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Motor Disorders Associated With Complex Regional Pain Syndrome

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Clinical Vignette

AR is a 31-year-old male without significant past medical history who sustained a left ankle injury while performing vertical jumps during a workout. He developed left posterior tibial tendinitis that failed conservative treatment. He underwent elective left posterior tibial tendon repair with excision of an accessory bone and was non-weight-bearing for six weeks. Postoperatively, he complained of worsening foot pain that resulted in multiple emergency department visits. A workup included an x-ray of the left foot (Figure 1) that demonstrated diffuse osteopenia and demineralization; left lower extremity arterial Doppler that demonstrated patent vessels; and an MRI of the lumbar spine that demonstrated no significant central or foraminal stenosis. The patient was diagnosed with complex regional pain syndrome (CRPS) and was treated with two lumbar sympathetic blocks, aggressive physical therapy, light massage, topical lidocaine gel, oral steroids, etidronate, high dose opioids, and neuromodulators.

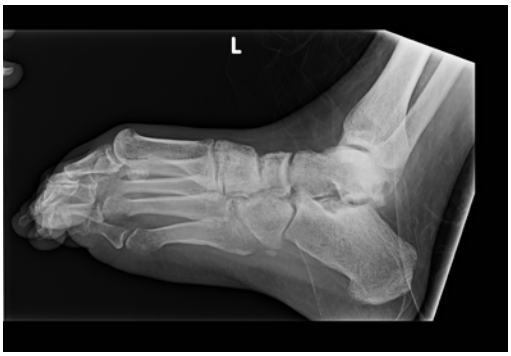

Figure 1: Lateral x-ray of the left foot demonstrating profound osteopenia in the hind, mid, and forefoot, in addition to marked flexion of the forefoot and toes.

Despite this treatment regimen, the patient continued to complain

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Disclosures

Doctors Ho, Drakeley, and Kandt report no relationships with proprietary entities producing health care goods and services.

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of severe foot pain that interfered with his ability to perform his job duties as a resident physician. The patient was admitted to the hospital twice over a four-week period, requiring a Dilaudid PCA pump and a ketamine infusion for pain control. After his second hospitalization, the patient was admitted to an inpatient rehabilitation facility to treat deficits in self-care and mobility. On physical examination, he was noted to have significant swelling, allodynia, and dystonic posturing of his left foot with all of his toes postured in a flexed position (Figure 2). Due to discomfort with the exam, strength and sensation were not fully assessed. On his initial therapy evaluation, he could ambulate only 11 feet using axillary crutches. The patient made limited progress in his first few days of inpatient rehabilitation due to inadequate pain control and poor tolerance with physical therapy. He requested additional treatments to improve his chances of success with rehabilitation.

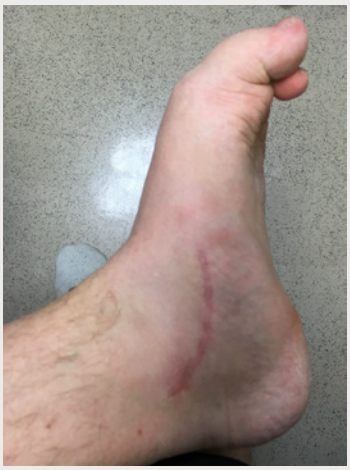

Figure 2: Picture of the left foot demonstrating marked flexion deformity of all toes.

Definition and Description

Complex regional pain syndrome (CRPS) is a chronic or excessive pain condition with associated sensory abnormalities, warmth, and/or swelling appreciated in the affected area. The exact pathophysiology is uncertain, but dysfunction of the peripheral or central nervous system with involvement of the sympathetic nervous system is observed.[1] CRPS is associated with abnormal blood flow[2] and trophic changes, which are soft tissue abnormalities resulting from interruption of nerve supply.[3] CRPS also commonly affects the motor system.[4] There are two forms of CRPS, described as Type I and Type II. Both types share the same symptoms and treatment approaches. Patients without a confirmed nerve injury are classified as CRPS Type I. Type I was previously known as reflex sympathetic dystrophy, or RSD. CRPS Type II, previously known as causalgia, is applied to CRPS cases with a confirmed nerve injury. Recent studies have identified small fiber nerve injury in CRPS Type I, blurring the distinction between the two categories.[5]

