Various Complications of Complex Regional Pain Syndrome (CRPS)

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***Abstract*:** Complex regional pain syndrome (CRPS) is an unrelenting pain syndrome that affects millions of people world wide. Most patients display the common signs and symptoms of CRPS. When patients have suffered for many years to decades they may develop many various complications of the disease. In this article we will discuss many of the various complications that are associated with CRPS.

Key words: *Complex Regional Pain Syndrome (CRPS), Internal Organ Involvement, Spread of CRPS, Various Complications of CRPS.*

INTRODUCTION

There are various ways complex regional pain syndrome (CRPS) can develop. Onset of this disease is usually caused by a minor trauma, soft-tissue injury (i.e. sprain ankle or wrist); other such causes are crush injuries, surgery, repetitive stress injury (RSI), electrical injuries (EI), and in some cases venipuncture injury (VP CRPS II) (1-4). Spread of the disease and internal organ involvement has also been reported in many patients who suffer from late stages of the disease (5-9).

HISTORY OF CRPS

The various symptoms that make up CRPS, and later, the formal naming of this medical condition, have been well documented throughout history. Ambroise Pare was one of the first to describe what is now called CRPS, through his account of the persistent pain that King Charles IX had suffered from in the 16th century (10). In the late 1700's British surgeon Sir Pervcivall Pott recognized burning pain and atrophy in injured extremities (1, 11). In 1813 Denmark reported a single case of a soldier who had an amputation due to burning pain (1, 12, and 13). In 1838 Hamilton had seen some cases in which his patients had symptoms of causalgia which resulted from accidental nerve injuries (14). Early in 1864 Paget had patients who had symptoms of constant warmth in their limb after nerve injury (15). Also, in 1864 Silas Weir Mitchell the father of American neurology gave the description of causalgia in his classic article Gunshot Wounds and Other Injuries of Nerves, but it was not until 1867 when he coined the term of causalgia from the Greek words, "Kausos" (heat) and "algos" (pain) to describe this syndrome (16). Since Mitchell's first description of this painful syndrome, there have been many other names giving to this awful disease. In 1900 Sudek named it Sudeck atrophy; in 1937 DeTakats named it Reflex Dystrophy; in 1947 Steinbrocker named it Reflex Neurovascular Dystrophy and Shoulder-Hand Syndrome; in 1947 Evans named it Reflex Sympathetic Dystrophy (RSD); and in 1994 Merskey, et al. named it Complex Regional Pain Syndrome (CRPS) (17-21).

STAGES OF CRPS

CRPS has been divided into four different stages. Depending on nature of injury, the stages vary in their duration. In the 17 patients suffering from venipuncture CRPS in our series, deterioration from stage I to stage III was measured in a few weeks up to less than 9 months. This is in contrast with CRPS in children in whom stages would stagnate, reverse or improve slowly (2,22).

Stage I, is a sympathetic dysfunction with typical thermatomal distribution of the pain. The pain may spread in a mirror fashion to contralateral extremity or to adjacent regions on the same side of the body (9). In stage one; the pain is usually SMP in nature.

In stage II, the dysfunction changes to dystrophy manifested by edema, hyperhidrosis, neurovascular instability with fluctuation of livedo reticularis and cyanosis - causing change of temperature and color of the skin in matter of minutes. The dystrophic changes also include bouts of hair loss, ridging, dystrophic, brittle and discolored nails, skin rash, subcutaneous bleeding, neurodermatitis, and ulcerative lesions.

Due to the confusing clinical manifestations, the patient may be accused of factitious self-mutilation and "Münchausen syndrome (2,23)." All these dystrophic changes may not be present at the same time nor in the same patient. Careful history taking is important in this regard (2,24).

In stage III, the pain is usually no longer SMP and is more likely a sympathetically independent pain (SIP). Atrophy in different degrees is seen. Frequently, the atrophy is overshadowed by subcutaneous edema. The complex regional pain and inflammation spread to other extremities in approximately one-third of CRPS patients (24-26).

At stage II or III it is not at all uncommon for CRPS to spread to other extremities (2,9,22,27). At times, it may become generalized. The generalized CRPS is an infrequent late stage complication (2,9). It is accompanied by sympathetic dysfunction in all four extremities as well as attacks of headache, vertigo, poor memory, and poor concentration. The spread through paravertebral and midline sympathetic nerves may be vertical, horizontal, or both (2, 9, 27-29). The original source of CRPS may sensitize the patient to later develop CRPS in another remote part of the body triggered by a trivial injury. The ubiquitous phenomenon of referred pain to remote areas (e.g., from foot or hand to spine) should not be mistaken for the spread of CRPS.

At stage III, inflammation becomes more problematic and release of neuropeptides from c-fiber terminals results in multiple inflammatory and immune dysfunctions. The secondary release of substance P may damage mast cells and destroy muscle cells and fibroblasts (30-33).

Stage IV identifies the final stage of CRPS manifested by (1, 2):

- Failure of the immune system, reduction of helper T-cell lymphocytes and elevation of killer T-cell lymphocytes.
- Intractable hypertension changes to orthostatic hypotension (34).
- Intractable generalized edema involving the abdomen, pelvis, lungs, and extremities.
- Ulcerative skin lesions which may respond to treatment with I.V. Mannitol, I.V. Immunoglobulin, and ACTH treatments. Calcium channel blockers such as Nifedipine may be effective in treatment (35).
- High risks of cancer and suicide are increased.
- Multiple surgical procedures seem to be precipitating factors for development of stage IV.

Stage IV is almost the flip side of earlier stages, and points to exhaustion of autonomic and immune systems. Ganglion blocks in this stage are useless and treatment should be aimed at improving the edema and the failing immune system. Sympathetic ganglion blocks, alpha blockers, including Clonidine, are contraindicated in stage IV due to hypotension. Instead, medications such as Proamantin (midodrin) are helpful to correct the orthostatic hypotension (2,36).

