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Complex Regional Pain Syndrome: A Scholarly Review

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COMPLEX REGIONAL PAIN SYNDROME: A SCHOLARLY REVIEW

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Abstract

Complex regional pain syndrome (CRPS) is a mystifying, often disabling, neurogenic pain disorder affecting millions of individuals. Although this condition was described in medical literature as early as 1864, CRPS remains controversial, often misunderstood, and frequently incorrectly diagnosed and treated. Patients afflicted with CRPS often suffer unnecessarily because of these factors. This paper reviews the history of CRPS, the evolution of its diagnosis and treatment, and the leading theories on its pathogenesis. This paper also includes case studies of two female patients currently suffering from CRPS. Their stories demonstrate some of the unique challenges confronting CRPS patients, including medical, financial, and health insurance issues.

Complex regional pain syndrome (CRPS) is a life-altering, mystifying neurologic pain condition that arises from a traumatic insult to an extremity or peripheral nerve (*2*). This condition is not widely understood by medical professionals. No single diagnostic tool definitively confirms a CRPS diagnosis. There is also no universally effective treatment for this condition (*1*, *2*, *6*). Because it is not fully understood, this condition can cause confusion and uncertainty among patients and treating physicians. Patients complaining of CRPS pain can sometimes be dismissed as drug-seeking (*15*). Signs and symptoms of CRPS frequently overlap with those of other chronic pain conditions, which can lead to misdiagnosis and underdiagnosis of CRPS (*9*). The lack of a single, definitive treatment for CRPS can lead to a long, frustrating clinical path for both patients and clinicians. Even when CRPS is diagnosed timely and treatment is initiated appropriately, the prognosis remains uncertain (*28*). This little-understood condition profoundly affects the quality of life of patients of all ages and walks of life. This review examines the existing medical literature regarding CRPS and also includes case studies on two patients currently suffering from the condition.

History

Doctors have described signs and symptoms consistent with CRPS since the 16th century. During the American Civil War, physician Silas Weir Mitchell recorded what is now thought to be the earliest careful, thorough description of CRPS. He described patients with complaints of severe burning pain accompanied by red, glossy skin (*2*). In his 1864 book *Gunshot Wounds, and Other Injuries of Nerves*, Mitchell first used the term *causalgia* for this condition, from the Greek words *causos* (heat) and *algia* (pain; *2*). Mitchell noted that all of the patients who exhibited these particular signs and symptoms had suffered peripheral nerve injuries (*4*).

The term *causalgia* was used as the diagnositic term for several decades for patients exhibiting these signs and symptoms (*3*). Then the term *reflex sympathetic dystrophy* (RSD) was coined by Massachusetts physician James A. Evans (*4*). Between 1946 and 1947, Evans described signs and symptoms exhibited by several of his patients that were very similar to those described by Mitchell (*4*). Evans chose the term *reflex sympathetic dystrophy* because he believed that reflexive abnormalities of the sympathetic nervous system, not necessarily a discrete injury to a peripheral nerve, caused the characteristic intense chronic pain as well as diaphoresis, atrophy, and red, inflamed skin (*4*). He noted that signs and symptoms characteristic of "causalgia" resulted primarily from fractures, sprains, and vascular complications rather than from direct insults to peripheral nerves, and he concluded that a different name for the condition was therefore appropriate. Thus, the term RSD came to largely replace the term *causalgia* (*4*).

This condition was destined to undergo yet another name change. In 1973, the International Association for the Study of Pain (IASP) was founded in order to standardize terminology used to classify chronic pain disorders, including RSD (*3*). In 1993, the IASP organized a consensus conference in Orlando, Florida, to devise diagnostic criteria specifically for RSD that would serve as the "gold standard" for clinical diagnosis (*4*). Before any criteria were drafted, however, it was agreed to change the name from *reflex sympathetic dystrophy* to *complex regional pain syndrome* (*3, 4*). The reason for the name change was that the term *reflex sympathetic dystrophy* implied a precipitating injury to a peripheral nerve, but clinicians recognized that many patients with RSD had not suffered a major nerve injury prior to the onset of pallor, sweating, edema, and other symptoms (*4*). The Orlando conference thus adopted the terms *CRPS-1* and *CRPS-2*. CRPS-1 replaced the term *RSD* for patients with no confirmed nerve injuries, and CRPS-2 replaced the term *causalgia* for patients with confirmed nerve injuries (*4*).

The Orlando consensus conference created the following criteria for the clinical diagnosis of CRPS:

1. A noxious event or immobilization able to start the process
2. Allodynia, hyperalgesia, or any pain out of proportion compared to the precipitating event
3. Presence of edema, changes in skin blood flow, or abnormal sudomotor activity of the affected region in any stage of the disease process

Notably, the diagnosis of CRPS can be excluded if the presence of this kind of pain and dysfunction can be related to other diseases.