Clinical Presentation

Pain is located in a specific region, which is usually a distal extremity. Initial symptoms include pain, warmth, swelling, temperature sensitivity, and/or erythema of the affected limb. The majority of patients will report some type of noxious insult within four to six weeks of presentation. Pain is neuropathic, with burning, tingling, or stabbing sensations.[6] Pain is usually constant and made worse with movement or contact. The patient also may complain of limited functional movement secondary to pain.

CRPS symptoms have historically been described in three distinct stages. The acute stage is associated with diffuse swelling, burning pain, allodynia, sweating, hyperpathia, and increased hair and nail growth. The second stage, often referred to as the dystrophic stage, is distinguished by the pain becoming more intense, with brawny edema, muscle atrophy, mottled skin, decreased range of motion, and the late development of

Table 1: Common Pain Terms That Describe the Symptoms of CRPS

Pain Term	Definition
Allodynia	Ordinarily non-noxious stimulus that becomes painful
Hyperpathia	Persistence of sensation after the stimulus
Hyperalgesia	Increased response to noxious stimulation
Dysesthesia	Unpleasant/abnormal sensation +/- pain
Paresthesia	Abnormal sensation perceived without apparent stimulus (i.e., pins/needles, tingling)
Analgesia	Absence of pain perception
Hyperesthesia	Increased sensitivity to cutaneous stimulation, such as light touch, pressure, or temperature

osteopenia. The third, or atrophic stage, is recognized by decreased pain, skin becoming pale with a smooth, shiny appearance, bone demineralization, and contracture formation. These stages have become less emphasized as recent research has not appreciated a clear course of disease progression.[7]

Epidemiology

Based on a study conducted in the United States in 2007, the incidence of CRPS is 5.5 cases per 100,000 persons.[8] CRPS is more common in females compared to males by a ratio of 3.4:1. It is also more common between the ages of 40 to 49.[8] The majority of people who develop CRPS report a noxious event, such as a fracture, surgery, deep bruise, or limb ischemia. The most common inciting event is a fracture, associated with 46% of cases.[8] Children are less likely to have a noxious inciting event, and psychological issues play a bigger role in the pediatric population.[9] Children respond better to therapy and are less likely to have long-term symptoms from CRPS.[10] There is a 10% to 30% chance of recurrence of CRPS, with children making up the higher end of that range.[11]

Movement Disorders Associated With CRPS

Patients with CRPS are at risk for developing movement disorders (MDs). Though the exact mechanism is not fully understood, there is clinical overlap between different types of MDs and CRPS, including loss of voluntary movement, bradykinesia, myoclonus, tremor, and dystonia. The lack of initiating movement is often overlooked in CRPS and attributed to pain inhibition, but abnormalities in attention and sensori-motor integration have been proposed to explain the loss of voluntary control.[12] Without voluntary movement, disuse atrophy occurs. Bradykinesia, defined as slowness of movement and seen in basal ganglia disorders such as Parkinson's disease, can be observed in CRPS. CRPS affecting one upper extremity also may demonstrate similar bradykinetic movement in the unaffected extremity, arguing that a more central pathology exists.[13] Myoclonus, or a brief involuntary jerking of muscles, has been estimated in 11% to 36% of patients with CRPS and is typically observed at rest and aggravated during activity.[14] Tremor, which is defined as an involuntary rhythmic oscillation or twitching movement of one or more body parts, can be observed in CRPS. A large prospective study of 829 patients with CRPS-I reported tremor in 49% of cases.[7] Dystonia is a debilitating MD in CRPS and is defined as sustained or repetitive muscle contractions that lead to abnormal twisting or posturing. A retrospective study found that 121 out of 185 patients with CRPS had an associated MD, with more than 90% having dystonia.[15] Younger patients with CRPS who develop dystonia are more likely to have the dystonia spread to other parts of the body.

