

Complex Regional Pain Syndrome: A Clinical Review

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Abstract

Complex regional pain syndrome is the most complicated neuropathic type pain syndrome. The pathophysiology of the disease is poorly understood and the treatment mostly based on anecdotal experience. In this article we tried to explain the possible pathophysiological mechanisms of the disease and review the current treatments and their scientific evidences.

BACKGROUND

Complex regional pain syndromes (CRPS) type I and type II formally known as Reflex Sympathetic Dystrophy (RSD) and Causalgia respectively, are the most complicated chronic neuropathic pain syndromes involving sensory, motor and autonomic changes. Historically they had been named as minor Causalgia, posttraumatic spreading neuralgia, shoulder hand syndrome, Sudeck's atrophy, sympathalgia, etc. In 1993 the International Association for the Study of Pain renamed regional sympathetic dystrophy syndrome (RSDS) as Complex Regional Pain Syndrome Type 1 and Causalgia as Complex Regional Pain Syndrome Type 2 because of the existence of disagreement in the diagnostic criteria and appropriate therapies for RSD and Causalgia among medical fields and experts. (1)

EPIDEMIOLOGY

The incidence of CRPS both type 1 & 2 are about 1% to 15%. (2) There appears to be higher occurrence of CRPS in females. The ratio of female: male is 3:1. (3) The affected age group is between 18 and 71 years with a mean age of 41.8 years. (4) CRPS can also occur in children. Children with diabetes have highest incidence of CRPS as compared to non-diabetic children (5)

ETIOLOGY AND RISKS FACTORS

Past research indicates several causes linking to the disease. The most common is being trauma. The severity of trauma may range from sprain to gunshot wound. There is no correlation between severity of insult to the severity of the

CRPS. Other causes are venipuncture, infection; surgery, arthritis, coronary artery disease, Parkinson's disease, head injury and stroke. (6) However, in a large number of cases it is hard to find any cause.

There are several risks factors that have been identified for CRPS; among them are immobilization, smoking, substance abuse, genetic, and psychological factors. Immobilization for prolonged periods of time of an injured limb could cause development of CRPS. (7) Smoking is also considered as a potential risk factor as suggested by one study but other well studies fail to prove it. (8,9) Another study concluded the higher percentage (30%) of substance abuse among patients with CRPS.

One retrospective study reveals the higher incidence of premorbid history of depression and anxiety disorder in CRPS patients. Although many studies fail to provide any specific personality factors for the development of CRPS but some studies suggest that patients with dependent personality and those who have problems with authority and slow promotion rate have higher incidence of CRPS. (10)

PATHOPHYSIOLOGY

The exact pathophysiology is unknown. The majority of investigators consider that dysfunction of the peripheral autonomic nervous system plays important role in the development of CRPS. (11) The proposed mechanism behind sympathetic hypothesis is the upregulation and supersensitivity of Alpha 1-adenoreceptor both in the peripheral nervous system and in the spinal cord as evident

by increasing in pain by injecting epinephrine locally in CRPS patients, (12) and collateral sprouting of sympathetic nerves around sensory neurons as proved by histochemical tests. Another alternative explanation is failure of endogenous opioids to inhibit overactivity of autonomic system in CRPS. The critics of this theory argue that majority of patients with CRPS fail to obtain pain relief from sympathetic block. They also have lower plasma level of catecholamines and microneurographic studies fail to show increase sympathetic activities in CRPS. (13,14,15)

Myofascial dysfunction (MD) is another popular theory put forth to explain the possible mechanism of CRPS. One prospective study showed that palpation of trigger point resulted in worsening of CRPS symptoms. (16) It is hard to know whether MD is primary or secondary but clinical experiences suggest that improvement in Myofascial dysfunction will also improve pain and other symptoms of CRPS

The scientific community agrees that damage to the soft tissue and nerves may lead to abnormal changes in the spinal cord and brain. Livingstone proposed that trigger points stimulation cause increased afferent input to the spinal cord. This results abnormal activity in the internuncial pool and a consequent stimulation of sympathetic and motor efferent fibers that lead to abnormal muscles spasm and activity. Studies also suggest the involvement of brain especially thalamus as demonstrated by Positron emission tomographic scanning in the CRPS patients.