The diagnostic criteria established at the Orlando conference are still used today. Those diagnostic criteria were purely subjective and based only on reported symptoms, however, which led to high rates of misdiagnosis and false positives (less than 50% specificity; *3*). As a result of the vague nature of the original diagnostic criteria put into place by the Orlando conference, some patients diagnosed with CRPS were in fact suffering from other medical conditions. Another conference was thus held, in Budapest in 2003, with the goal of creating new and improved diagnostic criteria and classification systems for CRPS (*4*), and these have since been subscribed to by a majority of medical professionals:

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 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 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

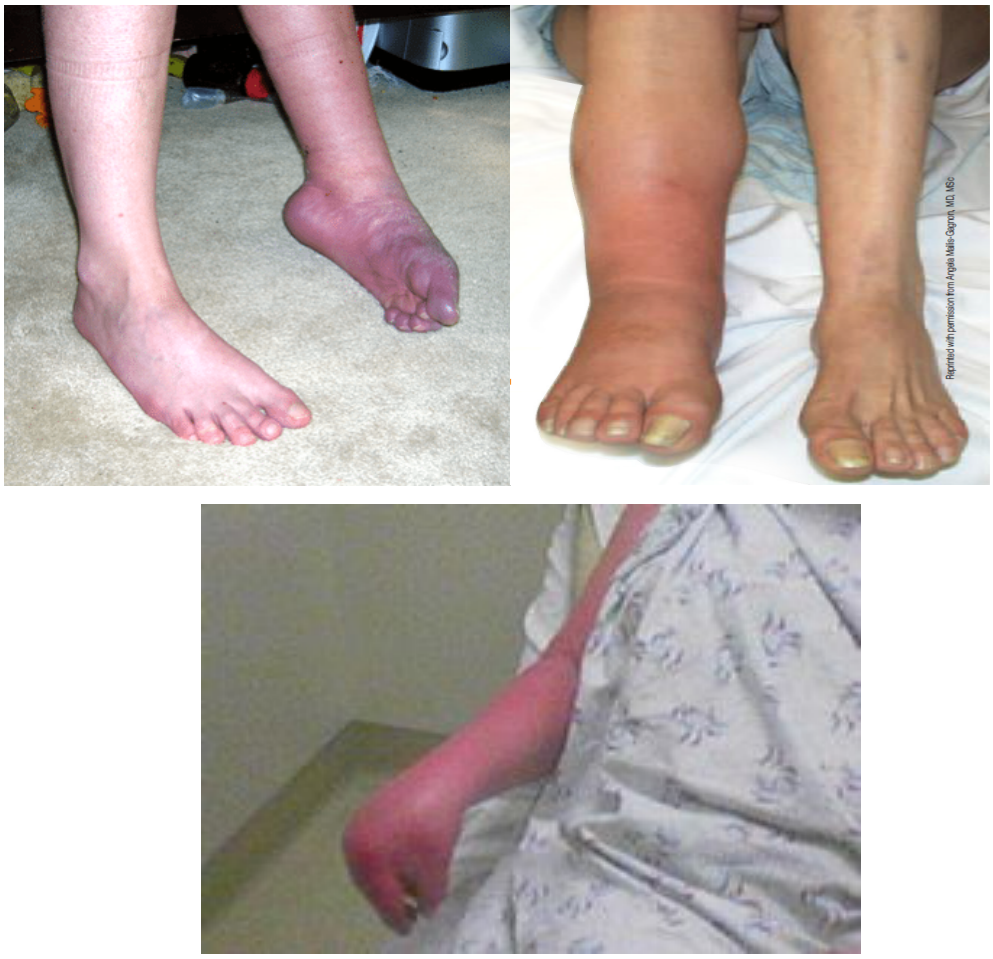
These diagnostic criteria are similar in nature to those drafted at the Orlando conference. As the name implies, however, the Orlando consensus conference

criteria were entirely consensus-driven and resulted in low specificity rates (*3*). By contrast, the Budapest criteria were research-driven and provided significantly higher specificity rates (69%; *3*). Since 2003, the revised Budapest diagnostic criteria for CRPS have been accepted by the IASP (*3*). These criteria have been increasingly utilized by medical professionals, as they allow for effective CRPS diagnosis and research (*3*). The result has been a reduction in the incidence of misdiagnosis and an increase in accurate diagnosis and initiation of timely treatment.