With passage of time, and types of treatment, CRPS goes through stages with variable time tables and sympathetic responses (5) (Table I).

Table I. Stages, Signs and Symptoms of CRPS	
Stages	**Signs / Symptoms**
Stage I: Dysfunction	Hyperpathia; allodynia; muscle weakness; flexor spasms; thermal changes
Stage II: Dystrophy	Edema; skin; hair and nail changes
Stage III: Atrophy	Muscle atrophy; neurovascular instability; cutaneous rash or skin ulcers
Stage IV: Irreversible disturbance of plasticity; autonomic failure	Systemic autonomic failure; visceral edema; irreversible low BP; MRSA; elephantiasis; cancer

VARIOUS COMPLICATIONS OF CRPS

Most patients suffer from the standard signs and symptoms of the disease. Over time a majority of patients that have suffered for many years to decades do develop various complications of the disease. Over the years we have recognized a large array of various complications associated with CRPS which often go untreated. Many of these complications are not well recognized by the medical community treating CRPS patients. However, CRPS continues to be a very complex disease to understand and to treat. These various complications can impede the proper treatment for spread of the disease and the underlying issues that arise from these complications.

It is very well known that during the long duration of the disease when patients reach stage IV, they start to develop various complications such as disturbance of the immune system (neurogenic inflammation), limbic system, cardiac system, endocrine system, and the respiratory system. These are just a few of the various complications later discussed in this article (1,2,4,7) (Table II).

Table II. Various Complications of CRPS	
Agitation	Internal Organ Involvement
Cardiac Disturbance	Interstitial Cystitis
Depression	Intractable Hypertension
Disturbance of Immune System	Irritability
Disturbance of Judgment	Keratitis Sicca (Dry Eyes)
Dysphagia	Limbic System Dysfunction
Endocrine System Dysfunction	Low Cortisol Levels
Fatigue	Movement Disorders
Gardner Diamond Syndrome (Spontaneous Bruising)	Respiratory System Complications
Gastrointestinal Complications	Skin Lesions, Rashes and Ulcers
GERDS	Spread of CRPS
Headaches (Migraine)	Tinnitus
Hearing Complications	Urological Complications
Hypothyroidism	Visual Disturbance
Insomnia	Vulvodynia

SPREAD OF CRPS

The spread of CRPS is not usually limited to one part of an extremity or one extremity. Usually, the pathological sympathetic function spreads to adjacent areas (1). CRPS can also spread to the oral facial region; it causes necrosis (death of cells) of the maxillary and mandibular bones in the areas of the root canals.

In the late stages of CRPS, due to prolonged immobilization, or improper treatment such as unnecessary surgery or application of ice, the disease shows a tendency to spread.

The spread may be vertical from arm to leg (or vice versa) on the same side or may be horizontal from arm to arm or leg to leg. The spread which occurs in about one third of patients is more likely to develop after surgical procedure (1,2,9,21,37-42).

The mechanism of spread is due to the fact that at the level of the spinal cord the sympathetic input has a tendency to cross the midline to the opposite side. The second reason for spread is a chain of relay stations of the sympathetic nerves in the form of sympathetic ganglia on each side of the spine (42).

The main reason for the CRPS becoming bilateral and spreading to other extremities is because in contrast to the somatic nervous system, the sympathetic nervous system has bilateral innervation. In the somatic nervous system (usual sensation and motor function) the abnormalities in dermatome in a specific nerve root distribution, whereas in CRPS the abnormality is distributed among the blood vessels, distribution of nerves (thermatomes) and to the sympathetic ganglia and their across the midline collections, the condition reflects itself on both sides rather than one side of the body. This bilateral manifestation through the sympathetic plexi across the midline explains the patient's problem with headache, dizziness, tinnitus, chest pain, and abdominal manifestations of CRPS (gastritis, diarrhea, cramps) and spread of CRPS to other extremities.

INTERNAL ORGAN COMPLICATIONS

CRPS invariably involves the internal organs. Usually the skin surface is cold at the expense of increased circulation to the internal organs. This increased circulation can cause osteoporosis, fractures of bone, abdominal cramps and diarrhea, disturbance of absorption of foods with resultant weight loss, water retention with aggravation of premenstrual headaches and depression, persistent nausea and vomiting, as well as severe vascular headaches mistaken for "cluster headache".

In addition, CRPS can cause the complication of intractable hypertension which responds best to alpha I blockers (Dibenzyline, Hytrin, or Clonodine). CRPS can cause attacks of irregular or fast heart beat, chest pain, coronary artery spasm (angina), as well as disturbance of function of other internal organs. A few examples are frequency and urgency of urination, respiratory disturbance such as dyspnea and apneic attacks, and attacks of severe abdominal pain.

Attacks of swelling of the internal organs complicated by intermittent constriction of the blood vessels to different organs can result in chest pain, attacks of sharp central pain (stabbing severe pain in the chest or abdomen), and changes in voice (suddenly developing a temporary "chipmunk" type of voice change). The sharp, stabbing, central pain can be helped with treatment with medications such as anticonvulsant (Tegretol or Neurontin).

The internal organs complication may become aggravated by traumatic effect of sympathetic nerve blocks. One such complication is accidental trauma to the kidney with resultant hematuria (blood in urine) and aggravation of hypertension.

Because of the above complex phenomenon, in CRPS the sympathetic nerves follow the path of the blood vessels rather than somatic nerve roots resulting thermotomal rather than dermatomal sensory nerve distribution (mistaken for hysterical sensory loss) may cause a complex clinical picture that baffles the clinician and forces the clinician to blame the patient as being hysterical, hypochondriac, and blaming the serious warning signs of CRPS complications as "functional and not organic".

