Complex Regional Pain Syndrome

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The following article is abstracted from a chapter by Dr. Steven Feinberg and Dr. Steven Stanos to be published in the next year.

CRPS is a syndrome usually affecting one or more extremities, but may affect other parts of the body. It is a disabling disease with simultaneous involvement of nerve, skin, muscle, blood vessels, and bones. CRPS is characterized by “regional”, not focal, disproportionate pain and multiple symptoms in addition to pain, which may include changes in skin blood flow resulting in a warm or cool extremity, discoloration or mottling of the skin, sweating and swelling. The skin may become dry, scaly and atrophic. There may be hair and nail changes. The joints may be tender and swollen. The individual typically shields the limb from contact and use due to extreme pain with even normal or light touch. With time, and particularly without adequate treatment, the syndrome progresses to include permanent changes in the skin, hair, nails and soft tissue along with muscle wasting and loss of joint motion and contractures. The bones may become osteoporotic from disuse. Some individuals develop tremor, muscle spasm and difficulty initiating movement. Edema or swelling of the extremity can be marked and intermittent. Chronic skin breakdown and ulceration may develop.

The cause may be unknown and there is nothing in the medical literature that explains why some injured individuals get CRPS while others with similar injuries do not.

There is an assumption that pain and other symptoms occur due to cellular damage initiated in the periphery possibly from mechanical, thermal, chemical, or ischemic events. Pain signals are relayed proximally to the dorsal horn of the spinal cord where they can be amplified and modified and then transmitted to cortical (brain) centers. The consequences and response of the individual are related to a complex interplay of physiologic events and psychological factors.

Early CRPS–like symptoms can be seen transiently after injury or illness but why some individuals have a prolongation of the symptoms and go on to develop true CRPS remains unknown.
For those patients that develop CRPS, signs and/or symptoms can be seen after neurological or orthopedic injuries (sprain, dislocation, fracture, crush injury, laceration, puncture wound, nerve injury and with amputation) or post-operatively, usually when these injuries involve an extremity.

There is often no correlation between severity of injury and intensity of resulting symptoms. It has been seen after intramuscular injection, venipuncture and subcutaneous allergy injections. CRPS can also develop after stroke, head injury, spinal cord injury, myocardial infarction, chest surgery or infection. It has also been reported with cancer, arthritis, burns, nerve entrapments, herpes zoster, diabetic neuropathy, and a number of other diseases. In some cases CRPS occurs without any obvious cause or just trivial trauma.

Despite the description of many conditions precipitating CRPS, the vast majority of cases are seen following nerve and orthopedic injuries or minor trauma. The normal steps in healing do not occur as expected and the stigmata of CRPS develop. Interestingly, the development of CRPS does not appear to be dependent on the magnitude of the injury.

Awareness of the disease and clinical observation are the most common means of diagnosis. Since symptoms can wax and wane during a single day and over a few hours, the history from the patient and the information in the medical record are of critical importance. It is sometimes appropriate to evaluate the patient on multiple occasions rather than during a single visit.

The evaluating physician or therapist should realize that patients do not usually present with classical, textbook symptoms. Evaluation can be complicated though by patients who have become "educated" about CRPS on the Internet or in support groups and have "learned" the appropriate symptoms. Affective distress (i.e. anxiety and depression) may in itself feed into the physical symptoms of the presentation, including sweating and color changes in the involved limb, as well as disuse or fear avoidance of use of the effected extremity or body part.

For the evaluating clinician, knowledge and a suspicion about CRPS is important. The patient who presents with early CRPS stigmata or otherwise presents with unexpectedly intense pain, stiffness, slower than anticipated recovery, poor pain relief with medications, and a high level of emotional distress should alert the clinician to the possibility of CRPS.

No specific test is available for CRPS, and no specific clinical feature identifies this condition. Rather, identifying a constellation of history, clinical examination, and supporting test and laboratory findings make the diagnosis.

