CHAPTER 9

Complex Regional Pain Syndrome

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INTRODUCTION

Complex regional pain syndrome (CRPS) is a neurological pain condition that is characterized by pain that is disproportionate to the inciting event. It may be induced by surgery, trauma, or a minor injury and has a varying course that ranges from mild and self-limiting to chronic and debilitating. CRPS is characterized by severe pain along with sensory, autonomic, motor, and trophic impairment. The pathophysiology is multifactorial and involves pain dysregulation in both sympathetic and central nervous systems (CNS), with genetic, inflammatory, and psychological contributions (1,2). The purpose of this review is to examine the current literature and to discuss the epidemiology, pathophysiology, and treatment of CRPS. Surgical considerations and complications are also reviewed.

DIAGNOSIS

There is no one clinical test, diagnostic imaging, or genetic test to diagnose CRPS. CRPS is a clinical diagnosis based on criteria from The Budapest Clinical Diagnostic Criteria for Complex Regional Pain Syndrome by the International Association of the Study of Pain (ISAP) (Table 1) and the Orlando Criteria for Complex Regional Pain Syndrome (3).

CRPS is classified into two types: CRPS type I, formerly known as reflex sympathetic dystrophy and type II, formerly known as causalgia (2). Type I and II are characterized by the absence or presence of an identifiable nerve injury (1). CRPS type I usually develops after an initiating event, is disproportionate to the inciting event and is not limited to a single peripheral nerve distribution. It commonly involves the distal aspect of the affected extremity and is associated with edema, changes in skin blood flow, abnormal sudomotor activity, allodynia, and hyperalgesia. CRPS type II occurs in the limb after (partial) injury of a nerve and is defined as burning pain, allodynia, and hyperpathia (3,4). CRPS can be subdivided into warm versus cold, and sympathetically maintained (SMP) versus sympathetically independent (SIP) (2).

EPIDEMIOLOGY

The incidence rate of CRPS type I was 5.46 per 100,000 person-years, and 0.82 per 100,000 person-years for type II based on a population study of Olmsted County over 10 years in 2003 using the IASP and Harden criteria (5). In contrast, another study retained cases based on a positive clinical diagnosis from a physician and found a higher incidence of 26.2 per 100,000 person-years (6). CRPS occurs 3 times more frequently in females than males, has a 3:2 ratio of upper to lower extremity involvement, and affects those ages 50-70 years (4-7). Risk factors include menopause, migraine history, osteoporosis, asthma, angiotensin-converting enzyme inhibitor therapy, tight cast or extreme positions, and smokers (5-7). Potential risk factors for CRPS type I include postmenopausal females, ankle dislocation or intra-articular fractures, immobilization, and higher than usual levels of pain in the early phases of trauma (7).

CRPS following surgery and fractures is a major concern, as it complicates postoperative management and has clinical ramifications. Rapid diagnosis and treatment are required to prevent the sequelae of edema, atrophy, osteoporosis, pseudo-arthrosis, joint stiffness, and tendon adhesions (1). Table 2 compares the incidence of CRPS following surgery versus fractures (8-11). A prospective study of patients with

Table 1. IASP CRPS diagnostic criteria.

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 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 deep somatic pressure and/or joint movement)
   - Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry
   - Sudomotor/edema: evidence of edema and/or sweating changes and/or asymmetry
4. There is no other diagnosis that better explains the signs and symptoms.

Table 2. Incidence of CRPS following lower extremity surgery and fractures.