The end result is the deadly phrase "it is all in your head" which practically almost all CRPS patients have had to deal with in the course of their treatment. The patient's symptoms and signs are real and they are not figment of their imagination.

The treating physician needs to take the time to learn and understand that the sympathetic system is complex, bilateral and diffuse.

Both Doctors Schwartzman and Veldman have reported that CRPS Type I and II are systemic disease that can affect any organ system (7,43).

IMMUNE SYSTEM COMPLICATIONS

The sympathetic system regulates the immune system. The sympathetic system is responsible for control of body temperature, control of vital signs and control of the immune system. Any kind of stress that stimulates the sympathetic system also stimulates the immune system.

In the first two years after the development of CRPS, the immune system is up regulated with high T cell lymphocytes causing low grade fever, neurodermatitis, trophic ulcers, spontaneous bruising, edema, clinical pictures of compression (entrapment), and neuropathies such as so-called carpal tunnel syndrome and thoracic ulcer syndrome, which can easily be corrected with conservative treatment rather than surgical treatment.

After two years, as the CRPS becomes chronic and the healing power (plasticity) of the nervous system and immune system becomes disturbed. The patient develops hypoactive, down regulated immune system with development of permanent elevation of killer T cell lymphocytes, suppression of helper T cell lymphocytes, and development of persistent skin pathology, such as persistent edema involving the paraspinal and upper and lower extremities. The patient also develops persistent pruritus and neurodermatitis, persistent trophic ulcers, spontaneous bruising, permanent dystrophic changes in regard to skin healing, and abnormal hair and nail growth.

CRPS is due to dysfunction of the sympathetic nervous system. The sympathetic nerves function in a dynamic fashion - at times being hyperactive and at other times being hypoactive. This is in regard to control of circulation and control of the immune system. From day to day the sympathetic control of circulation may fluctuate. This is usually in the form of neurovascular instability, meaning one day the hand or foot is bluish red, and the next day it is so white it looks like it is dead. The immune system control may undergo up-regulation or down regulation: one day the patient is feverish, and the next day the patient is "ice cold".

NEURO-INFLAMMATION COMPLICATIONS

The sympathetic system has three main functions:

1. Thermal regulation.

2. Control of vital signs (blood pressure, pulse and respiration).

3. Control of the immune system.

All three functions are essential for preservation of milieu interne. The neuroinflammation is a physiopathologic response of the body against any stressor. Neurodermatitis of emotional stress, edema of the extremity in CRPS, profuse skin ulcers in venipuncture CRPS II (3), sterile osteonecrosis involving the facial bone or bones in the extremities, and modulation of the T-cell lymphocytes in late stages of neuropathic pain and CRPS are some of the examples of neuro-inflammation. The sympathetic system shows a uniform response to a stressor be it infectious, traumatic, emotional, or prolonged inactivity. If the neuro-inflammation is not properly diagnosed and treated, the patient will end up with unnecessary surgeries for carpal tunnel, tarsal tunnel, or thoracic outlet syndrome. The trauma of surgery secondarily initiates a new round of more severe neuro-inflammation, edema, and entrapment.

Neuro-inflammation is the key to understanding the hyper-and hypothermic spots in Infrared Thermal Imaging (ITI). Peripheral nerve injury causes vasoconstriction distally, and vasodilation in the corresponding paravertebral nerve regions.

This hyperthermic vasodilation in the paraspinal regions is due to transmission of substance P (SP) and nitric oxide (NO), and other neurokines from periphery to the spinal cord.

Prolonged neurokine transmission and accumulation at paraspinal nerves distribution causes neck pain, low back pain, headache, and vertebral arteries constriction secondary to vertigo, falling attacks, and blurred vision.

Of these four principle manifestations of CRPS (pain, movement disorder, inflammation, and insomnia) the inflammation manifests itself in several different forms. This may be in the form of simple swelling of the extremities, joint pain, skin rash, blotching or cyanosis, trophic changes such as hair loss or fingernails degeneration, black and blue spots without any trauma to the skin, bleeding under the skin, and persistent itching.

Epidural and paravertebral nerve blocks correct this condition. However, any type of trigger point or nerve block injection should be done proximally rather than distally in the area of pathology. Any needle insertion in the distal portion of the extremity will add more trauma and aggravation of the neuropathic pain and vasoconstriction.

The inflammatory aspect of the CRPS is just as disabling as the pain or movement disorder.

MOVEMENT DISORDER COMPLICATIONS

Movement disorders are common in most CRPS patients (1,44) (*Figures 1 and 2*). As, Schwartzman has emphasizes “the movement disorder is frequently ascribed to hysteria and pain” (45).

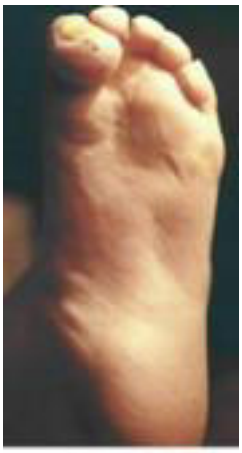

Figure 1. CRPS and movement disorder of the left foot, ankle, and toes.

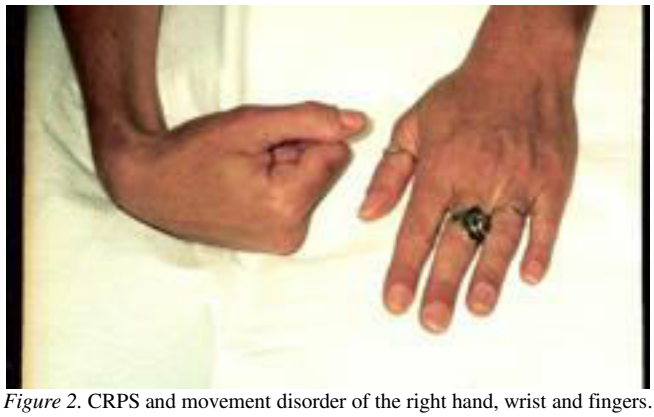

Figure 2. CRPS and movement disorder of the right hand, wrist and fingers.