While the symptoms and signs of the condition are obvious in some patients, the diagnosis, particularly in the early stages may be difficult. The patient may complain of severe pain while physical findings are minimal or absent. Although the majority of cases occur following trauma, the initial precipitating event may be trivial, and in some cases may not be remembered by the patient.

The diagnosis of CRPS remains a clinical diagnosis based on the historical and physical findings of the patient. A positive x-ray with signs of diffuse bone thinning, a bone scan with diffuse
changes in uptake of blood flow in the effected extremity, or a positive response to a sympathetic nerve block has been used as supportive of a diagnosis for many years, but are no longer needed or appropriate in isolation to confirm a diagnosis of CRPS. These tests may now help only to support the diagnosis indirectly or help to diagnose other conditions that may mimic CRPS.

The disease is often relentlessly progressive. Even with appropriate treatment, the patient may develop a chronic pain syndrome with a useless limb where nothing seems to help in the face of increasing discomfort, disability and dysfunction. Unfortunately, in some cases, CRPS symptoms spread to include other limbs and body parts.

There has been considerable controversy regarding diagnostic criteria of CRPS. There has been an ongoing international effort to develop a more accurate and valid diagnostic criteria for complex regional pain syndrome (CRPS) which included the use of both clinical and more strict research criteria. This article is not the proper venue to go into those details but the reader is referred to a review article by Dr. Harden and colleagues titled Proposed New Diagnostic Criteria for Complex Regional Pain Syndrome [1]. This proposed more structured criteria is now commonly used by clinicians, and has been approved by the Diagnostic Committee and Executive Committee of the International Association for the Study of Pain (IASP).

Clinical Diagnostic Criteria for CRPS

**General definition of the syndrome:** CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

**To make the clinical diagnosis, the following criteria must be met:**

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories:
   - **Sensory:** Reports of hyperesthesia and/or allodynia
   - **Vasomotor:** Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - **Sudomotor/Edema:** Reports of edema and/or sweating changes and/or sweating asymmetry
   - **Motor/Trophic:** Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories:
   - **Sensory:** Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   - **Vasomotor:** Evidence of temperature asymmetry (\(>1^\circ\) C) and/or skin color changes and/or asymmetry
   - **Sudomotor/Edema:** Evidence of edema and/or sweating changes and/or sweating asymmetry
   - **Motor/Trophic:** Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms.

**For research purposes,** diagnostic decision rule should be at least one symptom in all four symptom categories and at least one sign (observed at evaluation) in two or more sign categories.
The condition is variable in presentation and changes with time. Symptoms usually begin within hours, days or weeks of the accident or injury. A gradual or abrupt onset of severe aching, throbbing and burning pain at the site of injury can be accompanied by increased sensitivity to touch (hyperesthesia), pain with normal touch (allodynia), swelling/edema, muscle spasm, stiffness and limited mobility.

At the onset, the skin is usually warm, red and dry and then changes to cyanotic, cold, mottled and sweaty. There may be accelerated hair and nail growth along with early osteoporosis. The pain is increased by dependency of the affected limb, physical contact (the touch of clothes or bed sheets) or emotional upset. Visual and auditory stimuli may aggravate the pain. There may be muscle spasm and decreased range of motion.

Over a number of months the symptoms are characterized by continuous burning, aching or throbbing pain that is even more severe and diffuse. Hair growth may be altered and the nails may become cracked, grooved or ridged. Swelling spreads and changes from soft to brawny and indurated.

The skin is cool, pale, cyanotic, mottled and sweaty. Osteoporosis becomes more apparent and there is further loss of range of motion. Muscle wasting may be present. The joints may be thickened and a tremor may develop.

In the later stages, the pain spreads proximally and involves the whole limb and may become intractable, but at some point may actually lessen or stabilize. Dystrophic changes become more distinct and irreversible tissue damage occurs. The muscles atrophy, contractures develop, and the skin becomes thin and shiny. The nails are increasingly brittle and ridged. There is marked, diffuse osteoporosis. Tremors and involuntary severe jerking of extremities may be present. The disease may have spread to other limbs or body parts. Although the above stages are noted in some patients, many may not necessarily proceed in this manner, underscoring the significant variation and course in patient presentation.

