Overview of Complex Regional Pain Syndrome from the Perspective of the Primary Care Physician

As a family practitioner with more than 40 years’ experience, there are few disorders more poorly understood than Complex Regional Pain Syndrome. I am no longer incredulous when a patient tells me that they were in a local emergency room or in a specialty physicians’ office who related having no knowledge of the disease other than recognizing its existence. I am similarly no longer surprised when patients present relating that an evaluating physician felt that this was a purely psychiatric disorder. I think it is extremely important for all primary care physicians to have a fundamental understanding of Complex Regional Pain Syndrome not necessarily for the purposes of treating the disease but to recognize the problem, order the appropriate diagnostic screening tools, and triage the patient to a physician with a more comprehensive understanding of the disease and necessary treatment.

As with most disorders, time is of the essence. The RSD Association of America has theorized that the average patient will see 4.3 physicians before a diagnosis is made. Based upon my own personal experience, this number is probably low. By the time a patient reaches my office for assessment and treatment of CRPS, they have seen at least seven or eight doctors and interventional treatment has either been withheld or misdirected. It is the mandate of the family physician to assure rapid and appropriate treatment of these patients.

To assist them in doing so, it is important to understand the history of the disorder, the pathophysiology, diagnostic testing, and treatment options.

Historically, CRPS dates back to the 17th century when Ambroise Paré described the disorder as severe burning pain following a peripheral nerve injury1. Moving forward, in 1864, SW Mitchell in his paper “Gunshot Wounds and Other Injuries,” used the term causalgia meaning “burning pain” to describe these symptoms of the peripheral nerve caused by gunshots2. The term Reflex Sympathetic Dystrophy was coined by J. Evans in 19463. This term persisted for several decades until the end of the 20th Century when in 1993 the International Association for the Study of


Pain (IASP) initiated the term CRPS and then later subdivided this into CRPS Type I and Type II. These represented the “old” causalgia and RSD primarily differentiated by the presence or absence of an initiating event to a major nerve\(^4\).

Originally, the Committee for Classification of Chronic Pain of the International Association for the Study of Pain (IASP) produced a series of criteria in 1994 at a Conference in Orlando, Florida\(^5\). These criteria are as follows:

- The presence of initiating noxious event or a cause of immobilization.
- Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.
- Evidence at some time of edema, changes in skin, blood flow, or abnormal sudomotor activity in the region of pain.
- This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

At that time it was subdivided into CRPS Type I (without evidence of major nerve injury) or CRPS Type II (with evidence of major nerve damage). Ultimately, these criteria were modified in 1998 and further restructured in 2004/2007 at the Budapest Conference.

The Budapest Criteria called for the clinical diagnostic criteria for Complex Regional Pain Syndrome as follows:

1. Continuing pain, which is disproportionate to any inciting event.
2. Must report at least one symptom in three of the four following categories:
   a. sensory reports of hyperalgesia and/or allodynia,
   b. vasomotor reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   c. sudomotor/edema reports of edema and/or sweating changes and/or sweating asymmetry
   d. 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 (a sign is counted only if observed at the time of the diagnosis) at the time of evaluation in two or more of the following categories:

a. sensory evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
b. vasomotor evidence of temperature asymmetry and/or skin color changes and/or asymmetry
c. sudomotor/edema evidence of edema and/or sweating changes and/or sweating asymmetry
d. 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 symptoms.

These criteria were offered by Harden, et al.  

While these diagnoses are clinical and have given us a structure by which we can accurately diagnosis Complex Regional Pain Syndrome, it is also important to understand from the primary care physician’s perspective, it generally begins with pain. This pain is most often described as a “burning pain.” Some other terms which are frequently utilized include aching, throbbing, sharp, dull, or lancinating. Generally, this pain will begin in a single limb but more often than not spreads to other regions of the body such as another limb and, in many cases, to internal organs.

Again, to simplify, we see asymmetrical skin changes with the affected limb being either hot or cold in comparison to the “normal” limb, discolored to a bluish purple, fiery red, dusky or mottled status. Edema is frequently present with tight, shiny skin. Hyperhidrosis (increased perspiration) can be seen as well as hair growth and nail growth changes, these changes either being increased or decreased in comparison to the contralateral limb.

