

Overview of Complex Regional Pain Syndrome and Recent Management Using Spinal Cord Stimulation

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Complex regional pain syndrome (CRPS) is an enigmatic disease process affecting the upper and lower extremities. It consists of various combinations of sensory, autonomic, and motor abnormalities, the pathogenesis of which is unclear. Formally known as reflex sympathetic dystrophy or causalgia, CRPS has a revised taxonomy since 1994.

The International Association for the Study of Pain established 2 categories, type I and type II, based on precipitating events. This syndrome manifests in 3 progressive stages, displaying peripheral and central neurologic aberrancies. The exact triggering mechanism is unclear but appears to involve neurogenic inflammation from axonal damage to small-fiber distal nerves. Central sensitization independent of afferent input and

central somatotopic reorganization may be contributory in successive stages.

Treatment goals are twofold: management of pain and restoration of function. Time is critical, as therapeutic effectiveness is limited in the latter stage. Various treatment modalities, including medication regimens, sympathetic nerve blocks, and physical therapy have met with differing degrees of success. Recent advances in spinal cord stimulation are promising. Although initially costly, this may prove to be the least expensive and most effective treatment in the long term.

Keywords: Central sensitization, complex regional pain syndrome, cortical reorganization, neurogenic inflammation, spinal cord stimulation.

Complex regional pain syndrome (CRPS) is a chronic condition that usually affects both upper and lower extremities. It consists of various combinations of sensory, autonomic, and motor abnormalities. The main symptom is an intense burning pain. Additional symptoms include hypersensitivity, swelling, alterations in skin characteristics, changes in nail and hair growth, muscle atrophy, and decreased mobility in the affected limb. The pathogenesis of this disorder remains unclear. Neurologic symptoms that include both peripheral and central components add to difficulties in understanding this condition.

History and Review of Literature

There are 2 distinct classifications of CRPS based on the precipitating cause of the disease. Type I, historically referred to as reflex sympathetic dystrophy, results from an illness or injury that did not directly damage nerves in the affected limb. Type II, earlier termed causalgia, results from an identifiable nerve injury. Aside from the absence or presence of a clinically evident nerve lesion, the symptoms are similar.

In 1994, the International Association for the Study of Pain revised the taxonomy, as more information regarding CRPS became available (Table).¹ It is reasoned that the term *reflex sympathetic dystrophy* was not an accurate reflection of the disease process, as there was no good evidence to support a reflex arc.² The role of sympathetic

dysfunction presents with a high degree of variability, and dystrophy is observed only in a small subset of patients.²

The exact pathologic mechanism for both type I and type II is not known. However, persistent axonal damage to small-fiber distal nerves appears contributory.³ The disease exhibits 3 stages with variable progression among individual patients. Stage 1 symptoms include severe pain and swelling. Sensitivity to touch and cold, and skin changes may also occur.⁴ This stage lasts approximately 1 to 3 months. In stage 2, the skin changes become more obvious, swelling increases, and muscle and joint stiffening occur.⁴ This stage typically lasts 3 to 6 months. Stage 3 patients exhibit severe, permanent damage, including muscle atrophy, limited movement in the affected limb, contractures of the nearby digits, and irreversible skin damage.⁴

Early diagnosis and aggressive treatment yield the most promising results. In severe cases that are not amenable to therapy, patients have agreed to amputation as a last resort to control their pain. Even this drastic measure is not always successful, as some patients with CRPS experience phantom limb pain after surgical removal.

Complex regional pain syndrome is a multifactorial process that affects several parts of the nervous system. Advances in current research indicate a major role of the immune system in initiating and maintaining CRPS. Antibodies and immune cells involved in any inflammatory event can release or trigger the release of substances such as tumor necrosis factor- α (TNF- α), interleukin-1

Type I (reflex sympathetic dystrophy)

1. The presence of an initiating noxious event, or a cause of immobilization
2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Note: Criteria 2-4 must be satisfied.

Type II (causalgia)

1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve
2. 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

Note: All 3 criteria must be satisfied.