It is important to understand that no unequivocal diagnostic criteria for CRPS exist. The diagnosis is based on both subjective and objective criteria. Certain tests may be positive but a negative test result does not rule out the diagnosis.

The history and physical examination serve as the most important tool in the diagnosis. In addition to inspection, palpation, range of motion, and a musculoskeletal and neurologic examination, special attention is paid to temperature measurements, skin coloration, hair and nail changes, swelling and surface moisture (sweat patterns).

An x-ray which shows early patchy demineralization, a positive sympathetic block, or an abnormal triple phase bone scan may assist with the diagnosis and exclude other conditions but negative test/procedure results do not rule out CRPS.

A psychological evaluation may be extremely helpful in understanding the psychosocial stressors that may partly explain the individual’s presentation and response to treatment.
Approximately thirty percent of patients with CRPS are described as demonstrating proximal spread and/or spread to other extremities or body parts. Many times, “spread” of the condition may be incorrect and may be more accurately related to compensatory changes the patient is making. For example, the patient may have musculoskeletal discomfort related to poor body mechanics or excessive guarding of the limb. The patient with CRPS of one foot may develop back and knee pain from limping and postural abnormalities rather than from the spread of the disease. An example would be “overuse” of the non-affected extremity.

The duration of CRPS may vary. In mild cases it may last for weeks followed by remission while in many cases the pain continues for years and becomes chronic, permanent, and in some cases spreading proximally and to other limbs. Some patients experience periods of remission and exacerbation. Periods of remission may last for weeks, months, or years.

The selection of a treatment approach depends on the severity of symptoms and the degree of disability. Of paramount importance is that a successful treatment outcome for CRPS depends on a coordinated functional restoration multidisciplinary approach [2].

Building a therapeutic alliance between the patient and the treatment team is of critical importance.

Since pain and limb dysfunction are the major early complaints, pain control, education, physical rehabilitation and emotional stabilization are the main treatment objectives. Coexisting problems such as depression, sleep disturbance, anxiety, fear of reinjury, and generalized physical deconditioning should be evaluated and treated.

Therapeutic approaches include physical rehabilitation (i.e., physical and occupational therapy), psychological care including cognitive behavioral therapy (CBT), relaxation training, medication management, and a variety of techniques that, directly or indirectly, are aimed at blocking or interrupting chronic changes to an overactive nervous system (i.e., sensitization process) and in some cases decreasing sympathetic hyperactivity. Patients are encouraged to use the affected limb. Treatment is more successful if started early rather than later in the disease process.

While physicians and therapists have many tools in their treatment armamentarium, the single most important treatment for these patients is education and learning how to manage their chronic pain condition. Patients who can learn about the cause and meaning of their pain are able to make better choices regarding the use of their extremity which may improve the natural history of the disease process.

Medications may include treatment with oral, transdermal, topical agents and drug delivery patches. This may include steroids, anti-inflammatories, antidepressants, vasodilators, anti-spasm medications, and anti-convulsants type medications. Membrane stabilizers or medications that suppress sensitization of the nervous system and/or sympathetic activity including alpha 1 adrenoceptor antagonists. No single oral medication or injection is specifically approved by the FDA (Food and Drug Administration) for CRPS.
Topical analgesics include a number of products including tricyclic antidepressants, lidocaine patches and gels focused on decreasing skin sensitivity and blocking sodium channels in the peripheral nociceptors (pain receptors that function at time of injury or inflammation).

Besides pharmaceutical brand products, compounding pharmacies may provide various topical preparations that include a mixture of gabapentin, baclofen, cyclobenzaprine, ketamine, tizanidine, and lidocaine.

NSAIDs inhibit cyclooxygenase and prevent the synthesis of prostaglandins, which mediate inflammation and hyperalgesia. In addition to their peripheral anti-inflammatory action, NSAIDs may also block spinal nociceptive processing. Studies have not shown strong benefit for NSAIDS in CRPS.