There is controversy among some physicians as to whether or not CRPS spreads from limb to limb. Having seen almost 1100 patients with this disorder, I can affirm with absolute certainty that the disease spreads. The number of individuals who have “one limb” disease is, in my personal practice, less than five percent. The disease spreads horizontally (left arm to right arm, for example, and vertically left arm to left leg) in 95 percent of the time and diagonally (left arm to right leg) 6 R. Norman Harden, et al. Validation of proposed diagnostic criteria (the “Budapest Criteria”) for Complex Regional Pain Syndrome. 2010 International Association for the Study of Pain Medicine; 268-274.

7 Philip Getson, D.O. Complex Regional Pain Syndrome: From Diagnosis to Treatment. The Pain Practitioner, Spring 2015, Volume 25, Number 1.
five percent of the time. This information was documented in an article by Dr. Schwartzman, et al\textsuperscript{8} and has clinically proven to be the case.

**Differential Diagnosis:** The clinician who was evaluating the patients for chronic persistent pain must take into careful consideration the possibility of other disorders (hence the comment that no other diagnosis best explains the cause of the pain). Frequently this is difficult because of overlapping signs and symptoms.

It is imperative that anatomic lesions causing radicular type pain be identified. Discogenic pathology in the cervical and lumbar spines is a consideration that can be ruled out by MRI studies as well as clinical examination. Metabolic problems (primarily diabetes with neuropathy) is a consideration. CNS manifestations such as neoplasms, spinal cord injury, and radiculopathy and plexopathy are to be considered. Lyme disease, thyroid dysfunction, and other metabolic issues are also to be ruled out. Entrapment type neuropathies such as carpal tunnel, cubital tunnel, and tarsal tunnel syndrome are often mistakenly diagnosed and, unfortunately, treated surgically when in fact they are manifestations of Complex Regional Pain Syndrome and not purely entrapment type neuropathies. Morton’s neuromas are a frequent cause of lower body Reflex Sympathetic Dystrophy and brachial plexopathies are perhaps the most common cause that I have seen of upper body CRPS. Heavy metal exposures creating neurologic abnormalities, alcohol related disorders, and nutritional abnormalities are considered as well. Reynaud’s phenomenon which can be a manifestation of CRPS is often offered as a diagnosis rather than a symptom associated with this disease. Autoimmune and rheumatologic disorders must all be excluded.

**Diagnosis:** There are varying opinions as to the best way to diagnose CRPS. Clearly a comprehensive history and physical examination, as always, comes first. Individuals who meet the Budapest criteria are certainly considered to be afflicted with the disorder. However, it is important to rule out concurrent conditions which must be treated for the best possible outcome of the CRPS treatment. Borchers, et al\textsuperscript{9} offers a number of diagnostic tests that may be beneficial. He begins by mentioning electrodiagnostic testing (EMG and nerve conduction study) that he recommends to “exclude nerve lesions.” Unfortunately, it is with this particular recommendation that I disagree. First and foremost, CRPS is a disease of the sensory nerve fibers primarily and electrodiagnostic testing is a test of motor

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fibers. Therefore, the yield of positive outcomes is minimal. However, in addition, the use of electrodiagnostic testing with implantation of small electrodes and the concomitant electrical current is extremely discomforting and even exquisitely painful for patients with an allodynic response to the CRPS. I therefore do not recommend this test be done unless absolutely necessary.

There is a school of thought that suggests that fibromyalgia is a subsect of Complex Regional Pain Syndrome and in fact is not a separate entity. Dr. Martinez-Lavin, Chief of Rheumatology, in Mexico in 2001 offered this opinion in an article called “Is Fibromyalgia Generalized Reflex Sympathetic Dystrophy.” A similar opinion was offered by Dr. Jeffrey Littlejohn in a subsequent article. If one reviews the websites of the RSD Association of America and the National Fibromyalgia website, the similarities are striking. It is certainly worth considering the fact that these both may be one in the same disorder separated by varying changes in the symptomatology.

Further recommendations made include a Quantitative Sensory Testing to detect small nerve fiber dysfunction, laboratory tests to rule out autoimmune conditions and metabolic abnormalities, Laser Doppler Flowmetry to assess blood flow and peripheral vasoconstrictive reflexes. Anatomic testing such as MRI, CAT scans, etc. are done to rule out lesions of the nervous system.

Triple phase bone scans, long thought to be the “gold standard” of diagnostic testing has fallen into disfavor because of his lack of specificity. When done and when positive, it can be useful; however, the statistics suggest that this occurs in less than 20 percent of all studied individuals.