Myoclonic jerks are common forms of movement disorder in CRPS (2). In 38 of our 824 patients suffering from CRPS due to spinal cord injury, myoclonic jerks were invariably noted. In addition, myoclonic jerks were present in 44 of 63 CRPS patients secondary to electrical injury (2,44,46,47). This may be due to electricity going through the path of least resistance (afferent c-fibers) and secondarily originating spinal cord dysfunction (1,2,46).

In, Schwartzman and Kerrigan's study of 200 patients with RSD, subtle dystonia and movement disorder were seen in 10 patients (48).

In studies reported by Jankovic, movement disorders in CRPS have been accompanied by tremor and dystonia (1,49,50).

Also, Blümberg and Jänig have reported tremor and other movement disorders in more than 80% of CRPS patients (51). Veldman, et al. has noted movement disorder in 95% of 829 patients (43). In our series of 824 patients, the incidence was 78% (2).

Cervicogenic CRPS in rare cases can cause tremor in the hand and forearm, and in some cases it can be severe enough to cause writer's cramps and illegible handwriting. This complication of CRPS is more commonly seen after traumatic adjustment of the cervical spine (1).

LIMB DEFORMITY COMPLICATIONS

Limb deformity is another complication seen in some CRPS cases. Patients with limb deformity had an average lag time of 22.3 months delay between the onset of the disease and the first diagnosis of CRPS. This was in contrast with the non-deformity patients who had a lag time of 14.5 months between the onset and diagnosis.

The patients with limb deformity were treated with ice or hot and cold challenge for an average of 4.6 months versus the patients with no deformity for an average of 3.1 months. In both groups, the hypothermia therapy was usually discontinued due to the persistent protestation of the patient against ice treatment because of aggravation of pain.

CRPS-I (RSD) versus CRPS-II (Causalgia) categories: There was no statistical difference between the two categories in regard to the incidence of complication of limb deformity. However, the causalgic group developed the limb deformity earlier in the course of the disease. The average lag time between trauma and the development of the deformity in CRPS-II (causalgia) group was 7 months.

The risk factors contributing to the development of limb deformity consist of surgical procedures, exploratory operative procedures (such as looking for neuroma or looking for entrapment neuropathy), immobilization with cast or wheelchair, and prolonged use of cryotherapy (application of ice). The deformity evolved earlier in the CRPS-II (Causalgic) group than in the CRPS-I (RSD) group.

LIMBIC SYSTEM COMPLICATIONS

The neuropathic pain of CRPS is regional, and its polysynaptic sensory fibers terminate bilaterally in the limbic system (52). This explains the symptoms of insomnia, agitation, irritability and depression in CRPS (2,53) (*Figure 3*) (Tables III and IV).

Practically every patient suffering from CRPS demonstrates some degree of limbic system disturbance. These patients are expected to be depressed in more than 3/4 of the cases, anxious in practically every one of the cases, and to suffer from insomnia, agitation, irritability and poor judgment in practically every one of the cases. These manifestations are one of the four criteria for the diagnosis of CRPS. There is no way the limbic system can be left intact in the face of CRPS.

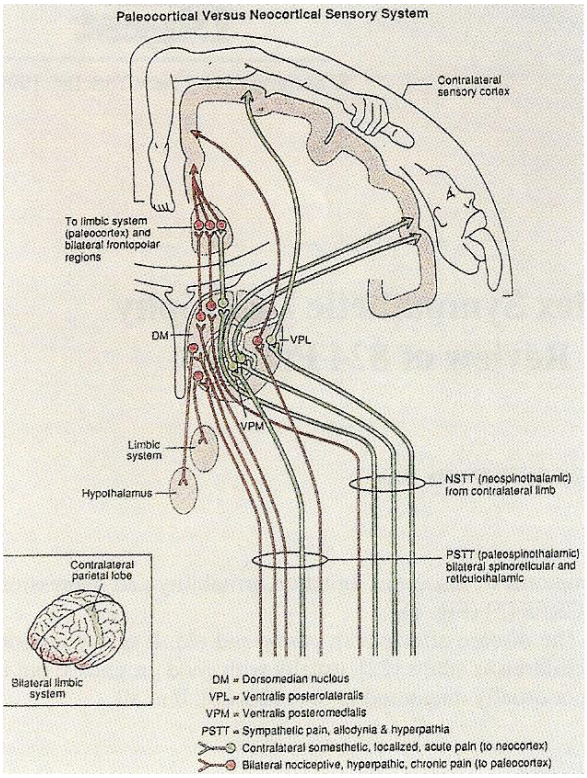

Figure 3. The afferent somatosensory nerves terminate in the contralateral parietal somatosensory cortex. In contrast, the unmyelinated c-fiber thermosensory nerves through synaptic relays terminate in bilaterally in limbic frontal temporale regions responsible for mood, memory and judgment. This explains the emotional disturbance, and insomnia in CRPS. With permission from CRC Press Publishers. (1).

Table III. Pain Perception
1. Somatic (Simple, Common Pain) Parietal Cortex
2. Sympathetic (Neuropathic)
3. Bilateral Limbic System/Anterior Frontal Temporal Lobes (52)

Table IV. CRPS Components
1. Sensory Burning Pain 2. Motor: Cold Extremity Tremor/Flexor Spasm (38,54) 3. Inflammation: Swelling, Skin Rash, Bruising of the Skin, Osteoporosis, Fractures, Fluid in Joints 4. Limbic System Dysfunction (Emotional Control Centers of Temporal and Frontal Lobes): Insomnia, Agitation, Depression, and Poor Judgment.