Other possible mechanisms include, aberrant healing response, exaggerated inflammatory response and protective disuse of the limb. In conclusion, the irritation of the site of injury sends messages to the spinal cord and the efferent autonomic system responds by a normal reflex of producing swelling and cooling of the limb. However, the traumatized cells will produce an increase in temperature and an area of localized edema. Normally, as healing takes place these afferent fibers stop sending the messages and therefore end the reflex. (17) However in CRPS the sympathetic nervous system becomes disoriented and efferent fibers will continue to send impulses back to the injured site producing a vicious cycle of pain and prolonged sympathetic overactivity

CLINICAL FEATURES

The common symptoms are pain, paresis, altered skin temperature, skin color change, limited range of motion, edema, hyperesthesia, sweating changes, tremor, muscle atrophy, altered nail and hair growth and skin atrophy. (See

table – 1)

Figure 1

Table 1: Stages I to III

Stages	Duration	Signs & Symptoms
Stage I	Usually last two to six weeks but may last up to six month	Skin changes: Initially warm and dry, later cold and cyanotic. Mottling of the skin Sweat changes: Hyperhydrosis Temperature changes: Usually increase Edema: Non pitting Pain: Usually not significant, tenderness and hyperesthesia may happen
Stages II	Starts two to six week after initial injury and may last up to three to six month	Skin changes: Cool, pale, mottled cyanotic and a shiny appearance Sweat Changes: Hyperhydrosis Temperature: Usually decrease Edema: Extensive edema with a indurated and brawny character. Pain: Diffuse, constant, burning, and increased by stimuli. Hyperesthesia, Hyperalgesia and allodynia may also be present
Stage III	Starts six to eight months after the initial injury, last for unpredictable period	Skin changes: Irreversible atrophy Fat and Muscles changes: Irreversible atrophy Temperature changes: Decrease Joint changes: Decrease range of motion and decrease strength. Pain: Intractable, Hyperesthesia, Hyperalgesia and allodynia may also be present X-rays Findings: Diffuse demineralization.

Classically, progression of CRPS has been classified into three stages but there are growing number of scientist and clinician who challenge the concept of staging. (18)

STAGE I

This stage of the disease usually last between two to six weeks but it can last up to six months. In this stage the skin is warm, red and dry initially but eventually it becomes cyanotic, cold and sweaty. There is mottling of the skin with patches of pallor on a pink, blue background. The other signs and symptoms of this stage are change in skin temperature, hyperhydrosis, hyperesthesia and edema. (19) The skin temperature usually increases at this stage. The edema is usually a hard, non-pitting type affecting the involved limb.

Pain is usually not significant at this stage but there may be tenderness on palpation or movement and is exacerbated by emotional stimuli. Hyperesthesia is reported to be in a stocking and glove distribution.

STAGE II

This stage can occur after 2 to 6 weeks but it can also occur even 3 and 7 months after the initial injury and can last for approximately 3 to 6 months. The pain is continuous, burning and becomes more diffused. Pain is also increased by stimulus. The skin has cool, pale, mottled cyanotic and a shiny appearance. Hyperhydrosis is also very common at

this stage. Edema may become more extensive with an indurated and brawny character. The other characteristics of this stage are stiffness of joints, atrophical changes in the muscle and skin and the nails become brittle, cracked or heavily grooved.

X-rays may show a patchy osteoporosis. The rarefaction of bone that may occur can be more often seen in the epiphyseal ends.

STAGE III

This stage can occur six to eight months after the initial injury. It is characterized by atrophy of skin, muscles and fascia. The atrophy of the fat pad, skin and muscle is usually complete and irreversible. The skin temperature decreases and the joints become weakened with limited range of motion. The digits become thin with associated tendon contractures. Pain is intractable and usually spreads to involve the entire limb in a proximal direction. However, the pain may be decreased or may not be present at all.

X-rays show diffused bony demineralization, which is indistinguishable from atrophy of disuse, senile atrophy and other conditions. Bones may also show marked decalcification with fixed articular rigidity, which may progress into a fibrous ankylosis.