Clinical Presentation

CRPS can occur in any person at any age, although females are at the highest risk for developing the condition (*6*). The exact reasons for this phenomenon are still unknown, but studies suggest that hormonal factors may be to blame (*6*). CRPS occurs mainly in distal extremities and can be caused by a variety of precipitating events (*1*). The most common causes of CRPS-1 (no apparent inciting nerve injury) include minor fractures, sprains, and dislocations (*1*). The immobilization (i.e., casting) period following one of these injuries has also been shown to increase the likelihood of CRPS development (*6*). CRPS-2 results from trauma to a peripheral nerve. Elective surgeries, myocardial infarction, and stroke have also been shown to cause CRPS. CRPS occurs more frequently in upper extremities than in lower extremities, and it typically affects only one limb (*2*).

The most common tell-tale symptom of CRPS is severe, burning pain (*1*). This pain is constant, chronic in nature, and typically disproportionate to the inciting injury or event (*6*). According to the McGill pain index, patients with CRPS experience the highest-ranking, most painful form of chronic pain (worse than amputation of a digit or unprepared childbirth). This pain is often debilitating and may cause a number of secondary conditions (discussed below). According to the Budapest diagnostic criteria, other common signs and symptoms of CRPS include inflammation, allodynia, hyperalgesia, edema, hyperhidrosis, skin-temperature abnormalities, and trophic changes (hair, nails, or skin). Several images of these signs and symptoms are shown below.



CRPS may progress through three distinct phases: the acute/warm phase, intermediate phase, and chronic/cold phase (*7*). The acute/warm phase is characterized by burning pain and localized inflammation (*7*). Inflammation results in redness and swelling of the skin, which leads to an increase in skin temperature. Stiffness, decreased range of joint motion, and unusual hair and/or nail growth also accompany this phase (*6*). This acute phase lasts for roughly one to three months following the initial onset of CRPS (*6*). An accurate diagnosis and proper treatment during this crucial initial phase result in the most favorable patient outcomes (*6*). The longer the condition goes undiagnosed and untreated, the less favorable the prognosis.

The intermediate phase is defined by a reduction in inflammation and, in some cases, a return to normal skin temperature (*7*), although pain continues to

worsen and muscles begin to atrophy (*6*). This phase lasts from three to six months following the onset of CRPS (*6*). During this time, the adverse effects of CRPS can still be remedied or reversed by effective treatment.

Studies have shown that a decrease in norepinephrine levels accompanies the acute phase of CRPS (*6*). The decrease in norepinephrine leads to vasodilation and increased skin temperature in the affected region. If the CRPS is left untreated, the patient's body eventually develops increased peripheral catecholamine sensitivity to compensate for this physiological change (*2*). This causes spasms in the affected peripheral musculature, as well as excessive vasoconstriction (*6*). Vasoconstriction causes skin in the surrounding area to become cyanotic and cold to the touch, which is a characteristic sign of the chronic, or cold, phase of CRPS. The chronic phase of CRPS is the most severe, clinically significant, phase of the condition (*6*). During this phase, pain spreads through the entire affected limb, and irreversible tissue damage may occur (*6*). Motor impairments (e.g., reduced hand function) begin to arise, causing a marked decrease in overall quality of life (*6*). It is important to note that not every patient will exhibit signs and symptoms indicative of each of the three major phases of CRPS (*6*), as the phases and rate of progression of CRPS are variable.

Diagnosis and Diagnostic Tools

As stated above, the currently accepted clinical diagnostic criteria for CRPS are the Budapest criteria, which are shown again below.

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 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 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 a confident diagnosis of CRPS, patients must display at least one symptom in three or more of the symptom categories and at least one sign in two or more of the sign categories. These diagnostic criteria are widely utilized by clinicians and serve as the current standard in CRPS diagnosis (*2*).

CRPS diagnosis can be difficult and is largely exclusionary (*8*). This means that conditions comprising the common differential diagnoses of CRPS must be ruled out before a CRPS diagnosis can be made definitively. Some of these conditions include neuropathy, erythromelalgia, cellulitis, lymphedema, deep vein thrombosis, vasculitis, and Raynaud's syndrome (*8*). Because of the overlap of signs and symptoms among these conditions, CRPS has been cited as one of the most underdiagnosed and misdiagnosed conditions in medicine (*9*).

There is no single gold-standard test for definitive diagnosis of CRPS, as the diagnosis is largely clinical (*1*). Several objective tests can support the diagnosis, however, including triple-phase bone scan (TPBS), MRI, thermography, and sweat-production test (*1*). The TPBS is a generally accepted diagnostic tool (*1*); a TPBS performed on a patient suffering from CRPS will show certain characteristic abnormalities that clinicians use to confirm the clinical diagnosis of CRPS. The TPBS utilizes a radioactive tracer, so if a patient does have CRPS, this test provides clinicians with images showing increased perfusion and unequal blood pooling in the affected extremity (*1*).