CARDIAC COMPLICATIONS

In our clinic we have seen many CRPS patients who have developed cardiac complications. Chest pain due to CRPS is quite common due to the fact that the cardiac sympathetic plexus surrounding the heart is a rich sympathetic nerve structure, and its dysfunction can cause severe chest pain.

CRPS causes three independent negative influences on cardiac function.

1. The sympathetic system is responsible for three main functions, i.e., temperature regulation, vital signs, and regulation of the immune system. The vital signs in the form of heart beat, blood pressure and respiration are up regulated and accelerated by stimulation of the sympathetic system. The CRPS is not a simple hyperactivity only stimulation of the sympathetic system. It is the result of dysfunction of the sympathetic system. This dysfunction shows instability of the sympathetic system at times causing fluctuation of blood pressure and at other times causing attacks of fast heart beat.

2. The second reason CRPS affects cardiac function is due to the anatomical innervation of the heart muscles. Of all the visceral organs, the heart has the richest innervation of the sympathetic system. This is in the form of cardiac plexus which is a rich plexus of nerves surrounding the heart. In any stressful condition, the natural response is rapid heart beat and rise of the blood pressure. The CRPS being a distressful type of dysfunction of the sympathetic system, results in repetitive pathological and exaggerated response of the sympathetic system to stress, chest pain, palpation, and bouts of high blood pressure.

3. One of the main principles of development of CRPS is inflammation. CRPS is a condition with four major features. First, the allodynia and hyperpathia is typical with pains seen with sympathetic dysfunction. Second, is motor response to such pain in the form of vasoconstriction, muscle spasm and muscle tremor. Thirdly, inflammation in the form of skin rash, swelling of soft tissues in the extremities, increased circulation in the visceral structures resulting in osteoporosis, pelvic inflammation, and attacks of vascular headaches. The same inflammation and increased visceral circulation causes distress on the heart.

Obviously if the patient has already had pre-existing cardiac disease, the distressful disease of CRPS is going to cause further stress on the heart on the basis of the above mentioned three principles.

Another symptom that we have seen associated with the cardiac complications of CRPS is a rash across the patient's chest wall.

Rasmussen and colleagues have reported that atypical chest pain is a common complaint in 94 % of CRPS patients (6,55).

Smith and colleagues published an article reporting that pre-syncope and syncope are complications in lower limb CRPS patients. These symptoms are related to autonomic dysfunction. In their study they reported 40% of CRPS patients showed symptoms of pre-syncope and syncope (56).

Unfortunately, cardiac complications of CRPS go unnoticed and the patients are blamed as being neurotic-especially due to the fact that many CRPS patients are young and they have no coronary artery disease.

SKIN LESIONS AND SKIN RASH COMPLICATIONS

A few years after onset of CRPS, the patient can develop neurodermatitis, trophic ulcers, Gardner-Diamond Syndrome (GDS) (spontaneous bruising), and skin rashes (6,57,58).

Doctor Goris has reported that 5% of patients with long-standing CRPS develop various skin problems that are very difficult to heal (59).

Trophic ulcers are not unusual in CRPS, being a sympathetic nervous system dysfunction, it manifests itself as follows:

1. Hyperpathic and allodynic pain (pain accompanied by change in vital signs, sweating and pain that becomes worse with simple touch or a breeze).

2. The response to the pain is in the form of motor response the spinal cord resulting in constriction of blood vessels, cold extremities, and muscle spasm, tremor and flexion deformity.

This disturbance of the immune system manifests in inflammation, spontaneous bruising and black and blue spots over the skin, neurodermatitis, edema and swelling that mimic conditions such as carpal tunnel and tarsal tunnel syndrome. In addition, the immune system disturbance in more severe cases not only cause neurodermatitis, but also causes trophic ulcers. Trophic ulcers usually develop after treatment with cast immobilization, wheelchair immobilization, surgical treatment or application of ice. At, times, the trophic ulcer and immune system disturbance are caused by incomplete pain management (*Figure 4*).

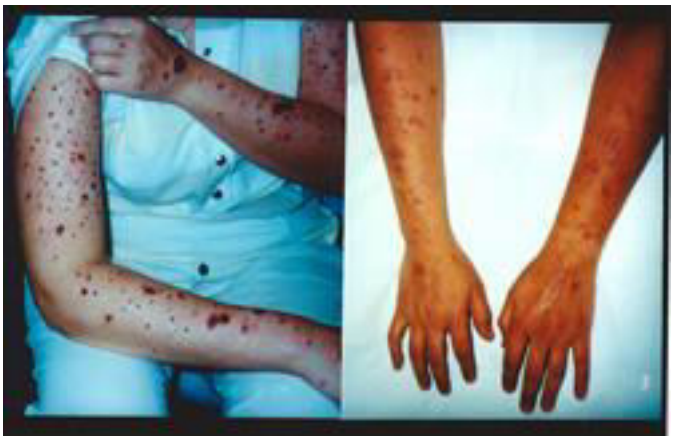

Figure 4. CRPS patient suffered for many years with severe lesions on both hands and arms. Treatment with I.V. Mannitol helped heal the lesions.

INFECTION COMPLICATIONS

Infections are another complication that is seen in advanced end stage of CRPS. In our clinic we have seen 12 patients who had end stage CRPS who ultimately had to have an amputation due to severe infections and edema (*Figures 5 and 6*).

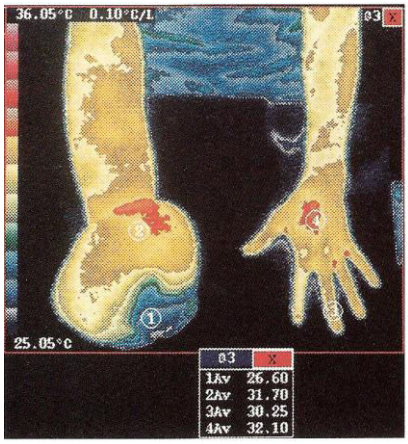

Figure 5. CRPS of seven years duration due to right hand injury. Two years of unsuccessful operations of right carpal tunnel, and 5 years of immobilization of hand have resulted in "Boxer's Hand Deformity" and ultimate amputation (2).