Oral steroids have been advocated for early treatment of the condition, but long-term clinical studies are lacking.

Anticonvulsant medications used in pain medicine for neuropathic pain may also be used for CRPS that may include gabapentin and pregabalin, which may decrease uptake of calcium and decrease peripheral and central neuronal sensitization and pain [3, 4]. Other anticonvulsants (phenytoin, levetiracetam, zonisamide, topiramate, and lamotrigine) may have multiple mechanisms of action including decreasing calcium conduction, glutamate and substance P activity (excitatory neurotransmitters) and increase GABA.

Oral tricyclic antidepressants (such as amitriptyline and nortriptyline, and desipramine) have multiple mechanisms of action but primarily increase serotonin and norepinephrine in the central nervous system, which may increase descending inhibition of pain signals. Tricyclic medications are limited by side effects including sedation, dry mouth, dizziness, sedation, cognitive impairment, and hypotension.

Treatment of bone resorption with bisphosphonate-type compounds (i.e., alendronate and pamidronate) may help to decrease osteoclastic activity and block the synthesis of cytokines [5, 6, 7].

There has been considerable interest in N-methyl-D-aspartate (NMDA) blockers and particularly the anesthetic ketamine. The NMDA receptor complex appears to play an important role in the development of both peripheral and central nervous system hyperactivity. By blocking and/or desensitizing the receptor may help to decrease pain. NMDA receptor antagonists include dextromethorphan, memantine, and ketamine. Ketamine is the most commonly used agent but has a very narrow therapeutic window and may cause significant adverse effects including hallucinations, mental slowing, and confusion [8]. There are 3 techniques for ketamine administration: intravenous subanesthetic dosing, intravenous high-dose anesthesia (“ketamine coma”), and topical administration. There is interest and controversy surrounding the use of ketamine which is still under investigation.

Anti-hypertensives (e.g., clonidine) and α-adrenergic antagonists (e.g., phentolamine, phenoxybenzamine, reserpine, and others) have been utilized in the treatment of CRPS without
good evidence from clinical research studies regarding efficacy. The rationale for their use is the recognized role of the sympathetic nervous system in CRPS and the theory that blockade will provide pain relief. Oral clonidine specifically has not demonstrated significant efficacy in neuropathic pain and is challenging to use due to its side effect profile. It is more widely utilized as a patch and in implanted pumps such as an intrathecal agent.

Opioid analgesics are widely used in managing this condition, but their efficacy for CRPS related has not been clearly established. Patients who are considered good candidates for opioid treatment should have a clear objective functional benefit that is uniquely provided by the medication. Appropriate and ongoing monitoring for misuse and diversion of medications is now standard of care if patients are to successfully remain on opioid analgesics. This can include opioid risk assessment tools, opioid agreements (contracts), and urine drug testing (UDT).

The ultimate goal of therapy is to reduce pain and improve function of the patient's affected area. Physical rehabilitation can be detrimental if not applied appropriately.

The evaluation starts with an assessment of appearance along with active and passive range of motion and measurement of swelling. A related soft tissues assessment, including that for myofascial trigger points, should also be included. The therapist also evaluates strength, sensation and pain response, coordination, dexterity, temperature changes and functional use ability.

Treatment is directed toward pain relief, desensitization, edema reduction, normalization of tone and sensation, proper posturing and positioning, range of motion and stretching to maintain and improve flexibility, stress loading, and strengthening. In more severe cases, splinting and bracing may be utilized. Prolonged splinting or bracing should be avoided and may contribute to development of other compensatory problems.

Treatment is a team effort and with adequate analgesia provided. Treatment in severe cases usually starts slowly with edema relieving techniques, gentle desensitization and the use of passive modalities followed by gentle flexibility and strengthening exercises.