Table. International Association for the Study of Pain Diagnostic Criteria for Complex Regional Pain Syndrome Types I and II

(Adapted from Merskey and Bogduk.¹)

(IL-1), and interleukin-6 (IL-6), thus inciting fundamental components of CRPS. The hypothesis of an aberrant, substance P-proinflammatory cytokine positive loop, explains several alterations associated with this disease. Although in its infancy, such research has also suggested involvement of other types of immune cells, immune-derived substances, and glial cells in CRPS pain modulation.⁵

One definitive factor in the pathology is neurogenic inflammation. This results from either facilitated release of neuropeptides (from primary afferents) or hampered inactivation of these substances.⁶ In addition to their sensory function, C-fibers demonstrate an efferent neurosecretory role. When stimulated, they release calcitonin gene-related peptide (CGRP) and substance P, which result in vasodilation and protein extravasation, respectively.⁶

Research conducted by Birklein et al⁶ examined the role of neuropeptides in patients with CRPS. Results indicate that these patients exhibit increased systemic levels of CGRP, which demonstrate a positive correlation with nerve lesions and degree of trauma. However, CGRP and pain demonstrate no correlation. Thus increased levels of CGRP likely contribute to the vasodilation, edema, and increased sweating observed in the early stages. Additionally, substance P is colocalized and coreleased with CGRP. It increases excitability of spinal interneurons and likely contributes to the motor disturbances demonstrated in CRPS.⁶

Neuropeptides also possess important trophic functions for skin and bone. If an injury ultimately results in denervation, with depletion of these substances, it can result in the thin, hypertrophic skin seen in many patients with longstanding CRPS. Skin samples from such patients, specifically assessed for neural-related proteins and mediators of nociceptive sensory function, demonstrate evidence of widespread cutaneous neuropathologic changes indicative of chronic manifestations of this disorder.⁷

Unfortunately, neurogenic inflammation cannot explain the sympathetic dysfunction noted in most patients with CRPS. Many researchers conclude that inflammation is just an initiating trigger within a multifactorial process. Interactions of the sympathetic nervous

system with damaged sensory fibers and afferent neurons can enhance the sensitized state and may provide the basis for sympathetically mediated pain.^{8,9} Damaged nerve fibers can ultimately “sprout” excessive terminals that result in aberrant communication pathways to sensory nerves. Subsequently, these sites can develop spontaneous activity as well as sensitivity to catecholamines and sympathetic activation.⁵

In an effort to explain symptoms such as allodynia, hyperalgesia, and motor disorders, Alexander et al¹⁰ searched for a mechanism that could explain the impairment of spinal circuits involved in sensory processing and sensory motor integration. Symptoms suggest a central sensitization, independent of afferent input. Animal models of neuropathic pain demonstrate activation of spinal glial cells, resulting in secretion of proinflammatory cytokines. These substances include interleukin-1 β , interleukin-6, and tumor necrosis factor- α . Each of these is capable of exciting pain transmission in neurons. These researchers compared cerebral spinal fluid (CSF) in normal individuals, those with painful conditions, and those with CRPS. Results demonstrated that the CSF from patients with CRPS had statistically significant increases in the proinflammatory cytokines, interleukin-1 β , and interleukin-6, in comparison with the other 2 groups. This result suggests that central neuroimmune activation can explain part of the pathogenesis of CRPS. Determination of the degree of such activation and its affect on neuropathic pain mandates further research.

Many patients with CRPS also exhibit pain-induced reorganization within their somatosensory cortex.¹¹ Cortical reorganization may explain the classic clinical sign of sensory abnormalities with the stocking or glove distribution. Moreover, the amount of central somatotopic reorganization positively correlates with mechanical hyperalgesia and overall CRPS.¹¹ Conversely, those patients manifesting a reduction in CRPS and clinical improvement exhibit a reversal in cortical reorganization.¹²

Discussion of State of the Art

Complex regional pain syndrome manifests as an intri-

cate set of symptoms resulting from a dynamic and progressive disease process. Difficulty arises from the unique combinations of possible symptoms displayed in individual patients. Because these symptoms result from dysfunction within various, yet discrete levels of the nervous system, no direct causative pathology or definitive cure has been realized.