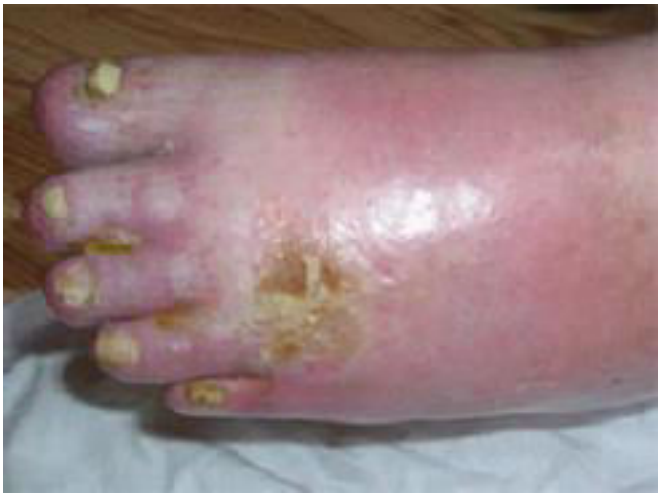

Figure 6. Twenty-Three years after onset of CRPS due to a car accident. The patient suffered from infections for over a year and half. I.V. and oral antibiotics were unsuccessful in treating the infections. Ultimately the left leg was amputated above the knee (A.K.A).

The patient in (*Figure 5*) suffered for seven years due to a hand injury. With two years of improper treatment, unsuccessful surgeries for carpal tunnel on the right hand and five years of immobilization of hand resulted in the patient developing a "Boxer's Hand Deformity"(2). After years of suffering the patient ultimately had to have the hand and arm amputated.

The patient in (*Figure 6*) developed CRPS in his left foot, ankle and toes after a car accident at age 20. The patient was misdiagnosed for 2 ½ years. During that time he did not receive any proper treatment. For the first three years after onset the patient was still able to walk on a painful deformed extremity which was a result of a movement disorder. In the third year after the onset of CRPS the patient had undergone an unsuccessful fusion surgery of the left great toe which caused spread of disease up the leg and into the trunk area. After the surgery the patient had lost the use of his left leg for over twenty years.

In the twenty-first year after onset of the disease the patient had severe relapsing infections in the left foot and toes. The patient suffered for a year and a half with these very painful infections. He was treated for a year and a half with oral and i.v. antibiotics that were unsuccessful in treating the infections.

In, the twenty-third year after onset of CRPS the patient had to ultimately undergo a two-stage above the knee amputation (AKA) of the left foot and leg. The patient's amputation was considered successful due to the fact that he has been able to use a prosthetic (a c-leg) and learn how to walk again after not walking on two feet for over twenty plus years.

It has been over 30 years now since the patient's onset of CRPS and it's been 7 ½ years since the patient's amputation. He still suffers from some of the symptoms of CRPS in his residual limb and he also has developed phantom limb pain (PLP) from the amputation.

Veldmand et al. have reported 19 patients with chronic lymphedema due to CRPS. The chronic relapsing infections were resistant to treatment. They reported that 5 patients in their study required amputation (43).

Dielissen and colleagues reported the results of amputation in 28 CRPS patients who had undergone 34 amputations in 31 limbs (60). Only two of 28 patients reported partial pain relief. In 26 of 28 patients, stump involvement with CRPS made it impossible to wear a prosthetic (2,60).

In van der Laan et al. research of 1,006 CRPS patients; they reported that 74 patients (7%) developed one or more severe complications in the affected extremity due to infections, ulcers, chronic edema, dystonia, or myoclonus (61).

According to Rowbotham, "amputation is not to be recommended as pain therapy (62)."

Amputation should be avoided by all means due to its side effects of aggravation of pain and tendency for spread of CRPS (2).

ENDOCRINE SYSTEM COMPLICATIONS

Another complication of CRPS is the endocrine system dysfunction. Schwartzman et al. have reported that one third of CRPS patients suffer from Hypothyroidism and low serum cortisol levels in 38% of CRPS cases (7,63). Schwartzman also reported that 69% of patients described unusual fatigue and severe tiredness (6).

Rhodin et al. reported that cessation of narcotics can help reverse endocrine system dysfunction (6,64).

HYPERTENSION COMPLICATIONS

CRPS can cause the complication of intractable hypertension which responds best to alpha I blockers (Dibenzyline, Hytrin, or Clonodine). CRPS can cause attacks of irregular or fast heart beat, chest pain, coronary artery spasm (angina), as well as disturbance of function of other internal organs. A few examples are frequency and urgency of urination, respiratory disturbance such as dyspnea and apneic attacks, and attacks of severe abdominal pain.

Attacks of fluctuating blood pressure may also be accompanied by constriction of the blood vessels to the kidney resulting in periodic bleeding in the urine as well.

PSYCHOLOGICAL COMPLICATIONS

In our review of 824 CRPS patients, one or more of the limbic system dysfunctions were present in every case except three. These consisted of insomnia (92%), irritability, agitation, anxiety (78%), depression (73%), poor memory and concentration (48%), poor judgment (36%), and panic attacks (32%) (2).

Doctor Mary Lynch reviewed the subject of psychological aspects of CRPS (2,65). Her conclusion was there is general agreement that profound emotional and behavioral changes can follow these types of pain. Opinions have varied widely on the issue of psychological etiology. It has often been suggested that certain personality traits predispose one to develop sympathetically related pain syndromes. A review of the literature reveals no valid evidence to substantiate this claim."