Surgery	Tibia	Sarangi et al, 1993 (9)	31% (9:20)
	Ankle and foot	Rewhorn et al, 2014 (8)	4.4% (17:373)
Fracture	Tibia	Sarangi et al, 1993 (9)	30% (9:21)
	Ankle	Beerthuizen et al, 2012 (10)	15.2% (21:117)
	Fifth metatarsal	Beerthuizen et al, 2012 (10)	2.9% (3:100)

tibial fractures had an incidence of CRPS after surgery of 31%; with 33.3% treated with intramedullary nailing, 28.6% treated with screws, and 28.6% with external fixation (9). A retrospective study of elective ankle and foot surgery found an incidence of 4.4% in 390 patients; 3.6% CRPS type I and 1.8% in type II (8). Another study investigated the occurrence of CRPS type I after fractures of the upper and lower extremity in 596 patients. The overall incidence was 7.0%, with 15.2% cases occurring after ankle fracture, and 2.9% after fifth metatarsal fracture (10). A study of 30 patients with tibial fractures treated with plaster casting had an incidence of 30%, but the symptoms resolved within 6 months (9). These studies are all limited, due to lack of a gold standard diagnostic criteria and limited cohort sizes.

A retrospective review of patients with a history of CRPS shows these patients are more likely to develop a secondary CRPS if they undergo surgery or sustain trauma to another extremity (11). Of the 93 patients identified with CRPS, 20.4% developed CRPS in an additional extremity. Several articles advocate for the counselling of surgical patients and prevention of CRPS by avoiding tourniquet use and intravenous mannitol infusion (11-14).

PATHOPHYSIOLOGY

The clinical presentation of CRPS is variable, due to the underlying mechanism being multifactorial. It involves abnormal neuronal transmission, autonomic dysregulation, and central sensitization (2). At the site of injury there is a pro-inflammatory and immunological response including the release of interleukin 1b (IL-1b), IL-2, IL-6, tumor necrosis factor (TNF), along with neuropeptides including calcitonin gene related peptide, bradykinin, and substance P. Clinically in the initial phase there is pain, edema, erythema, increased temperature, and impaired function (1).

Some studies demonstrate a reduction in C-type and Ad-type cutaneous afferent neuron fiber density and an increase in aberrant fibers of unknown origin, which exaggerates pain sensation in the affected limb (1). There are also alterations in the CNS and PNS. In the CNS, there is alteration of nociceptive processing and an increased excitability of secondary central nociceptive neurons in the spinal cord (1). This clinically leads to hyperalgesia, increased pain from noxious stimuli and allodynia, pain in response to non-noxious stimuli. There are decreased levels of circulating plasma norepinephrine in the acute warm phase, which triggers the compensatory upregulation of peripheral adrenergic receptors causing hypersensitivity to circulating catecholamines. In the chronic cold phase, the affected limb is cyanosed and clammy as a result of vasoconstriction and sweating suggesting excessive sympathetic nervous system outflow (1).

Immunoglobulin G (IgG) autoantibodies are present against surface antigens on autonomic neurons, suggesting autoimmunity may influence the development of CRPS (15-17). In a mitochondrial inheritance pattern, siblings of CRPS patients under 50 years were three times more at risk of developing CRPS (18,19). Human leukocyte antigen (HLA) B62 and HLA-DQ8 were correlated with CRPS development (20). The immune related factors and genetic influences are ongoing research. There is inconclusive evidence, but some studies hypothesize that the presence of psychological factors (anxiety, depression) and/or psychiatric illness may affect the development or propagation of CRPS (1).

MANAGEMENT

First line treatment of CRPS includes physical and occupational therapy, with the goals of overcoming fear of pain and gaining functional use of the limb. It is recommended that newly diagnosed CRPS patients meet with a psychological provider, because chronic pain affects the quality of life and has an emotional and psychological burden on the patient.

The medical management of CRPS requires combination therapy. Corticosteroids and nonsteroidal anti-inflammatory drugs reduce inflammation and are commonly used in CRPS. Oxygen free radicals are generated by the inflammatory process. Therefore, anti-oxidants including topical dimethyl sulfoxide and N-acetylcysteine may offer pain relief. The most efficacious preventative therapy for CRPS development is vitamin C (21,22). A randomized controlled trial of 875 patients showed the risk was decreased by prophylactic treatment with 500 mg of vitamin C daily (22). There is evidence of symptom relief utilizing gabapentin for acute and chronic neuropathic pain, topical or intravenous use of the NMDA receptor antagonist ketamine, and alpha-2 adrenergic agonists phenoxybenzamine and clonidine for acute and sympathetically mediated pain.

