMMPACT recommendations that have been validated. Treatments are directed to regaining function, reduction of muscle spasm, and the use of whichever measures are most appropriate to address the associated severe pain. Pharmacological treatment is directed at a particular pathophysiology or current symptoms. Myofascial dysfunction, almost invariably present, together with allodynia and/or hyperalgesia, can adversely interfere with PT and OT, requiring the use of muscle relaxants, analgesics, and antidepressants. Severe allodynia may require a trial of anticonvulsants, desensitization, or some intervention such as SCS. When neurostimulation fails, it may be appropriate to use IDD in particular ziconotide.

Psychological management may be necessary either on an intermittent or continuing basis depending on the individual impact of this syndrome. Understanding the pathophysiology should help to select those medications and measures that will help to minimize the permanent impact of CRPS on affected tissues – severe ischemia, axonopathy, atrophy, skin breakdown, and central nervous system dysfunction.

CRPS in children requires a far greater use of behavioral treatments. In only a very few instances is there any need to use interventional measures (less than 6%). These however should not be withheld in the face of resistant allodynia/hyperalgesia and deteriorating function that prevent the continuing use of physical modalities. Within the foregoing framework, a high response to therapy can be achieved.

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