On the other hand, De Good et al. found patients suffering from CRPS, when compared to patients suffering from back pain and headaches, had the highest level of pain intensity, but demonstrated relatively less emotional distress (2,66).

Haddox reported that psychological disturbances have never been proven in CRPS patients (67). Also, in van Spaendonck et al. study of 165 CRPS patients they did not find any psychological disturbances in these cases either (68).

Understanding the nature of emotional components of CRPS spares the patient from misdiagnosis and improper treatment (2).

PARESIS COMPLICATIONS

According to Veldman paresis is one of the most frequent finding in CRPS (43). In these patients they complain of weakness of the affected limb. These patients have episodes of dropping objects out of their hands, difficulties of walking or lifting their foot.

He also reports that this form of paralysis is not present at the onset of the disease and it can not be attributed to nerve injury (43).

Weakness is actually an independent symptom of CRPS that may or may not be accompanied by chronic fatigue. The weakness in the muscles of CRPS patients is not simply because of fatigue, but it is due to the fact that the anterior horn cells and anterior lateral horn cells of the spinal cord are not functioning in coordination and getting in each others way. In CRPS, the anterior lateral horn cells of the spinal cord are contributing to the secretion of alpha adinergic chemicals causing vasoconstriction, muscle spasm, and movement disorder. The movement disorder may be in the form of weakness in the extremity, muscle spasm, flexor spasm, tremor, dystonia, clumsiness, flexion of the elbow and knee with resultant inability to move around smoothly, and difficulty with coordination of rapid or repetitive movement of the extremity. The end result is weakness of the extremity.

The long standing disturbance of nerve and muscle function as mentioned above also results in gradual disuse atrophy of the extremity with the CRPS being pushed into stage III with atrophy and weakness of the extremity.

GASTROINTESTINAL COMPLICATIONS

Many patients also develop gastrointestinal complications such as GERD 73% and Dysphagia in 17% as reported by Schwartzman (6). Other complications are diarrhea, IBS, and severe constipation seen in 90% of CRPS patients (5,6).

Intestine and Bowel complications are often the signs of inflammation in CRPS. This is very similar to the same inflammation that involves the extremities.

HEADACHE COMPLICATIONS

The term migraine has been relatively loosely applied to any type of neurovascular headache-be it migraine, cervicogenic, or the rare case of vascular headaches due to sympathetic nervous system failure seen in late stages of CRPS especially after several stellate ganglion blocks treatments.

This rare phenomenon was seen in only 5 of 824 CRPS patients (2). This type of headache was accompanied by spontaneous development of bilateral Horner's Syndrome, acute craniofacial edema, bilateral severe headache and vomiting non-responsive to Sumatriptan. Two of five patients had acute theta-delta generalized slow waves on electroencephalography (EEG) suggestive of increased intracranial pressure due to cell membrane dysfunction secondary to long standing cell membrane secondary to CRPS.

The use of ITI showed a homogenous hyperthermia of the craniocervical regions pointing to a generalized failure of sympathetic function. These headaches respond beneficially and cleared up with treatment with a combination of I.V. Mannitol, cervical epidural and occipital nerve blocks containing Bupivacaine and 5-10 mg Methylprednisolone.

ITI has a useful role in differentiating cervicogenic headaches from migraine. The cervicogenic headache shows areas of hyper - and hypothermia in distribution of posterior sensory nerve branches of C2 through C4 nerve roots, and occipital nerves. Nerve blocks in these areas provide excellent relief (2,69).

VISUAL AND HEARING COMPLICATIONS

CRPS patients frequently develop blurring of vision, reading difficulty, problem with focusing, and dizziness in the form of vertiginous attacks (either the body or the objects moving around). As well as hearing problems such as buzzing in the ear (tinnitus).

It is immaterial which part of the body has had the damage causing CRPS. As the sympathetic nervous system is intermingled and connected through sympathetic ganglia which are on each side of the vertebrae from lower cervical spine region all the way down to the tailbone. This chain of sympathetic connections causes the spread of CRPS to symptoms and signs both across the midline of the opposite side (from hand to hand or from foot to foot) and vertically up and down the spine. As a result, the patient may have CRPS due to a knee injury or injury to the foot or hand and yet may develop stimulation and abnormal function of the sympathetic system causing constriction of the blood vessels to the brain. When the blood vessels are constricted in the distribution of vertebral arteries in the cervical spine and in the distribution of the blood vessels providing circulation for the hearing center and brainstem, the patient develops attacks of dizziness, trouble with focusing with the eyes (due to brainstem dysfunction which has the responsibility of coordinating the eye movements), and buzzing in the ears (tinnitus).

Treatment with alpha blockers (such as Clonodine, Hytrin, etc.), as well as antidepressants such as Trazodone or Zoloft, and muscle relaxants such as Baclofen and Trizanidine can provide excellent relief for the above symptoms. At times the original injury that has caused CRPS may cause retinal detachment (damage to the retina of the eye) or bleeding of the eye. For this reason, the patient should have careful eye examination by an ophthalmologist as well.

Proper cervical, paravertebral and epidural blocks can help correct the above symptoms.

Keratitis Sicca which is due to CRPS at early stage causing pain and irritation in the eye with secondary excessive secretion tears. As the condition becomes chronic, the tear glands become exhausted, causing "dry eye" (Keratitis Sicca).

Hyperacusis is a condition associated with painful sensations to sound. De Klaver et al. reported that 38% of patients with CRPS related dystonia had symptoms of hyperacusis. De Klaver and his group found that hyperacusis is common among patients suffering with CRPS related dystonia. Hyperacusis in these patients may reflect the spreading of central sensitisation to auditory circuitry (70).