DIAGNOSIS

CRPS is a clinical diagnosis. There is no laboratory test for CRPS although certain laboratory testing may be helpful as diagnostic aid. In 1994 IASP established the diagnostic criteria for CRPS. Following are the diagnostic criteria ⁽²⁰⁾

1. The presence of an initiating event.
2. A cause of immobilization
3. Continuous pain, allodynia and/or hyperalgesia
4. Skin temperature changes more than 1.0°C difference from the homologous body part.
5. Evidence at some time of edema, skin color changes and abnormal pseudomotor activity in the area of pain.
6. No existence of other condition that would otherwise account for the degree of pain and dysfunction.

Some clinicians criticize the CRPS criteria. They object

that current criteria do not adequately define the minimum requirement for diagnosis while others find high false positive percentage using the current criteria. ⁽²¹⁾ Based on multi-center clinical study the following recommendations are proposed to change the current criteria. ⁽²²⁾

1. Presence of at least two symptoms: Hyperesthesia, temperature and/or skin color changes, edema and/or sweating abnormalities, decrease range of motion, weakness and tremor.
2. Presence of at least two signs: Allodynia and/or hyperalgesia, objective temperature and skin color abnormalities, objective edema and/or sweating abnormalities, objective range of motion, weakness and tremor.

A thorough patient history should be obtained detailing all medications and past medical and surgical procedures. Then a complete clinical examination should be performed. There should be an emphasis on identification of any neurological, musculoskeletal and vascular pathological conditions. ⁽²³⁾ The actual diagnosis of CRPS is difficult and patients may need to be seen by several health disciplines before this diagnosis is attained.

Laboratory tests may be helpful as a diagnostic aid but they are certainly not required to establish a diagnosis of CRPS. Radiological findings show osteoporotic changes. However these changes are nonspecific and could also be found in disuse of the limbs. These changes can be seen as early as the third week, but do not usually appear until the sixth week and can progress for about a year. It takes approximately 4 to 8 weeks of continuous collateral hyperemia for osteoporosis to occur. Initially there is a spotty decalcification of the small bones of the foot and the metaphysis of the long bones. The osteoporosis tends to occur in the juxta-articular regions of the short bones. This mottling bone atrophy later becomes more diffused which can make it indistinguishable from osteoporosis of other origins. Three phase bone scan demonstrates distinctive pattern of radiotracer uptake. Early stages show increase in blood flow, whereas late stages show total decrease in blood flow. The diagnostic sign is periarticular pooling especially in the late phase of the scan. However this is only sensitive within the first 20-26 weeks of the onset of CRPS and after 26 weeks there is a poor correlation. Even at 26 weeks the sensitivity is only 50%. ⁽²⁴⁾ Thermographic imaging is also used for measuring skin temperature. This test may demonstrate the difference of

temperature between affected and unaffected limbs. A temperature difference of 0.60 C is considered significant.

Often sympathetic blocks are performed to determine the involvement of sympathetic nervous system in CRPS. Stellate ganglion block and lumbar sympathetic block are commonly performed for upper and lower extremity CRPS respectively. An optimal block increases the temperature of the skin of the affected part. The Horner’s syndrome (meiosis, ptosis, anhidrosis and enophthalmos) often develops after successful stellate ganglion block. Sweat secretions changes are a common finding in CRPS. Quantative sudomotor axon reflex test (QSART) helps to quantify the abnormalities of sweat secretion.

Skin conductivity test may show an exaggerated sympathogalvanic reflex in an affected limb as compared with the unaffected limb.

TREATMENT

There is no curative treatment for CRPS. Most of the recommended treatments are anecdotal not based on the results of controlled clinical trials. Most of the clinicians agree that treatment in the early stages of the disease and multidisciplinary approach significantly increases the success rate. The recommended treatments include pharmacological management, sympathetic nerve blocks surgical procedures, physical therapy and psychological therapies.