MRIs are also used by clinicians as a diagnostic tool for CRPS, as they can reveal a multitude of tissue abnormalities common among patients with CRPS (*1*). Some of these abnormalities include soft-tissue edema, skin thinning/thickening, and, in severe cases, muscle atrophy (*12*). According to a study by M. E. Schweitzer and colleagues (*12*), MRIs can be used to distinguish between the three common phases of CRPS, particularly the acute and chronic phases. The authors found that in 35 patients with acute-phase CRPS, 31 exhibited skin thickening. No muscular atrophy was observed in the acute-phase cohort, but of five patients with chronic-phase CRPS, four exhibited muscular atrophy (*12*). This study by Schweitzer and colleagues provides evidence that MRIs can be useful in differentiating between distinct stages of CRPS, although conflicting evidence exists regarding the efficacy of MRIs in the initial clinical diagnosis of CRPS (*1*).

Thermography tests are highly accurate diagnostic assessments that easily detect the temperature asymmetry of the skin that is seen in patients with CRPS (*11*). The findings presented in a study by Gulevich et al. and reported by Sjoerd Niehof and colleagues (*11*) show that the sensitivity and specificity of infrared thermography used in the diagnosis of CRPS were 93% and 89%, respectively (*11*).

Futhermore, Niehof and colleagues sought to examine the effect of alterations to ambient temperature on the sensitivity and specificity of thermography tests used to aid in the diagnosis of 12 CRPS patients (*11*). They found that the patients' affected and unaffected extemities did not exhibit optimal obtainable temperature differences at room temperature but exhibited much more pronounced temperature differences at warm and cold ambient temperatures (*11*). These findings suggest that alterations in ambient temperature act to further improve the sensitivity and specificity of thermography tests in the diagnosis of CRPS.

Along with skin-temperature abnormalities, abnormal diaphoresis commonly accompanies CRPS (*12*); sweat-production tests are thus commonly used to aid in the diagnosis of CRPS. These tests measure the levels of sweat on two limbs and may indicate a case of CRPS if the sweat levels are unequal (*1*).

Pathogenesis

The pathogenesis of CRPS is complicated and multifaceted. During the early phases of CRPS, exacerbation of neurogenic inflammatory mechanisms occurs (*13*). CRPS-related neurogenic inflammation occurs when Group C nerve fibers (essential in nociception) become continuously strained (*13*). Several neuropeptides—importantly, calcitonin gene-related peptide (CGRP)—are released in response to C-fiber stimulation (*13*). CGRP increases vasodilation while promoting sweat-gland activation and hair growth (*13*). Exacerbation of neuroinflammatory mechanisms with subsequent release of CGRP in patients with CRPS likely explains the characteristic increase in skin temperature, edema, and increased hair and nail growth seen in the early phases of CRPS.

Interestingly, the use of angiotensin-converting enzyme (ACE) inhibitors has been shown to increase the risk for CRPS development (*14*). ACE acts to inhibit CGRP; thus, the inhibition of ACE further enhances release of CGRP and causes neurogenic inflammatory effects (*14*). A study by de Mos et al. (*14*) revealed that a high dosage and prolonged use of ACE inhibitors further increases the incidence of CRPS.

Another key feature of the pathogenesis of CRPS is the onset of peripheral sensitization and, in some cases, central sensitization (*15*). In general, sensitization is defined as an increased responsiveness of neurons to normal input or recruitment of a response to subthreshold inputs (*15*). Sensitization arises when a continuous noxious stimulus, such as the chronic pain of CRPS, causes afferent neurons (and other nociceptive mechanisms) to exhibit heightened sensitivity over time (*15*).

This causes the brain to interpret previously nonpainful stimuli, such as light touch, as painful, which is indicative of primary hyperalgesia/allodynia (*16*). If left unchecked, peripheral sensitization itself can lead to central sensitization (*15*). According to a study by Latremoliere and Woolf, a noxious stimulus must be severe, recurrent, and sustained in order to induce central sensitization. This means that the abnormally high pain signals from CRPS cause peripheral sensitization, which in turn can lead to central nervous system (CNS) sensitization. Once the CNS becomes abnormally sensitized because of CRPS, a patient can experience severe pain in response not only to light touch but also to stimuli such as sound, light, and alterations in barometric pressure (*15*).

Glial cells of the CNS play a major role in the onset of central sensitization (*15*). Glial cells normally function in the CNS to form myelin and to provide support and protection for neurons (*15*). These cells are normally dormant in the CNS, but during central sensitization, they become active and produce inflammatory mediators (called cytokines), which in turn cause nerve inflammation (*15*). Two of these inflammatory mediators are tumor necrosis factor alpha (TNFα) and interleukin-1β (IL-1β). TNFα and interleukin-1β act on the dorsal horn of the spinal cord, which contains cell bodies of sensory neurons (*16*). The action of these inflammatory mediators on the dorsal-horn neurons may result in secondary hyperalgesia, which is defined as a spread of pain hypersensitivity past the original point of peripheral injury (*16*).