Chronic pain can be managed with the calcium channel blocker nifedipine, which helps manage the vasoconstriction, and the GABA agonist baclofen, which reduces dystonia and pain. As CRPS progresses there can be decreased use of the affected limb leading to a reduction in bone mineral density. There is localized bone resorption and remodeling leading to bone pain, osteopenia, and osteoporosis. Calcitonin preserves bone mass, and bisphosphonates slow down bone resorption and increase mineral density (23). IV immunoglobulin (IVIG) is an anti-inflammatory and immune-modulator, which may offer pain relief in chronic CRPS (24). The literature has mixed views on opioid therapy. It is helpful in the acute phase, but long term it is less effective and requires larger doses, which can result in tolerance, addiction, misuse, immunosuppression, endocrine dysfunction, and overdoses leading to death (1).

Sympathetic blockade may provide pain reduction and longer analgesic duration (25). It can be used in combination with botulinum toxin. In patients unresponsive to sympathetic blockade, neuromodulation may be helpful to treat CRPS. Spinal cord stimulation and physiotherapy have been shown to decrease pain. Chemical and radiofrequency sympathectomy is a permanent sympathetic blockade and is used only when other treatment options have failed (1). Amputation can offer pain reduction and improve mobility and sleep; however, patients may suffer from phantom pain and recurrence of symptoms in the residual limb (26,27).

EMERGING TREATMENTS

Due to the multi-factorial nature of the disease, there are studies and trials evaluating different mechanisms to decrease the symptoms and stop propagation of CRPS. Immunomodulation with anti-cancer drugs, lenalidomide, and thalidomide have shown promise in pain relief within 4-6 weeks of treatment in one-third of the patients (1). Hyperbaric oxygen therapy has an anti-nociceptive effect. In a randomized controlled trial of 71 patients with post-traumatic wrist CRPS, 15 daily 90 minute HBOT sessions lowered visual analog scale scores 45 days after treatment. The treatment was started within 6 weeks of the initial injury, so rapid diagnosis of CRPS would be warranted (1).

Kharkar et al looked at pain relief with botulinum toxin-A (BTX-A). There was no control in this study. There were 37 patients with focal tonic dystonia and 97% of them reported significant pain relief, with 43% reduction at 4 weeks post treatment (28). Overall there is limited information of BTX-A use in CRPS, and more clinical trials are needed. The recent understanding of the fact that auto-immunity plays a role in CRPS has led to studies evaluating plasma exchange therapy, which is used in other autoimmune disorders (1). Other agents under investigation are naltrexone, which is antagonist to TLR-4 to suppress inflammation; MDA7 which regulates cannabinoid receptor-2 and chemokine fractalkine receptor to suppress edema, microglial activation and expression in the spinal cord; and a selective agonist against adenosine A2A receptor called polydeoxyribonucleotide, which decreases secretion of inflammatory cytokines (1).

In conclusion, CRPS is a chronic neurological pain condition involving the extremities, which is characterized by pain that is disproportionate to the inciting event. It is defined by the presence of distinct clinical features including allodynia, hyperalgesia, sudomotor and vasomotor abnormalities, and trophic changes. Patients with CRPS require input from various clinical specialties including orthopedics, anesthetists, rheumatologists, rehabilitation, and pain management physicians.

The Food and Drug Administration officially named CRPS a disease in 2014, which has spurred renewed interest and drug development. CRPS is a challenging condition for clinicians and researchers due to the complexity and variations in pathophysiology and symptoms. More evidence has been published on CRPS type I than type II, and most studies are limited case series or small pilot trials. The use of combination therapy will likely prove the most advantageous for pain relief for the patient. More research is needed to combat CRPS.

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