PHARMACOLOGICAL MANAGEMENT

Several medications have been used for the treatment of CRPS (see table-2). Unfortunately none of them have a definitive controlled clinical trial evidence and or long-term clinical experience for CRPS treatment. Two small studies document the beneficial effects of corticosteroid if used within 2 to 3 month of injury but none of the studies reported long-term follow-up data. (25)

Figure 2

Table 2: Pharmacological Treatment

Drugs	Doses	Routes	Common Side Effects
Gabapentin	3600 mg in divided doses	P.O	Low side effect profile Somnolence, dizziness, nystagmus, dry mouth and impaired memory
Amitriptyline	50 to 150 mg QD	P.O	Dry mouth, drowsiness, urinary retention, constipation and tachycardia.
Clonidine	0.1 to 0.3 mg patch q 72 hr	Transdermal	sedation, hypotension, and bradycardia
Opioids a- Morphine b- Oxycodone c- Long acting Oxycodone d- Methadone e- Fentanyl patch	Starts with small dose and titrate until patient report relief of pain or intolerable side effects.	P.O Transdermal	Sedation, constipation, itching, impaired cognition, urinary retention and addiction.

Gabapentin has also been used for the CRPS treatment. Clinical experience shows that titrating the dose of medication can successfully control the symptoms. Because of its low side effects profile and excellent safety record, some clinician recommend to titrate the dose up to 3600mg per day in divided doses. Experts have recommended transdermal clonidine patch. Uncontrolled clinical data suggest that Transdermal clonidine reduces

allodynia and hyperalgesia. (26) Side effects like sedation, hypotension, and bradycardia limit its titration to a higher dosage. Tricyclic antidepressants are considered as a gold standard medicine for neuropathic pain but they fail to provide any significant reduction of symptoms of CRPS. Many patients also report intolerable side effects.

The role of opioids in the management of CRPS is controversial. In general the recommendation for opioids dose is to titrate the dose until patient report relief of pain or intolerable side effects. Clinical experience reported mixed results. Some of the clinician found opioid very useful in reducing pain and improving daily activities. While other clinician contradict the above claim but none of them can back up their claims with good controlled clinical studies. Some other medications that are being used for CRPS treatment are beta-blocker, calcium channel blockers, calcitonin and local anesthetic antiarrhythmias such as lidocaine and mexilitine. Each of the above mentioned medication fails to prove their effectiveness by clinical studies.

SYMPATHETIC BLOCKS (SB)

Many physicians consider sympathetic blocks as a mainstay treatment for CRPS. Current data does not support the long-term effectiveness of sympathetic block for the treatment of CRPS. The advocates for SB believe that it decreases the abnormal hyperactive sympathetic tone and thus decreases the pain. (27) The opponents of SB argue that several studies have shown no correlation between sympathetic dysfunction and pain relief obtained from SB. (28)

Different techniques utilizing for SB are selective sympathetic ganglion block, stellate ganglion block, lumbar sympathetic block, intravenous regional sympathetic block, and epidural clonidine injection. Techniques describe above except intravenous regional sympathetic block depend upon many factors such as experience of the physician, anatomy of the patient, position of the patient, site of injection, identifications of land marks, either the procedure is being done blindly or under Fluoro, CAT scan, or MRI guidance, and the volume of the local anesthetics. For example in our experience if a stellate ganglion block performed blindly utilizing standard technique, injection at cervical 6 vertebra level, fails to relief CRPS pain. We repeat the injection under fluoroscopic guidance at lower level either at Thoracic 1 or 2 level, which very often relieves pain. The reason behind this is, in 10 to 20% of human, the sympathetic nerve supply to the upper extremity comes from the lower thoracic ganglions instead of higher cervico-thoracic ganglion. Although many physicians are utilizing these techniques for the management of CRPS based on anecdotal results. Yet several serious problems exist regarding their effectiveness. First no well controlled clinical trial has been done to support the efficacy of SB for CRSP treatment, second pain relief obtained by SB by using local anesthetic might be because of blockage of somatic nerves and third many response transiently both from SB and intravenous lidocaine infusion. Several agents have been used for intravenous regional sympathetic blockage. Among them are Bretylium, Lidocaine, Guanethedine, and Phentolamine. Only one study showed that pain relief after Bretylium infusion is significantly longer as compared to lidocaine infusion. (29) The mechanism of action is thought to be depletion of norepinephrine. Guanethedine is also commonly used but several studies demonstrate that intravenous sympathetic block with Guanethedine provides ineffective analgesia as compare to placebo. (30,31) Phentolamine infusion is becoming a popular method of sympathetic block among physician for CRPS treatment. The mechanism of action is

believed to be the alpha 1 antagonism. It contains not only local anesthetic properties but also has serotonergic and cholenergetic activities. Clinical trials have shown mixed results.