The goals of therapy for CRPS are twofold. Alleviation or management of pain is one priority. Restoration of function is another. Time is an important factor in these goals. Early diagnosis is optimal because the effectiveness of treatment is limited in patients with stage 3 disease. Unfortunately, difficulties arise, particularly in CRPS type 1, because small-fiber axonal damage lacks any familiar motor signs, rendering electromyography insensitive. Furthermore, their action potentials are slow and weak, thus undetectable by nerve conduction studies.³ As a result, there is frequently a delay in diagnosis, resulting in waste of valuable time.

Multiple and variable treatment options are employed for the management of CRPS. However, no single remedy or regimen has proved overwhelmingly successful. Therapies include medications such as opiates, nonsteroidal anti-inflammatory drugs, steroids, sympatholytic drugs, and endocrine agents to reduce bone resorption. Other options include sympathetic nerve blocks and surgical or chemical sympathectomy, physical therapy, massage, acupuncture, and transcutaneous electrical stimulation.

One interesting therapeutic option, with encouraging results is spinal cord stimulation (SCS). The gate control theory of pain, introduced in 1965 by Melzack and Wall,¹³ provided the initial framework for the development and use of SCS for the treatment of neuropathic pain. This theory posits that nociceptive (pain) stimuli are transmitted to the spinal cord via unmyelinated C fibers and lightly myelinated A δ fibers. These fibers terminate in the superficial laminae of the dorsal horn, that is, the “gates,” of the spinal cord. Heavily myelinated A β fibers, carrying sensory information such as touch and vibration, also pass through these gates.¹³ Furthermore, these A fibers emit small branches terminating in the dorsal horn, where they exert inhibitory effects on nociceptive conduction. Thus, stimulation of these large fibers will close the gate to the reception of the small-fiber pain stimuli.¹⁴ The result is analgesia.

In the early stages of neurostimulation, the primary target was the dorsal column. Here the effects of SCS appear to result from activation of large-diameter fibers that “close the gate” to the smaller pain fibers. However, it became clear that successful treatment involved more than just the direct inhibition of these dorsal horn cells. It frequently included neurostimulation to lateral and ventral tracts. Theorists have postulated as many as 10 mechanisms of actions to explain the results of SCS. Recent technological advances have allowed greater specificity in targeting a variety of ad-

ditional sites within the intraspinal canal. These include the dorsal root entry zone (DREZ), the dorsal root ganglion (DRG), and the spinal nerve roots.¹⁵

Placing leads in proximity to excitable neural structures of the spinal cord (ie, cord, ganglion, nerve) allows recruitment of these various neuronal structures by increasing the amplitude of stimulation.¹⁵ Inhibitory stimulation occurs at subsensory levels of intensity threshold, whereas perceivable suprathreshold sensory stimulation occurs at slightly greater intensities, and motor stimulation occurs at even higher levels. Neuronal fiber size, degree of myelination, surface proximity of the neurons, and lead placement all contribute to this differentiation.¹⁵

Through multiple mechanisms, electrical neuromodulation affects spinal and supraspinal sites, resulting in decreased sympathetic outflow. Subsensory (inhibitory stimulation) produces local effects within the DRG-DREZ-dorsal column axis.¹⁵ It specifically inhibits the hyperexcitability of dorsal horn neurons by inducing the release of γ -aminobutyric acid (GABA).⁸ Ultimately this results in preventing release of excitatory amino acids in the dorsal horn, decreasing neuronal sprouting in the dorsal horn and DRG (in response to nociception), and suppressing neuronal pain transmission and sympathetic outflow.

Sensory level stimulation produces additive results through inhibitory effects on central sympathetic systems. Activation of supraspinal loops, relayed by the brain stem or thalamocortical systems, provides ascending and descending inhibition. It also results in stimulation of the periaqueductal gray matter in the brain.^{15,16} Stimulation of this area produces analgesia in 2 ways: by activating descending pathways to inhibit nociceptors in the laminae of the spinal cord and by causing stimulation of opioid receptors within the spinal cord.¹⁶