It is my opinion, however, that infrared imaging (Thermography) is the best diagnostic test for a conclusive diagnosis of Complex Regional Pain Syndrome. I have been involved with Thermography since 1982 and have used infrared imaging in several hundred patients with suspected Complex Regional Pain Syndrome. Because of the nature of the study (it is noninvasive, non-radiologic, and non-painful) and because it specifically targets the sensory nerve fibers, it is not only easy to perform and inoffensive to the patient, but the level of accuracy has been


incredible. In my own private practice, I have never seen a patient with clinical manifestations of CRPS that were not evident on thermographic testing.

Moreover, time and time again I have seen individuals who present with localized CRPS in one limb who have sympathetic dysfunction in other areas thermographically. Invariably, in 100 percent of the cases, these patients will develop sympathetic dysfunction symptomatology in the “new” limb in a period of six to twelve months.

**Symptomatology:** The symptoms manifested by patients with Complex Regional Pain Syndrome are extremely wide reaching. First and foremost, in almost all patients, is the subjective complaint of pain. The characteristics of pain have been described above. It is also noted that this pain more often than not seems disproportionate to the inciting event.

**Cardiac:** Patients have cardiac complications with atypical chest pain\(^{12}\). Most of these patients have a neuropathic intercostobrachial nerve traction injury. Many patients with this particular injury also seem to have an uncommon amount of coronary artery disease disproportionate with age and risk factor. This pain is generally described as deep or aching pain as opposed to burning pain. It seems to be accelerated by elevation of the arms.

Other complications include tachycardia and bradycardia, the former more often seen in individuals in the 20-40 age group and the latter in the 40-70-year-old group. The bradycardia can be severe enough to warrant pacemaker implantation despite the absence of intrinsic heart disease on a comprehensive cardiac workup.

Fifteen percent of patients complain of shortness of breath\(^{13}\). Ninety percent of patients with longstanding disease manifest some component of neurogenic edema\(^{14}\). This appears to be resistant to the use of oral diuretic therapy. It does, however, frequently lead to infections due to stretching of the skin and poor perfusion of the skin.

Profound muscle weakness is frequently seen particularly in the leg muscles. MRIs of these limbs frequently show bone marrow edema and some patients demonstrate microfractures of the bones in the distal limbs.

Approximately one-third of moderate to severe CRPS patients suffer hypothyroidism\textsuperscript{15}.

Seventy-one percent of patients reported skin color changes within five years and up to eighty-one percent after 15 years. These include a combination of erythema, mottling, livedo reticularis, and cyanosis\textsuperscript{16}. Shininess of the skin accompanying the neurogenic edema is frequently noted. Neurodermatitis is a common finding. Changes consistent with Reynaud’s phenomenon are seen due to sympathetic dysregulation. Gardner-Diamond Syndrome is common in CRPS patients\textsuperscript{17}.

Another interesting finding is Dercum’s disease, a painful occurrence of multiple lipomas frequently in the abdomen and trunk area but potentially present anywhere throughout the body.

Urologic manifestations occur in 25 percent of patients\textsuperscript{18}. In many instances, these parallel interstitial cystitis but more often are the result of a neurogenic bladder.

Gastroenterologic symptoms are extremely common. In the work of Schwartzman, et al\textsuperscript{19}, it suggests that constipation was most frequently reported followed by nausea, vomiting, intermittent diarrhea, indigestion, and irritable bowel syndrome. Dysphagia was commonly seen. GERD was noted at a rate of 73 percent.

In my personal practice, gastroparesis was a major problem in virtually all patients. Gastric emptying studies more often than not show a significant delay and the specific treatment that has shown the most promise is endoscopically guided injection of Botulism Toxin A into the pyloric sphincter. Symptoms of eyes, ears, nose, and throat include diplopia, photophobia, otophobia, headaches (generally

the result of hypersensitization of the greater occipital nerves), and frequent deterioration of dental hygiene. It is all too frequently the case that because the nerve roots of the mouth leading to the teeth are affected, teeth begin to fall into disrepair or even fall out. Unfortunately, I have seen many individuals with full dental extractions at a young age because of the horrific nature of their teeth for this reason (in combination with polypharmacy).

**Treatment:** Treatment of Complex Regional Pain Syndrome must be multifaceted and requires individualized and multidisciplinary approach. First and foremost is mobility. Movement of the affected limb can in instances prevent secondary complications such as frozen shoulders with upper extremity/brachial plexus injuries. Physical therapy and/or occupational therapy should be initiated when the benefits of such therapy do not outweigh the risks of worsening the condition. The PT/OT specialist should be well-versed in the “do’s and don’ts” of their specific therapeutic regimen and, in my estimation, it is imperative that the ordering physician be cognizant of their level of experience and be involved in the decision-making process of their therapy to assure that such therapy does not cause a further stretching of injured nerves or worsening of their condition.