Pathophysiology

The exact pathophysiology of CRPS is not fully understood. Early studies demonstrated increased adrenergic receptor expression on nociceptive pain fibers after nerve injury, implicating the sympathetic nervous system in CRPS.[16] There is decreased density of C and A pain fibers.[17,18] A common explanation for the development of chronic pain associated with CRPS is through a process called central sensitization, which is the enhancement and amplification of nociceptive pathways due to increased membrane instability and excitability of neurons in the spinal cord. One of the components of central sensitization is the "wind-up" phenomenon. Wind-up occurs when repeated C-fiber stimulation elicits a progressive increase in action potential firing over the course of each subsequent stimulus.[19] Pain-related neuropeptides (such as substance P and bradykinin) and excitatory amino acids (such as glutamate) may also contribute to the development of central sensitization after tissue or nerve injury.[20] A similar sensitization process is thought to occur in the periphery and is mediated by pain-related neuropeptides that are released from the primary afferent fibers in the injured area.[21] The neuropeptides released in the periphery cause local vasodilation and increased capillary permeability, leading to edema and neurogenic inflammation as a potential contributor to the development of chronic pain.[22]

Cortical reorganization occurs in the primary somatosensory cortex in patients with CRPS, but subcortical contributions, such as those from the basal ganglia, may also contribute to pain processing. Functional neuroimaging studies in pediatric CRPS have shown increased activity in multiple basal ganglia regions,

including the putamen and globus pallidus.[23] Secondary dystonia, which can be a feature of CRPS, has been described in focal caudate lesions.[24] Basal ganglia dysfunction, which is also seen in Parkinson's disease, could be an explanation for the existence of motor disorders seen in CRPS.

Examination and Diagnosis

CRPS is a clinical diagnosis, but assessment tools and guidelines have been proposed to aid in making the diagnosis. Introduced in 2007, the Budapest Criteria is a useful diagnostic tool in cases of suspected CRPS. This diagnostic tool was found to be very sensitive (0.99) and fairly specific (0.79).[25] In order to meet diagnosis requirements under the Budapest Criteria, a patient must have continuing pain out of proportion to any inciting event, and the symptoms cannot be explained by another diagnosis. A specific algorithm using the Budapest Criteria is listed in Table 2.

Table 2: Budapest Criteria for CRPS

All of the following statements must be met:

- The patient has continuing pain that is disproportionate to any inciting event
- The patient has at least 1 sign in 2 or more of the categories below
- The patient has at least 1 symptom in 3 or more of the categories below
- No other diagnosis can better explain the signs and symptoms

Category	Signs and Symptoms
Sensory	Allodynia and/or hyperesthesia
Vasomotor	Temperature asymmetry and/or skin color changes and/or skin color asymmetry
Sudomotor/ Edema	Edema and/or sweating changes and/or sweating asymmetry
Motor/Trophic	Decreased range of motion and/or motor function (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

Diagnostic Testing

Though CRPS is a clinical diagnosis, investigative tests can aid in making the diagnosis. The autonomic nervous system can be evaluated with a quantitative sudomotor axon reflex test, or QSART. During this test, iontophoresis is used to stimulate sweat glands, and the volume of sweat production is measured. QSART testing is not widely available, but there is evidence this test can help in diagnosing CRPS.[26]

If the diagnosis is unclear, a more general workup may be indicated to rule out other pathologies. Screening blood work should include complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and antinuclear antibody to assess for systemic causes. Venous duplex ultrasound can evaluate for a venous thrombus.