Desensitization therapy can be a critical component to a successful rehabilitation plan. Desensitization techniques are aimed at normalizing sensation and consists of progressive stimulation with soft materials increasing to rougher textures as tolerated over time. It can include light touch progressing to deep pressure. Desensitization approaches may also include graded increases in carrying light objects for short periods of time, a number of times per day, or scrubbing or loading the affected limb on a daily basis. Vibration at different frequencies can also be used to assist in desensitizing the affected extremity. Contrasts baths (switching back and forth from hot to cold water) is utilized and leads to increased hot and cold tolerance. A desensitization program is thought to reestablish normal sensory and motor integration and complex maladaptive connections between the brain and effected body part.

Edema is managed by the use of specialized garments or wrapping techniques and therapy is directed towards manual edema mobilization techniques and education so the individual can
practice edema reducing therapies at home and not in formal treatment. Treatment may include stress loading (distraction and compression), elevation and active range of motion exercises.

Postural training and positioning are important and can minimize protective guarding, promote balance and facilitate improved functional use of the extremity.

As the patient improves, treatment consists of more aggressive range-of-motion exercises, stress loading, strengthening, and general aerobic conditioning.

While the importance of maximizing functional use of the affecting limb cannot be overstated, it is just as important to realize that some individuals with residual symptoms of CRPS, will need to learn proper pacing of activities and avoidance of pain inciting events. The individual will need to learn skills to perform some functions in an alternate and less symptom provoking manner. Additional skills such as diaphragmatic breathing, relaxation techniques, imagery, and special mind-body exercises such as Tai Chi or Feldenkrais may be beneficial.

Normalization of use and functional rehabilitation comprise the final stages of therapy. This stage may include work hardening, vocational rehabilitation or retraining, and workplace modification. Patients may need weeks to several months to progress through this stage.

Patients need to understand their disease, which allows them to become active, educated participants in their treatment. The “locus of control” is patient-centered. Rehabilitation is a full-time effort. Those in the early stages of the condition typically respond better to vigorous therapy than those with more advanced cases.

Specific physical and occupational therapy approaches include: stretching, mobilization, active and passive exercises, aquatics therapy, strengthening, transcutaneous nerve stimulation (TENS), electrical stimulation, edema control (including massage, gradient pumps and compressive stockings or gloves), splinting, modalities (deep heat, such as ultrasound), thermotherapy (heat or ice packs) and a program of tactile desensitization (whirlpool, contrast baths, massage, gentle tapping and other sources of stimulation). Patients are encouraged to exercise and use the affected extremity. A home treatment program is essential, since even several hours a day with trained therapists may not be sufficient.

An education program is important for the patient so they can understand what has happened to them and what they can do about it. Since treatment often involves a 24-hour a day, seven days a week effort, the patient must be empowered to be able to provide self-treatment and gain confidence.

Patients with chronic pain problems benefit from psychological services offered in conjunction with physical rehabilitation and medical management techniques. Regardless of the individual’s prior psychosocial history, it is a rare person who after a period of time does not have emotional dysfunction related to chronic illness and pain.

Psychological services may include counseling for the patient and significant others, as well as a variety of techniques for pain control and reduction. This can include biofeedback, stress
reduction, meditation, relaxation training and hypnosis. Services should be time limited, goal oriented, and coordinated as part of a multidisciplinary or interdisciplinary treatment approach.

“Multidisciplinary” approaches include treatment directed by one clinician with multiple disciplines included such as physical and occupational therapy, pain psychology, relaxation therapy, medical management, vocational rehabilitation, and nursing education. Multidisciplinary treatment plans commonly use disciplines at different sites. In contrast, an “interdisciplinary” approach may utilize the same disciplines as mentioned above, but is more collaborative and structured. Care is delivered in one facility, where therapists can better communicate and adjust care. These programs are usually structured, out-patient, day programs, multiple hours per week, for weeks at a time and include both individual and group therapies [9].

Usual procedures employed in diagnosis and treatment can include: stellate ganglion or thoracic sympathetic block; lumbar sympathetic block; intravenous regional sympathectomy; phentolamine infusion and intravenous lidocaine infusion. Sympathetic blockade may provide a useful adjunct to aggressive medical therapy, but it should not be considered as a sensitive or specific test for the diagnosis.