NMDA receptors—membrane-bound ion (importantly, calcium) channels that are numerous in the CNS and found on sensory neurons (*15*)—are also crucial in the development and maintenance of central sensitization (*31*). Peripheral sensitization and inflammation can alter the properties of these receptors and, in turn, the sensory neurons that they mediate (*15*). Typically, the calcium-channel gates of NMDA receptors are blocked by magnesium, but this magnesium block is released during the central sensitization process, resulting in a rapid influx of calcium ions and subsequent sensitization of neurons (*31*).

Evidence suggests that people with CRPS experience certain perceptual abnormalities. This may be caused by a phenomenon known as brain plasticity, or neuroplasticity, which is the ability of the brain to "rewire" itself and its connections (*16*). This is what allows the brain to develop from infancy to adulthood (*16*). In people with CRPS, this reorganization of the nervous system (particularly the brain cortex) is thought to occur in response to continuous painful stimuli (*16*). Several of the perceptual abnormalities resulting from brain plasticity in CRPS patients include an inability to identify objects by touch without visual

input, finger proprioception abnormalities, abnormal body scheme, and defects in the mental representation of the affected limb (*16*). According to Kuttikat et al. (*16*), one potential cause of these perceptual disturbances is reorganization of the cerebral cortex. This region of the brain functions in sight, hearing, and memory as well as sensory and motor function; thus, cortical reorganization may disrupt typical somatosensory functioning and lead to the sensory and motor impairments noted above (*16*). A study by Cohen et al. (*17*) examined 22 patients with chronic CRPS-1 to assess for parietal-lobe dysfunction. They found that 15 of the 22 patients had some form of parietal-lobe dysfunction and exhibited symptoms such as sensory extinction and dysynchria. They also found that increased parietal-lobe dysfunction was correlated with increased body-surface allodynia (*17*). Although studied extensively, the exact physiological underpinnings leading to nervous-system reorganization in CRPS patients are still unknown. This phenomenon greatly affects activities of daily living and can result in lifelong somatosensory dysfunction (*16*).

Treatment

Although clinicians employ a multitude of treatments for CRPS, the efficacy of some of these has yet to be established through peer-reviewed research. This section addresses only those treatment options that have been reported as efficacious in peer-reviewed literature. In terms of pharmacological treatment, evidence compiled by Perez et al. (*21*) suggests that subanesthetic ketamine, gabapentin, dimethylsulphoxide (DMSO), N-acetylcysteine (NAC), and others are at least partially efficacious at alleviating some of the pain experienced by patients with CRPS. Stellate ganglion blocks, spinal cord stimulation, and surgical sympathectomy have also been proven to be therapeutic in relieving CRPS pain (*18*). Additionally, physical therapy and occupational therapy are effective noninvasive, nonpharmacological treatments for CRPS (*18*).

As noted above, a number of evidence-based pharmacological treatment options for CRPS exist. It should be noted, however, that the scientific evidence for these treatments is somewhat limited (*18*). Ketamine infusions are commonly administered to people with CRPS (*18*). A study by Correll et al. (*18*) reviewed case notes for 33 CRPS patients who had undergone subanesthetic ketamine infusions for pain relief, in order to determine if ketamine was indeed effective in reducing pain. All 33 patients underwent ketamine infusions at least once; 12 underwent a second course of ketamine therapy, and 2 underwent a third (*19*). Correll et al. (*18*) found that after the initial administration of ketamine, 25 patients

reported complete pain relief, 6 reported partial relief, and only 2 reported no relief. The degree of pain relief also appeared to increase with multiple ketamine infusions, as the 12 patients who underwent second and/or third infusions all reported complete pain relief (*19*). The duration of reported pain relief ranged from three months to three years, and the patients who had undergone more than one infusion reported longer durations of pain relief (*19*). Although ketamine has been shown to effectively relieve CRPS pain, it may cause significant side effects, which can include hallucinations, dizziness, intoxication, and nausea (*18*, *19*).

Gabapentin, an anticonvulsant, has also been shown to reduce neuropathic pain consistent with CRPS (*18*). An eight-week study by Serpell and the Neuropathic Pain Study Group (*20*) assessed average daily pain scores in 305 patients with various neuropathic pain syndromes. Of these 305 patients, 153 were given three separate, progressively increased doses of gabapentin while 152 were given a placebo (*20*). At the culmination of the eight-week study, it was found that the average daily pain scores of patients treated with gabapentin improved (i.e., decreased) by 21% (*20*). These findings are promising, but the study's sample cohort consisted of patients with various neuropathic pain disorders, not only those with CRPS; thus, more evidence is needed to determine how effective gabapentin is in the treatment of CRPS pain specifically (*18*).