If CRPS is still suspected and further confirmatory testing is desired, there are multiple options but no clear next step. Serial skin temperatures can assess differences between the affected and unaffected limbs. This method has a sensitivity of 73% and specificity of 67%.[27] Plain radiographs may show patchy osteoporotic lesions, but the sensitivity of this test is low.[28] Bone scintigraphy is a more sensitive technique that shows increased radiotracer uptake during the mineralization, or third phase, in the affected limb.[29] CT scan may show focal osteoporosis resembling "Swiss cheese" on imaging, but it is not recommended due to the cost and radiation exposure.[30] MRI may be useful in narrowing the differential diagnosis but offers no support in trying to prove CRPS. Electromyography and nerve conduction studies may be helpful in identifying an underlying neuropathy that may be inducing CRPS. Sympathetic ganglion blocks can sometimes aid in making a diagnosis, but evidence thus far has been lacking.[31]

Treatment

Physical and Occupational Therapy

Physical and occupational therapy are first-line treatments for CRPS.[32] During treatment, patients may attempt mirror therapy, relaxation techniques, edema control, splinting, and/or functional activities. Mirror therapy uses a mirror to create a reflective illusion of the affected limb in order to trick the brain

into thinking movement has occurred without pain. Studies have shown this type of therapy to be effective in CRPS.[33] The exact mechanism underlying mirror therapy is unclear, but it appears to modulate the motor cortex.[34] Researchers also are incorporating virtual reality with mirror therapy.[35]

Occupational therapy can implement desensitization techniques to provide a constant stimulus to the affected area for short intervals throughout the day. Tactile stimulus provides sensory input that helps to lessen the maximal pain response. There are no large, controlled trials studying the effectiveness of desensitization, but the evidence is promising.[36]

Physical therapy can address gait normalization and range of motion to the affected limb to prevent secondary musculoskeletal issues, such as contractures. Myofascial release or soft tissue mobilization can help with myofascial pain related to CRPS. Some therapists are beginning to apply graded motor imagery, as there is evidence it reduces pain and swelling in CRPS.[32] Motor imagery consists of quickly recognizing right from left using a series of pictures displaying hands and feet. Then, patients imagine completing movements with the affected limb.

Psychological and behavioral management may be beneficial in patients who have concurrent depression and/or anxiety, or fear associated with movement related to chronic pain due to CRPS. Techniques include relaxation, biofeedback, imagery, and cognitive behavioral therapy.

Medication Management

Nonsteroidal anti-inflammatories (NSAIDs) are often used as the initial treatment, but they are not well studied in CRPS patients.[37] Anticonvulsants, such as gabapentin and pregabalin, are also commonly utilized, although a randomized-controlled trial with 58 patients showed no significant pain reduction with gabapentin versus placebo.[38] Bisphosphonates have demonstrated efficacy in multiple, albeit small, randomized-controlled trials in patients with osteoporotic changes in the affected limb.[39] Oral glucocorticoids have shown better efficacy than NSAIDs in acute CRPS following stroke, but steroids can induce systemic effects.[40] Topical analgesic options for treating CRPS include capsaicin cream, lidocaine, amitriptyline, ketamine, and dimethylsulfoxide. There is limited evidence supporting the efficacy of topical lidocaine. Topical ketamine was evaluated in a double-blind, placebo-controlled study involving 20 patients and found to inhibit allodynia associated with CRPS.[41] A *Cochrane Review* analyzing topical dimethyl-sulfoxide for CRPS found weak supporting data.[42]

Ketamine infusion may be effective in the treatment of CRPS but requires continuous monitoring of vital signs. In one study, ketamine infused over five days demonstrated a significant decline in pain scores for the following 11 weeks compared to placebo. However, by week 12 there was no significant difference in pain.[43] The reduction in pain over the first 11 weeks may provide a window of opportunity to allow participation with physical and occupational therapy.