ALLERGIC REACTION COMPLICATIONS

Usually, a year to 2 years after onset of the disease, the immune system becomes dysfunctional. The patient develops skin rash, de novo allergies, asthma, even severe coughing and bleeding from the lung and bronchi. Treatments consist of epidural blocks, proper analgesic, (but not opioid agonists such as MS Contin, Oxycontin, etc). Treatment with effective, analgesic antidepressants (especially Trazodone), and analgesic anticonvulsants such as Trileptal (for stabbing pain), and/or Neurontin (only for burning pain) are quite helpful. In late stages, treatment with I.V. Immunoglobulin may be the last hope for the patient.

RESPIRATORY COMPLICATIONS

In Schwartzman's study of 270 CRPS patients, 42 patients (15%) suffered from shortness of breath. In a report by Irwin and Schwartzman they recognized that Dystonia is a major complication in CRPS and it can affect the chest wall and muscles which can cause restrictive lung disease (71).

UROLOGICAL COMPLICATIONS

In severe and chronic stages of sympathetic dysfunction, neuroinflammation results in interstitial cystitis, pelvic inflammatory disease (PID) and sterile abscess (72).

Schwartzman and colleagues have reported urological complication in 25% of CRPS patients (7,73). The International Association for the Study of Pain calls interstitial cystitis as a form of CRPS (74).

According to Galloway et al. interstitial cystitis might be a form of CRPS, in which the target organ is the urinary bladder. They also reported a similarity between the clinical course of CRPS and interstitial cystitis (72).

VULVODYNIA COMPLICATIONS

The complication of Vulvodynia is the most intractable and most severe pain in medicine. In this condition the sympathetic system is the sole driving mode of the severe intractable pain. Because of the involvement of the genital organ, the disease involves the entire region. This is the reason for the new terminology calling reflex sympathetic dystrophy (RSD) "complex regional pain syndrome (CRPS)."

The involvement of the pelvic area with the sympathetic dysfunction is manifested by the following features. Spread of pain to the abdominal region, lumbar spine, and lower extremities as well as spread of the pain upward through the chain of sympathetic ganglia to the cervical spine regions causing severe headache, neck pain, dizziness, blurring of vision, insomnia, and depression.

In vulvodynia, the immune system becomes rapidly dysfunctional. One of the reasons for the immune system becoming rapidly dysfunctional is the fact that the spread of the pain, inflammation, and poor circulation to the pelvic abdominal regions causes neuroinflammation of the ovaries, disruption of the Estrogen secretion, and causes interstitial cystitis in the form of frequency and urgency of urination and even incontinence of urine.

Obviously, most patients who have this painful complication of CRPS are worked up for other kinds of immune system dysfunctions. So, it becomes obvious that the only reason for the patient's immune system disturbance is the CRPS-vulvodynia.

The treatment should consist of epsom salt baths which are very effective, but the amount of epsom salt added to the bath should be started as a small amount and gradually increased. Any treatment should not aggravate the pain, so every form of treatment should take into consideration the severe hypersensitivity, hyperpathia, and allodynia that such patients have.

In addition, there are specific types of nerve blocks that can be given that calm down the neuroinflammation of CRPS-vulvodynia. These consist of caudal nerve blocks, for the sensory nerves, as well as nerve blocks for the sensory nerves of the genitalia. Obviously, the needle should not be stuck in the vaginal region, but it should be applied proximally. The patient also needs to have IV Immunoglobulin treatment to prevent further deterioration of the immune system.

Most important, is that the patient needs to have proper pain relief. This is achieved by opioid antagonists such as Buprenex, Nubain, or Butorphanol. The use of opioid agonists should not be used because of the fact that they cause a problem with rebound (withdrawal) phenomenon, and the strong opioid agonists such as Fentanyl or Methadone or Morphine do not reduce the pain any more than from 10 down to 7-8 which is not much of a relief.

Also, the use of opioid agonists causes a withdrawal pain which keeps the patient awake all night. The patient needs to be treated with antidepressants and anticonvulsants, but not with Elavil (Amitriptyline) which causes systemic side effects and makes the patient gain 7-16 pounds of weight a year.

The anticonvulsants should not be limited to Neurontin which is only good for burning pain, but other types that are more effective should be used.

Obviously, the patient does not need any sympathetic ganglion nerve blocks. The fact that she has erythematous (reddish discoloration and heat emission) areas over the vulvar region, points to sympathetic dysfunction and sympathetically independent pain (SIP), so doing any sympathetic ganglion block is too late to do any good for the patient and will be more destructive than good.

Other blocks such as lumbar epidural blocks and caudal blocks are far more effective, and specifically they are different from the lumbar ganglion blocks or pelvic ganglion blocks because they contain Depo-Medrol as an anti-inflammatory medication that provides pain relief for 2½-3 months rather than the sympathetic ganglion blocks providing pain relief for a few hours or a day, if that. Performing a biopsy should never be done. This condition is severe enough and the trauma of a biopsy can aggravate it further (74).

CONLUSION

In medicine there is a trend. When a disease becomes confusing, the physicians become desperate and give it new names. Each of the above mentioned names reflect some features of CRPS (16-21).

CRPS is a very complex pain syndrome with many various complications that are not recognized by most treating physicians.

Most treating physicians do not understand the full mechanisms of CRPS and they do not believe that this disease can spread and cause various complications.

In most cases of CRPS the patient does experience spread of the disease to other extremities and into internal organs. There have been many published reports that back up this theory of the spread and the various complications of this painful disease of the sympathetic nervous system (1,2,9,21,37-42).

CRPS cannot be brought under control unless the pain is brought under control. CRPS is defined as a state of constant burning and pain which is severe, incapacitating, and is aggravated by even a breeze or a simple touch to the involved area (allodynia). This pain is accompanied by swelling, inflammation, disturbance of the immune system function, movement disorder (flexion spasm, tremor, etc.) and emotional disturbance in the form of insomnia, depression, agitation, and irritability.

With proper understanding the nature of CRPS and its various complications of the disease it will help spare the patient from years of added suffering.

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