Some studies indicate that the free radical scavengers DMSO and NAC may be effective in treating CRPS patients (*18*). One study by Perez et al. (*21*) sampled 146 CRPS patients and sought to compare the effects of these two free radical scavengers on CRPS pain. The patients were divided randomly into two groups and were treated for 17 weeks. One group was treated with 50% DMSO cream five times per day, and the other was treated with 600-mg NAC tablets three times per day (*21*). Researchers concluded that both treatments were moderately effective in reducing CRPS pain. Interestingly, 50% DMSO cream was more therapeutic for patients with acute/warm-phase CRPS, and the 600-mg NAC tablets were more therapeutic for patients with cold-phase CRPS (*21*).

Treatment of CRPS with stellate ganglion blocks is widely utilized by medical professionals (*15*), and studies support the efficacy of stellate ganglion block therapy. One study, by Yucel et al. (*22*), included 22 patients with CRPS-1 who had suffered either distal radial fractures or soft-tissue hand traumas or had undergone surgery for carpal tunnel syndrome. All patients received three total stellate ganglion blocks, with one week in between each injection, and a 0–10 pain scale was used to evaluate each of the patients before treatment and two weeks after treatment (*22*). Wrist-joint range of movement (ROM) was also assessed before and

after treatment (*22*). Stellate blocks were found to significantly improve both CRPS pain and joint ROM in all patients (*22*). Overall wrist flexion improved from 50.2 ± 13.8 degrees to 69.4 ± 8.1 degrees; overall wrist extension improved from 38.9 ± 12.8 degrees to 58.7 ± 7.8 degrees; and overall supination improved from 41.1 ± 11.6 degrees to 63.1 ± 8.0 degrees (*22*). Blocks significantly improved pain in all patients as well ($p < 0.05$; *22*). The study by Yucel et al. indicates that stellate ganglion blocks do indeed alleviate CRPS-related pain and improve joint ROM.

Spinal cord stimulation has been shown to reduce pain in individuals with chronic CRPS (*18*, *23*). In a study by Kemler et al. (*23*), 36 patients with chronic CRPS were divided into two treatment groups, one receiving spinal cord stimulation with physical therapy and the other receiving physical therapy alone. Pain levels were assessed using a visual analog scale, with 0 cm being the lowest level of pain and 10 cm being the highest (*23*). The researchers found that after six months, patients who received spinal cord stimulation with physical therapy exhibited a mean reduction of 2.4 cm on the visual analog pain scale, whereas patients participating in physical therapy alone exhibited a mean reduction of only 0.2 cm (*23*). Although spinal cord stimulation significantly reduced pain in chronic CRPS patients, no improvement of functional capacity was noted (*18*, *23*). There is also no evidence of pain reduction due to spinal cord stimulation for patients with non-chronic CRPS (*18*). It therefore appears that spinal cord stimulation is effective in reducing the subjective pain levels of patients with chronic CRPS, though it has not been shown to increase their level of function.

Surgical sympathectomy, in which a portion of the sympathetic nerve chain is severed in order to prevent nerve signals from passing into a specific area (i.e., the affected limb in CRPS), has been shown to relieve pain in patients with CRPS (*18*, *24*). A study by Duarte et al. (*25*) sought to examine the effects of endoscopic thoracic sympathectomy (ETS) on pain levels of seven patients with CRPS. An ETS was performed on each of the seven patients, and subsequent pain levels were measured using the 0–10 visual analog scale (*25*). In all seven patients, resting pain completely disappeared following the ETS (*25*). Four of the patients reported pain upon movement, although the pain was less severe than it had been prior to surgery (*25*). All patients reported improvements in quality of life (*25*). Follow-up studies cited in the literature by Perez et al. (*18*) determined that pain relief due to surgical sympathectomy declined over time and that patients who received the surgery within three months of the initial inciting event exhibited the most favorable prognosis.

Both physical therapy (PT) and occupational therapy (OT) are increasingly common treatment interventions for patients with CRPS and are typically given in conjunction with medications (*18*). A study by Oerlemans et al. (*26*) compared the efficacy of both PT and OT in the treatment of CRPS, assessing a cohort of 135 patients with upper-limb CRPS of less than one year's duration. These patients were assigned to a group receiving PT, a group receiving OT, or a control group (*26*). Pain was measured prior to the initiation of treatment using a visual analog scale and the McGill Pain Questionaire (MPQ) and was reassessed after six weeks, three months, six months, and twelve months (*26*). ROM was also assessed regularly (*26*). At the conclusion of twelve months, patients who had undergone PT—and, to a lesser extent, OT—reported greater improvements in visual analog pain scores and less pain on the MPQ than did patients in the control group (*26*). ROM of the upper distal extremities also improved with PT and, to a lesser extent, OT (*26*). It is evident that both pain and ROM can be significantly improved by PT and OT in patients with upper-limb CRPS. PT and OT have also increasingly become part of the standard course of treatment in patients with CRPS (*18*). Limited research exists on the benefits of these therapies in patients with chronic CRPS, however, and no studies exist regarding the efficacy of OT and PT in patients with lower-limb CRPS (*18*).