**Medication:** As mentioned in a previous article\(^\text{20}\), there are, in my estimation, four separate “pains” in CRPS and each one of these must be dealt with individually.

The first of these is spastic pain of muscular involvement. Physical therapy is important to keep the muscles well-toned and utilized and muscle relaxant medication can provide an adjunct to such therapy by relieving excessive spasm. Frequently, the movement disorder of CRPS is mistaken for muscular spasm. Physicians who are using Baclofen or Tizanidine for muscular spasm are not recognizing the difference between spasm and spasticity and the “jerky” movement disorder that frequently accompanies CRPS. These latter two medications are best used in the evening which, coincidentally, is when the symptomatology seems to be worse as they are both sedating to varying degrees.

The second “pain” of CRPS is the inflammatory component. Anti-inflammation medicines can be utilized with caution to protect the gastrointestinal tract. Topical anti-inflammatories have been used more and more and compound creams have come into great favor in the last decade. These creams, applied directly to the

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affected areas, include a number of component parts, one of which is the specific anti-inflammatory medication and are helpful in patients with limited involvement.

The third “pain” is the burning and associated neuropathic pain which, as a general rule, have been treated with anticonvulsant medications. Gabapentin, Topiramate, etc. all have been utilized with varying degrees of success. The drugs tend to have side effect panels that must be carefully observed by the treating physician especially with the use of Gabapentin which, in relatively sedentary female patients, has been shown (in my practice) to cause a great deal of weight gain. The failure of one of these drugs to provide relief does not preclude the fact that other medications in this drug classification group may be of benefit.

Finally, there are those patients who require analgesic medication. Many patients are on relatively high doses of opioid medication. The risk of opioid induced hyperalgesia must be considered. I have found in my practice that titrating patients off of opioids almost invariably causes an improvement as opposed to a worsening of the pain. (It is a great psychological issue to convince patients who are led by public perception to believe that their pain will get better with opioid medications to withdraw themselves from same, but when I find an individual who is motivated to do so, the results are almost uniformly positive.)

There are a number of other agents that have been used anecdotally for the treatment of CRPS including calcium channel blockers, Dextromethorphan, tricyclic antidepressants (which like Gabapentin tend to be weight producers in women), Amantadine, and serotonin-norepinephrine reuptake inhibitors (SNRIs) as well as SSRIs.

I have found that antidepressants are generally of little value in the treatment of the chronic pain and, for that matter, in the treatment of the accompanying depression. The depression is due to multifactorial problems, not the least of which is the ongoing pain and the accompanying dysfunction and loss of lifestyle. Treating someone with an SSRI or SNRI is not going to eliminate the underlying problem and unless the level of depression is interfering with their ability to deal with life on a day-to-day basis, I do not utilize antidepressants at all. I would like to mention for the record that withdrawing patients from SSRIs and SNRIs is frequently more difficult than withdrawing them from opioid medications. The side effect panel of withdrawals from these antidepressants can last months and the post-SSRI/SNRI recurrent symptomatology can occur spontaneously up to a year following their withdrawal.
Interventional procedures by trained specialists in pain management include sympathetic blocks to the stellate ganglia or lumbar sympathetic chain. Eighty percent of patients have been found statistically to have sympathetically dependent pain meaning that the pain will improve with sympathetic blockade. Twenty percent have sympathetically independent pain and will not respond to blocks. If such a block is given without success on two occasions, it is my opinion that they should be considered sympathetically independent patients and other means for treatment should be sought.

There is a current school of thought that suggests that sympathetic blocks are no longer beneficial. I have found them to be of great use early in the process of the treatment of CRPS and, sometimes in conjunction with other interventional procedures even if they have been minimally successful at the beginning of treatment.

Epidural injections are beneficial not for the treatment of CRPS but concurrent radicular problems from discogenic pathology.

Spinal cord stimulators are used by many interventional practitioners. Personally, I have an issue with the use of such stimulators in individuals whose disease has extended beyond the initial limb. I have found that this requires further intervention with multi-lead placement and causes problems and decreases efficacy. In some individuals who have single limb involvement, the insertion of a spinal cord stimulator can be most helpful. However, I have encountered problems in some cases where patients developed CRPS type pain in the incisional site from the insertion of the permanent implant. The pain that this has produced is described as being far greater than the pain in the limb that was treated with the stimulator. This has been problematic. It has necessitated the attempts to inject the area around the incision but because of the exquisite alldynia this too is difficult. A risk-benefit ratio must be considered when implanting such a device. Also, in my opinion, it is imperative that the initial overture be done as a percutaneous insertion to determine the benefit to be derived from the stimulator as opposed to the potential risks. Finally, intrathecal pumps have been utilized for patients on polypharmacy to bypass the medication in the gastrointestinal tract. This, to me, is a treatment of last resort in that it is sentencing the patient to use of medication to control the pain as opposed to attempts to rectify and can treat it.