Implantable stimulator devices have been in existence for approximately 40 years. Advances in technology and increases in clinical information have resulted in definitive improvements in the design and application of the electrodes (leads) and frequency generators. The leads house electrode arrays, which can deliver a stimulus with programmable hertz (frequency), pulse width, and potential (voltage) that results in paresthesias.¹⁷ Contemporary leads consist of an array of contacts connected to a pulse generator. Two types of leads are currently available: percutaneous and paddle. The percutaneous leads are round, thin, and flexible, and are introduced through a needle into the spinal column. Paddle leads are flat and wide and require surgical placement (laminotomy or laminectomy).¹⁸

Programming lead contacts to generate an electric field causes stimulation of specific nerve fibers in the spinal column. This results in inhibition of pain pathways (lateral spinothalamic tracts) and increased activity in descending antinociceptive pathways. Optimum results occur through neural selectivity, or control over targeted nerves, while avoiding stimulation of undesired

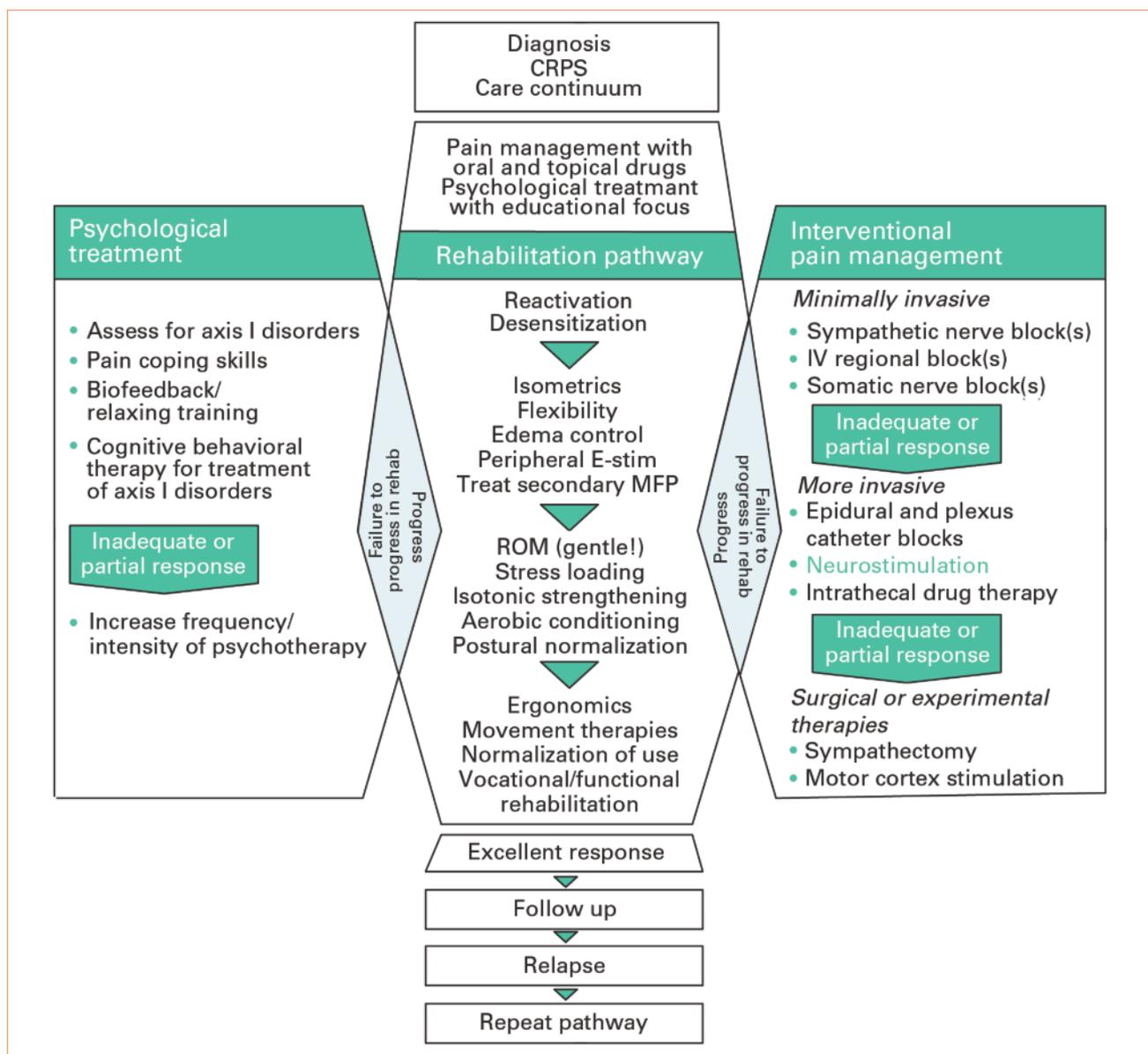


Figure. Revised Therapeutic Algorithm for Complex Regional Pain Syndrome

CRPS indicates complex regional pain syndrome; MFP, myofascial pain syndrome; E-stim, electrical nerve stimulation; ROM, range of motion; IV, intravenous.

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neurons. Thus, recruitment is a graded function, requiring a high degree of selectivity.¹⁸

Current treatment aims at very specific lead placement and precise titration of the amplitude of stimulation. The best results appear to be from a dual-lead, multichannel, and multiprogrammable system. The flexibility of this system allows revision of parameters as necessitated by the patient, because neuronal plasticity may alter this target over time. Such revisions are possible without further surgical interventions.¹⁷

The generated paresthesias, which patients describe as “tingling,” capture or replace the prior pain sensation. Successful therapy requires the generated paresthesia to completely and constantly cover the patient’s area of dis-

comfort.¹⁹ Parallel placement of dual, staggered leads (electrodes) has proved to be the most efficacious method.²⁰

Successful results include dramatic reductions in pain perception, allodynia, muscle dysfunction, and improvement in blood flow.²¹ When applied early in the course of the disease, spinal cord stimulation can support gains in the functionality of the affected limb. Some recent studies estimate success rates at more than 70% with a combination of SCS and physical therapy.²⁰ This includes a decrease in pain, often by 50% or greater, as well as a substantial improvement in the health-related quality of life assessment score.