There are treatment options to specifically address dystonia associated with CRPS. Oral medications, such as diazepam, which binds to the $GABA_A$ receptors, is used in the pediatric population. Intramuscular magnesium sulfate was evaluated in a double-blind, randomized placebo-controlled trial in CRPS dystonia. The results showed no significant improvement with dystonic episodes, pain, or functionality.[44]

Intramuscular botulinum toxin injections, which are commonly used for managing spasticity and dystonia related to neurologic conditions (such as stroke, cerebral palsy, and traumatic brain injury), may have a role in treating movement disorders associated with CRPS. Botulinum toxins act at the presynaptic neuromuscular junction, blocking the release of acetylcholine by inhibiting binding of the vesicle to the SNAP 25 protein complex. In addition to muscle relaxing effects, botulinum toxin injections have antinociceptive properties. A retrospective study of 17 patients with upper extremity dystonia related to CRPS underwent EMG-guided botulinum toxin injections, with 97% of patients having significant pain relief and an average 43% decrease in their mean pain score.[45]

Intrathecal baclofen (ITB), which is administered centrally as a GABA agonist, has been evaluated in a single-blind, placebo-controlled study of 42 patients with dystonia related to CRPS. In this study, intrathecal baclofen was found to improve dystonia,

pain, disability, and quality of life, which was maintained at one-year follow-up.[46] ITB has also been shown to have antinociceptive properties in patients with CRPS, specifically reducing the symptoms of pain.[47]

Interventional Procedures for CRPS

Sympathetic blockade has been widely used in the treatment of CRPS, but the effectiveness has been debated. In a recent *Cochrane Review,* there was insufficient evidence to support or refute the use of local anesthetic sympathetic blockade as an effective pain management option for CRPS.[48] For upper extremity CRPS, a stellate ganglion block can be used after failure of other conservative therapies. For lower extremity CRPS, a lumbar sympathetic block can be performed.

Spinal cord stimulation (SCS) can be useful after the patient has failed conservative measures. In a prospective, randomized controlled trial of SCS, 50% of patients experienced more than 50% improvement in pain when compared to the control group, which received physical therapy.[49] Similar results were demonstrated at two years, but the benefits disappeared by five years.[50,51] Traditional SCS uses a tonic frequency between 30-80 Hz, but burst and high frequency stimulation have been introduced with greater success.[52-56] Due to a lack of precision with SCS, dorsal root ganglion (DRG) stimulation has been proposed as a method to minimize unwanted side effects that can occur with traditional SCS. In a recent study, pain relief and treatment success were greater with DRG stimulation (81.2%) than traditional SCS (55.7%), with less postural variation and reduced extraneous stimulation.[57]

As with any interventional procedure, complications can occur that lead to surgical revision or removal of the implant. The most common reasons for revision or removal were internal pulse generator discomfort and lead migration.[58] The infection rate is listed between 3% and 5%.[59]

Clinical Vignette Outcome

The patient's pain and debility was related to his persistent spasms and dystonic posturing of his left foot. As a result, he underwent ultrasound and EMG-guided onabotulinumtoxinA injections to the left flexor digitorum brevis (70 units), flexor digitorum longus (70 units), and flexor hallucis longus (60 units). The patient subsequently had improved pain control and could tolerate rehabilitation. At the time of discharge, he was ambulating 200 feet using axillary crutches at a supervision level. As an outpatient, he continued to improve and returned to work as a resident physician. Around three months postinjection, the patient experienced worsening spasms and posturing of his left foot, for which he presented to the emergency department for pain control. It is postulated that the patient had recurrence of his symptoms as the onabotulinumtoxinA injections wore off, which is in accordance with the expected duration of action of the toxin.

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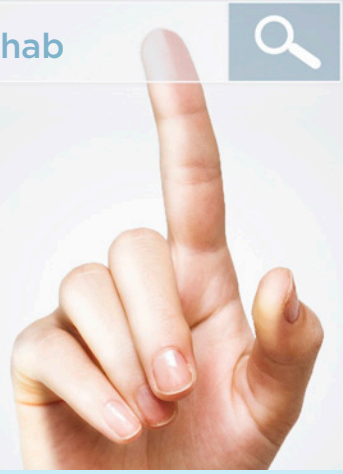

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