Recently there has been a great deal of emphasis placed on the use of bisphosphonates for the treatment of Complex Regional Pain Syndrome. The original bisphosphonate used was Pamidronate which in limited study was shown
to be effective in a small percentage of patients and a limited number of studies. Bisphosphonates require normal renal function and careful monitoring of the kidneys on an ongoing basis. My own personal experience with bisphosphonates has not been particularly encouraging but this has only been on a handful of patients and cannot be considered an accurate representation of the benefits of Pamidronate or lack thereof.

There is currently an ongoing study with Neridronate, a second generation bisphosphonate, being conducted worldwide based upon a study of 21 female individuals in Italy who apparently benefited from the use of bisphosphonate therapy. The results of the study will be known in the future and the increased use of bisphosphonate will likely be contingent upon the results of that study.

At the present time, the treatment that has been proven to be most effective and refractory CRPS is Ketamine infusion therapy. The onset of the use of Ketamine began with a paper written in 2002\(^1\) and the escalation of Ketamine usage in a sub-anesthetic dose has been rapid. Three years later, in 2005, a second article was written regarding the benefits of Ketamine for perioperative pain management\(^2\). Additional articles were written with regard to Ketamine in sub-anesthetic and anesthetic doses.

Finally, a research study was completed with the use of intraoperative Ketamine for the attempt at prevention of extending CRPS as a result of surgery. Many surgeons are hesitant to operate on patients who clearly need surgery for fear of extending the disease. The article\(^3\) clearly stated that the use of intraoperative Ketamine was beneficial in preventing the spread. Since that article, of which I was coauthor, there have been dozens of cases of my own personal patients who have gone to the operating room for various types of surgery. None of whom have extended the CRPS with the use of intraoperative Ketamine. While the number of patients involved is limited (less than 40), this is certainly a promising statistic.


Currently, sub-anesthetic Ketamine is being utilized in over 75 sites across the country. Various protocols for the use of the Ketamine have been implemented and a conference is scheduled for October of 2016 to consolidate opinions and come up with a consensus on the most efficacious means of treatment. However, in my practice, 80 percent of patients treated with outpatient sub-anesthetic Ketamine have shown improvement based upon diminished symptomatology (alldynia, hypersensitivity, color and temperature changes, and edema) diminished pain on a VAS pain scale, increased physical activity and capability, and reduction of medication.

Other Modalities of Therapy: I have found that concomitant “alternative” therapies have been beneficial in treating patients. I always instruct patients in a healthy diet. We have learned that abolishing gluten has caused an almost immediate reduction in pain. Reduction or elimination of sugar, dairy, and caffeine has helped as well. We encourage patients in smoking cessation and decreasing alcohol intake.

Alternative therapies such as acupuncture, Reiki, etc. have been extremely beneficial in improving the patient’s overall wellbeing.

Exacerbating Factors: It is important to note that there are many things that can cause an acceleration of the symptoms of CRPS in addition to the obvious one of additional trauma (however slight). These include infection, weather changes, uncontrolled medical illness, and most especially psychological trauma. The effect of the latter cannot be diminished. Patients who undergo trauma such as death of a loved one, loss of a job, etc. invariably have a significant and almost immediate increase in discomfort. Direct intervention and counseling between the clinician and the patient is necessary to reassure them that this can be short-lived and controllable.

It is important to have psychological experts on board for the treatment of refractory depression or anxiety beyond the scope of the family clinician. Additionally, in my opinion, it is imperative to have familial support. I will frequently bring other family members into the office to answer questions that they have and reassure them that while cannot necessarily “see” the disease process from which the patient is studying, it is clear and evident that this is in fact a significant problem.

Conclusion: Complex Regional Pain Syndrome is certainly that...“complex.” It involves a great deal of time on the part of the treating physician to evaluate and
assess the patient and work in collaboration with other physicians and family members to deal with this extremely complicated problem. More awareness is the key to earlier intervention and better result. By educating the primary care physicians, we can perhaps arrive at an earlier accurate diagnosis and facilitate referral for intervention at a time when it is most beneficial.

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