Prognosis

The prognosis for CRPS patients is variable and uncertain. The most reliable prognostic factor is timing of diagnosis and initiation of treatment. As previously stated, the earlier the condition is diagnosed and treated, the more favorable the prognosis. Studies indicate that some patients with CRPS experience spontaneous remission of symptoms, and in some cases, remission is permanent (*28*). More commonly, however, patients experience only partial remission, in which signs of CRPS linger (*28*). Even among patients who experience spontaneous complete remission in symptoms, relapse can occur (*28*).

Studies are mixed with regard to the prognosis for patients diagnosed with CRPS during childhood and adolescence. Some studies have found that patients with CRPS diagnosed during childhood have more favorable outcomes than do those diagnosed as adults. Other studies have found no significant difference in prognosis for childhood-onset versus adult-onset CRPS. A study by Wilder et al. (*29*) conducted primary and follow-up assessments of 70 adolescents (mean age of 12.5 years) with CRPS. It was found that younger patients experienced less-severe CRPS symptoms and more-favorable prognoses than did older patients (*28*, *29*).

Additionally, upon follow-up, younger patients exhibited a shorter duration of deleterious symptoms related to CRPS (*28*, *29*).

Several studies contradict the findings of Wilder and colleagues, however. In a study by Tan et al. (*30*), a quality-of-life survey was given to 42 adults who had been treated for childhood-onset CRPS-1. The average time between childhood diagnosis and survey response was 12 years (*30*). More than half of the patients reported pain at the time of follow-up, and many of the typical signs and symptoms of CRPS had remained unchanged through the course of the disease (*30*). Fifteen patients also reported relapse in symptoms (*30*). These findings suggest that children with CRPS may have a less-favorable prognosis than earlier studies have indicated.

The implications of these latter studies for young people diagnosed with CRPS are extremely dire. The direct and secondary effects of living with chronic pain, taking medications that carry serious side effects and risk of dependency, depression, and other secondary health conditions such as overuse injuries are likely compounded over the course of a lifetime; thus, early diagnosis and initiation of treatment in children with CRPS is paramount for the preservation of long-term quality of life and well-being.

Secondary Health Conditions

CRPS can lead to debilitating secondary conditions that profoundly affect quality of life. Several common secondary conditions related to CRPS include depression, anxiety, sleep disturbances, drug dependency, and overuse injuries in non-affected extremities (*15*). These secondary conditions are certainly not unique to CRPS, as they are commonly seen in a variety of chronic pain conditions.

Interestingly, secondary conditions were prominent in both patients profiled in the case studies in this paper. Patient 1, who was diagnosed with CRPS more than three years after the initial inciting trauma, has reported significant life-altering secondary conditions as a result of her chronic CRPS. Patient 1 is moderately depressed and unable to carry out previously simple activities of daily living (such as holding her children) and has reported severe pain in the non-affected extremity because of overuse. She also reports widespread allodynia. These physical and psychological symptoms, combined with her inability to perform customary household activities, have strained her marriage significantly.

Patient 2 does not have to juggle a career and raising young children like Patient 1 does; nevertheless, she reports significant secondary conditions related to

her CRPS. These include moderate depression and overuse injury in her non-affected extremity.

Case Studies

Patient 1

Patient 1 is a 30-year-old female. She experienced a household accident on Christmas morning of 2016 and was seen at the emergency department of a local rural community hospital for a laceration of the extensor tendon in the left ring finger. She also experienced numbness and tingling in the lacerated finger. She met with a hand surgeon the following day. Upon physical examination, there was no active flexion at the flexor digitorum profundus (FDP) joint or ability to flex the tip of the finger. The surgeon suspected a ruptured FDP tendon and promptly recommended surgery. An exploration of the left ring finger was performed on December 30, and it was found that the FDP tendon and the ulnar digital nerve were significantly damaged. The FDP tendon and ulnar digital nerve were then repaired, and an Axogen nerve guard was implanted. This patient sustained two distinct, significant insults to the ulnar digital nerve: the initial laceration, followed by the surgical repair; this patient's CRPS would therefore be categorized as CRPS-2.