Each of these procedures is designed to alter the function of the nervous system temporarily. During this temporary alteration, patients are evaluated to see if pain, function and evidence of sympathetic dysfunction have been positively influenced. Frequently, patients will receive several of the above procedures as a trial to determine which, if any of them should be integrated into the multidisciplinary management plan.

The goal of each of these techniques is to provide a temporary but effective pause in neuronal hyperactivity, a contributor to the pain, thereby allowing the rehabilitative care to restore more normal healing and function to the affected tissues. If following a trial of the different procedures mentioned above, the treating physician feels that a significant benefit has been gained, then repeated administration of these procedures over a period of six to twelve weeks (and in some cases longer) is viewed as appropriate.

The desired outcome from each procedure should be as long a period of effective decreased pain and improved functional capacity as possible. The majority of practitioners recognizes a response profile of several days to a week as being optimal for the initial intensive treatment and would be willing to repeat these blocks on a weekly or perhaps twice weekly basis in order to facilitate the rehabilitation process. One should recognize, however, that sympathetic blocks on their own infrequently, if ever, “cure” patients. These blocks should be viewed as any other medical treatment; an effective form of temporary palliation and a useful tool to help the patient with the remainder of the multidisciplinary management provided by physical rehabilitation and psychological services.

Patients may have a tendency to view the medical components of treatment as curative alone and it is the job of the therapy team to reinforce the rehabilitative and psychological components as being critical, while the medical interventions are primarily palliative. This continued de-emphasis of the medical components of treatment will help to prevent patients from viewing the locus of control with regards to their ongoing improvement in this disease as being outside of
themselves or within physician control. In other words, the patient should be responsible and in charge of their rehabilitation and pain management.

More aggressive medical strategies employed include the use of selective spinal analgesics and spinal cord or peripheral nerve stimulation.

Selective intrathecal spinal analgesia via an implanted pump incorporates the delivery of extremely potent and selective analgesic medications to sites of action near the spinal cord and nerve roots, generally bypassing the brain and higher central nervous system. This selective delivery by intrathecal infusion pump potentially avoids many of the problems seen with systemic (oral or intravenous) administration of analgesics and may provide partial pain relief.

In addition to selective intrathecal spinal analgesics, there have been documented cases of clear beneficial effects from spinal cord stimulation (SCS) wherein small electrodes are placed in the epidural space outside the spinal cord to deliver microelectrical currents to the descending portions of the spinal cord. These currents induce activity in the patient’s own intrinsic pain modulating system.

Both selective spinal analgesics via intrathecal infusion pump and spinal cord stimulation are potential treatments, but because of the associated risks and costs, should be considered only after conservative efforts at aggressive conservative management mentioned above have failed.

Before permanent implantation, a trial period is warranted. Permanent implantation should depend on objective evidence of benefit including improvement in functional capacity and in the overall rehabilitation program in order to justify the risk and expense associated with chronic implantation. Additionally, these modalities should be utilized only by physicians experienced with these techniques in a multidisciplinary setting. Patients who receive these therapies should be selected by careful medical and psychological screening.

All medical therapies whether conservative or sophisticated spinal cord stimulation or implanted drug delivery systems need to be presented to the patient and reinforced as approaches that are used to provide a “window of opportunity” for functional restoration therapy where they can be aggressively and intensively rehabilitated.

The most effective approach for many CRPS patients involves a functional restoration multidisciplinary or interdisciplinary chronic pain program [10]. These programs are cost-effective and involve an individualized, but highly structured, medication optimization, behavioral/psychological rehabilitation and physical conditioning program in a group setting.

Individuals engage in stretching, strengthening, aerobic conditioning and desensitization techniques, while learning behavioral and psychological approaches to better manage pain along with educational activities and work simulation. Some programs include art therapy and vocational counseling.
Dependency on the doctor and therapist is discouraged and the program is geared towards healthy behaviors and return to leisure and work activities. The group setting provides friendship among patients and encourages mutual support.

Reference Citations