Several studies have shown that spinal cord stimulation is a cost-effective treatment of CRPS. Although ini-

tially expensive, because the implantation procedure is costly, mean lifetime savings, when comparing costs of SCS with other treatments such as medications and physical therapy, averaged \$48,000 to \$58,000.²⁰ Trial procedures afford reliable demonstrations of success before the permanent implants are placed.

Until the pathogenesis of this syndrome is determined, a cure is not probable and treatment will likely remain limited to alleviating the individual patient's symptoms. It is important that primary care providers, surgeons, and the public become knowledgeable about this condition. The innocuous events surrounding its onset and variable early presentations render diagnosis elusive in many cases, yet functional rehabilitation depends on early, aggressive management.

Aggressive management encompasses use of several available treatments in locating the "right" combination. Flexibility is paramount in preventing a plateau in the rehabilitation pathway.²¹ The maximum period for any therapeutic trial is 12 to 16 weeks. In their 2006 publication, Stanton-Hicks et al²¹ provided a revised algorithm for the therapeutic management of CRPS (Figure).²² Because experience has shown that early, aggressive treatment is necessary for maximum restoration of function, there is no benefit in the continuation of ineffective therapy.

Summary

Complex regional pain syndrome is a puzzling condition characterized by various abnormalities involving the peripheral and central nervous system. Its precise cause and progressive stages are under investigation, as little definitive knowledge currently exists. The primary initial symptom of burning pain is frequently accompanied by more severe and disabling pathology as the disease advances. The unique symptoms and presentations within individual patients make it paramount for practitioners to keep abreast of progress in the diagnosis, management, and outcomes of CRPS.

Early diagnosis and aggressive treatment is imperative for maximum benefit in pain relief and rehabilitation. Several treatment modalities have met with varying degrees of success. Optimal management often encompasses use of a combination of treatments.

Recent advances in the technology and design of implantable spinal cord stimulators have yielded dramatic results. These minimally invasive systems are proving cost effective because of high success rates in both pain relief and functional rehabilitation. Benefits include availability of reliable trials and design flexibility for initial programming and future revisions. Success rates of more than 70% have been reported with SCS and physical therapy.

Timely management and adaptable treatment plans are paramount in achieving maximum functional rehabilitation. Plateaus in the rehabilitation pathway are unacceptable for these patients.

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