Several months after the initial surgery, Patient 1 continued to report significant pain in the left ring finger. The injury had already affected her employment status, and she needed regular PT. She also began to develop tendinitis in the right wrist from overuse. After careful examination of the finger by a second surgeon, Patient 1 was diagnosed with an ulnar digital nerve neuroma. Surgery was performed in order to remove the neuroma. Importantly, following this second surgery Patient 1 began to develop pain in the left shoulder and neck area, as well as skin temperature changes. Her doctors believed that this pain was mechanical in nature, perhaps due to an intraoperative traction injury. For the next three years, the patient's symptoms persisted and gradually worsened. Over time, the left finger pain traveled up the entire left arm with a cold sensation. A "sunburn" type sensation in the left arm, accompanied by hyperalgesia, was also noted. In the fall of 2019, Patient 1 was diagnosed with CRPS-2 in the left upper extremity.

CRPS has affected every aspect of this patient's life. She is a nurse and worked 38–42-hour weeks prior to the injury to her left finger. Following the initial injury, she was out of work for roughly five months. Since that time, she has been able to work only part time, as the left-hand and arm pain from CRPS have become almost unbearable. This has affected her family's finances. Her doctors have

recommended regular ketamine infusion therapy, but this treatment is not covered under her health insurance, and her limited work schedule has made it impossible for her to pay for the ketamine infusions out of pocket.

Patient 1 is married and has two children. Since the initial injury and onset of CRPS, the simple action of holding her children has become impossible. This has greatly affected her marriage and her ability to care for her children. These life-altering events have led to a diagnosis of depression (a common secondary condition of CRPS) in this patient.

Below is a list of Patient 1's current CRPS symptoms.

- Shoulder and neck pain following surgery
- Shooting pain from left ring finger to left side of neck
- Hypersensitivity of left ring finger (spread to other areas of the body)
- Cold skin on left hand and arm
- Temperature changes
- Color changes in left hand and arm
- Edema
- Numbness in left hand
- "Sunburn" type sensation throughout entire left upper extremity
- Abnormal sensations
- Plastic appearance of left hand compared to right hand
- Sleep disturbances due to pain in left upper extremity
- Trophic changes on left hand
- Cyanotic appearance of left upper extremity

Patient 2

Patient 2 is a 64-year-old female. She suffered a fall in February of 2017 while walking on a sidewalk with uneven pavement. She landed on her outstretched right arm and felt immediate severe pain in her right upper arm. She was taken to a local emergency department via ambulance. X-rays revealed a fracture of the right proximal humerus involving the surgical neck and greater tubercle. She was discharged with a sling and was told to follow up with the orthopedic doctor of her

choice. She did so, the fracture healed routinely, and she did well on the prescribed pain medications; however, in May of 2017, she began to develop pain and numbness in her right hand and fingers. She also had extreme grip difficulties. Her treating physician suspected CRPS and ordered a TPBS. The TPBS showed increased blood flow with soft-tissue inflammation and osseous uptake in the periarticular regions of the right upper extremity consistent with CRPS. This confirmed the treating orthopedist's clinical diagnosis of CRPS. A second opinion also confirmed the CRPS diagnosis.

Since the time of her diagnosis, Patient 2 has reported referred pain in her neck and in her left (uninjured) arm. She has been prescribed gabapentin, tramadol, and ibuprofen and has been participating in regular PT. Unfortunately, these therapies have not resolved her severe pain. Her doctors have recommended that she undergo a stellate ganglion block, but Patient 2 has a severe phobia of needles because of complications that her mother suffered during a medical procedure years ago. In the spring of 2020, Patient 2 had decided to go forward with the injection therapy despite her phobia, because the pain had become unbearable, but the procedure was canceled because of the COVID-19 pandemic, and at the time of this writing, she was in the process of rescheduling her injection.

Below is a list of Patient 2's current symptoms.

- Right-hand pain, swelling, and numbness
- Right-hand hyperhidrosis
- Tingling in right hand and arm
- Sensitivity to cold weather
- Feeling of intense cold in right hand
- Skin-color changes in right hand
- Trophic changes in right hand
- Sleep disturbances due to pain in right upper extremity
- Allodynia in right hand and arm
- Decreased motor function in right hand and arm

Patient 2 presents an interesting case, in that she was diagnosed with CRPS early, within several months of the inciting trauma. Because of her phobia of needles and resulting apprehension toward the evidence-based stellate ganglion block therapy, however, she has been unable to avail herself of the most promising

therapies for her condition. It remains to be seen if the injections that will be done roughly three years after diagnosis will be effective.

Both case studies featured above demonstrate the real-life barriers that individuals experience when attempting to receive the best, most effective treatment for the management of CRPS.

Conclusion

CRPS is a fascinating yet challenging condition for medical professionals. Accurate, timely diagnosis and effective treatment can be elusive with even the most experienced and conscientious physicians. Patients suffering from CRPS live with persistent severe pain, and this can affect every aspect of their lives, including career, family life, mental health, and overall quality of life. Additional research on CRPS is therefore vitally important and will, hopefully, lead to improvements in the diagnosis, treatments, and outcomes for patients with the condition.

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