Epidural clonidine injection is considered as an effective method of obtaining analgesia. A double blind study has proven statistically significant pain relief of CRPS after epidural clonidine injection, however the same study also reports the significant side effects such as sedation, hypotension and bradycardia with the administration of epidural clonidine.

SYMPATHECTOMY

The surgical or chemical Sympathectomy is usually performed on those patients who consistently report transient pain relief after a series of nonablative sympathetic blocks. Depending on the series and the duration of follow-up, the success rate of sympathectomy varies from 12% to 97%. Radiofrequency neurolysis (RFN) is becoming a popular method of sympathectomy among pain specialists. The advantages of RFN over chemical and surgical sympathectomy are decrease incidence of neuritis, avoidance of tinnitus, blindness and urethral stricture that can occur with chemical sympathectomy, amelioration of anesthetic and surgical risks and early ambulation of the patient. The reasons for the failure of sympathectomy are incomplete sympathectomy, extensive interconnection of chains of sympathectomy ganglia cause rerouting of sympathetic impulse after removal of short chain of ganglia, and hypersensitization of adenoreceptors in the sympathectomized area.

SPINAL CORD STIMULATION

The use of spinal cord stimulator has increased tremendously since 1990 for the treatment of neuropathic pain. It is also getting popular for the treatment of CRPS. The exact mechanism of action is unknown. The possible mechanisms of actions are activation of nerves in the dorsal column, direct blockage of nociceptive input, and sympathetic inhibition. A retrospective case study reported excellent pain relief in 8 patients out of 12, with 41-month follow-up. (32)

INTRATHECAL DRUG DELIVERY SYSTEM

Historically this system was designed to deliver morphine intrathecally in cancer patients with intractable pain syndromes. The advantage of this system is that it delivers very small amount of morphine to the spinal cord producing very effective analgesia without causing any significant side

effects. As time passed, this system also became popular for the treatment of non-cancer pain syndromes. Now this system besides morphine can also deliver other drugs such as Fentanyl, Sufentanil, Bupivacaine, Baclofen, Clonidine, Ziconotide and others. Some small-uncontrolled studies report the moderate improvement of CRPS pain with intrathecal opioid therapy. At this time it is usually reserved for those patients who have failed to respond to other medical therapies.

PHYSICAL THERAPY

The goal of physical therapy is the restoration of the function by eliminating the guarding postures and substitute movements, restoration of normal range of motion, strength and motor control, increasing total daily activity time and decrease pain responses to noxious stimuli.

Exercise program, which may be active, active assisted, passive graded relaxation exercises, gait training, work or diversion activities. Some physicians recommend sympathetic blocks or nerve blocks before starting physical therapy. (33) But others find this approach impractical. Mobilization is the most important aspect of treatment particularly during the acute phase. Lenggenhager believes that when physical therapy fails to achieve considerable progress then mobilization of a partially stiffened joint under anesthesia is warranted. The physical therapy modalities aimed at the lower limb involve a gradual increase of the weight bearing capability of the limb. Forceful manipulation of the extremity should be avoided.

PSYCHOLOGICAL THERAPIES

Psychological interventions play a very important role in the management of CRPS. The goal of the treatment is to help the patient fight against fear of reinjury, and worsening pain, overcome anxiety, and depression and other psychological co-morbidities. Common psychological strategies are cognitive-behavioral psychotherapy, group psychotherapy and symptom specific psychological treatments such as biofeedback and hypnosis.

Cognitive-behavioral therapy helps the patient to decrease catastrophizing thoughts and beliefs, restructure cognition, goal setting, increase participation in pleasurable activities and stress management. Group therapy helps the patient to come out from social isolation and reestablish relation with the society. Biofeedback is a useful technique for learning relaxation skills and decreasing pain by increase sense of self-control.

CONCLUSION

CRPS is a very complicated neuropathic pain syndrome. Early diagnosis is crucial. The best recommended treatment is a multidisciplinary approach with the goal of symptom control and restoration of functionality. Aggressive medical and physical therapies should be administered as soon as possible under proper supervision. Psychological therapies should also initiate at the same time. Ablative sympathectomy and placement of spinal cord stimulator should be reserved for those patients who have failed conservative therapies.

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