SPREAD OF COMPLEX REGIONAL PAIN SYNDROME(CRPS)

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Abstract. *Complex regional pain syndrome (CRPS) is usually caused by a minor injury, and requires proper evaluation and multi-disciplinary treatment addressing the multifaceted pathological processes that evolve during its chronic course. Patient's age, the nature of pathology, and mode of therapy influence the outcome of treatment. If at all possible, surgery, ice and cast applications should be avoided. There is a desperate need for research in proper management of CRPS.*

Descriptors. *complex regional pain syndrome (CRPS), internal organs, spread, surgery, sympathetically independent pain(SIP), sympathetically maintained pain (SMP).*

INTRODUCTION

The spread of complex regional pain syndrome (CRPS) in vertical or horizontal fashion (upper and lower extremities, or both upper or both lower extremities) has been recognized ever since 1976 (1). The surgical procedure facilitates the spread of the CRPS (2). More recently, the phenomenon of the spread of the disease has been proven by Schwartzman, et al (3,4). The chain of sympathetic ganglia from base of the skull to sacral regions on the right and left sides, spread the pathologic impulse to other extremities (5).

The phenomenon of referred pain should not be mistaken for spread of the disease.

CRPS is a disease of stress - be it psychological or physical - affecting the sympathetic nervous system. This system is bilaterally innervated. The bilateral innervation is due to the fact that at the level of spinal cord, the thermoregulation originates from the periaqueductal gray matter of the spinal cord and influences the sympathetic function on both right and left extremities (6,7,8). Immersion of one hand or one foot in a bucket of ice water, after less than one minute, results in marked hypothermia of the contralateral extremity (1,8). With passage of time, the same phenomenon leads to bilateral pain and hypothermia, and a full scale picture of spread of the CRPS.

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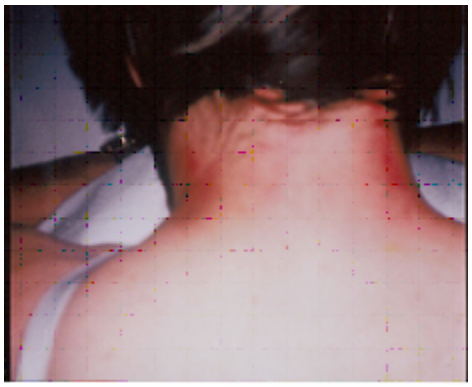
CRPS is not usually limited to one part of an extremity or one extremity. Usually, the pathological sympathetic function spreads to adjacent areas (5).

The first areas becoming involved are the pathway of the sympathetic nerves between the end organ (e.g., foot or hand) and the spinal cord. This results in an inflammation and irritation of the nerves all the way from the end organ to the spinal cord. This is manifested by muscle spasm in the cervical and lumbar spine region, secondary back and neck pain, headache, dizziness, and tinnitus (buzzing in the ears).

In the path of the areas of inflammation, the posterior sensory nerve branches corresponding to the level of the involved nerves and secretes substance P (a painful substance half the molecule of endorphine and practically identical to jalopena pepper extract). This secretion of substance P under the skin in the paraspinal regions can be identified by exerting equal pressure on the two sides of the vertebra, and observing the so-called "red reflex"(Figure 1). Pressure on the normal areas causes no reddish discoloration. On the other hand, pressure on the areas of sensory nerve irritation causes a reddish discoloration of the skin which is accompanied by Travaill's Jump Sign. This area of reddish

discoloration can be easily blocked and dissipated by injection of local anesthetic such as Marcaine and if the condition is chronic and severe, one can add a small amount of Celestone or Depo - Medrol® to it. This nerve block provides excellent relief of pain and reversal of constriction of the blood vessels.



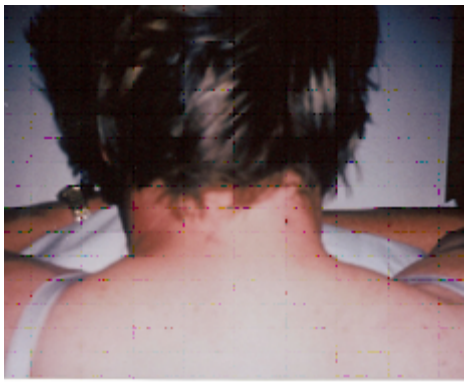


Figure 1. Cervical neuropathic pain represented with hypothermia on ITI in the paravertebral area. Gentle pressure exerted over the cervical spine (Left) revealed reactive release of inflammatory chemicals and blushing of the skin in the hypothermic area. Treatment with paravertebral nerve blocks (Right) provides pain relief, and dissemination of irritative substances P. Massage therapy after paravertebral nerve blocks provide a longer lasting relief for the patient.

Another area of involvement of CRPS is the spinal cord itself. This is manifested by movement disorder, muscle spasm, weakness of the extremity, as well as urgency and frequency of urination and disturbance of erection.

Invasive procedures such as the insertion of a spinal cord stimulator (SCS) can flare-up such an involvement of the spinal cord and it can cause "idiopathic paralysis" due to flare-up and constriction of blood vessels to the spinal cord. The same can be noted in rare cases of insertion of a catheter for sympathetic nerve blocks in the paravertebral or epidural regions.

In the visceral involvement of CRPS the skin is usually cold and the deep structures are hot and have an exaggerated blood circulation. This results in osteoporosis, fracture of the bones, areas of swelling and fluid formation between the bones and joints identified on MRI, and severe pain as well as weakness in the deep structures. This causes a high risk of amputation for the patient. Amputation is totally unnecessary and should never be performed. Just simple weight bearing under the effect of a strong analgesic such as Stadol or Buprenorphine (Buprenex) along with the use of moist, warm water and epsom salt, exercise and massage for the extremity to reverse the vasoconstriction on the surface and to increase the circulation in the deep structures corrects this situation without the need for amputation. Amputation in CRPS is a slow, painful, gradual suicide.

The next structures being involved in some cases of CRPS are the blood vessels to the kidney with resultant episodes of sudden brief and temporary bleeding through the kidney accompanied by a marked elevation of blood pressure. The same principle can cause attacks of nose bleeds, severe headache, dizziness, passing out spells as well. Application of Clonodine Patch in the area of the kidney in the flank (in the back) usually results in good relief of such spasm and inflammation of the blood vessels. The patient should be treated with Dibenzyline or Hytrin which are life saving in such patients.

The involvement of other sympathetic midline connections and plexi such as celiac (abdominal pain, peptic ulcer, nausea, vomiting, and weight loss), superior and inferior mesenteric plexi (diarrhea, abdominal cramps, and weight loss), and cardiac plexus (chest pain, abnormal heart beat, tachycardia, and heart attack), and carotid and vertebral plexi (severe vascular headaches, dizziness, tinnitus, attacks of falling spells, and syncopal attacks), should be identified as such and should be treated with the help of Clonodine Patch, Hytrin, or Dibenzyline as well as proper treatment applied to the source of CRPS (definitely avoiding ice, but encouraging exercise, moist heat, warm water and epsom salt, and newer antidepressants are the best analgesics of choice for CRPS).

The involvement of the same midline plexi explains the reason for the involvement of other organs symmetrical on the opposite side such as the opposite hand or opposite foot or opposite side of the head in regard to headache and face pain or involvement of the removed areas such as involvement of right hand because of left knee injury)(Figure 2).

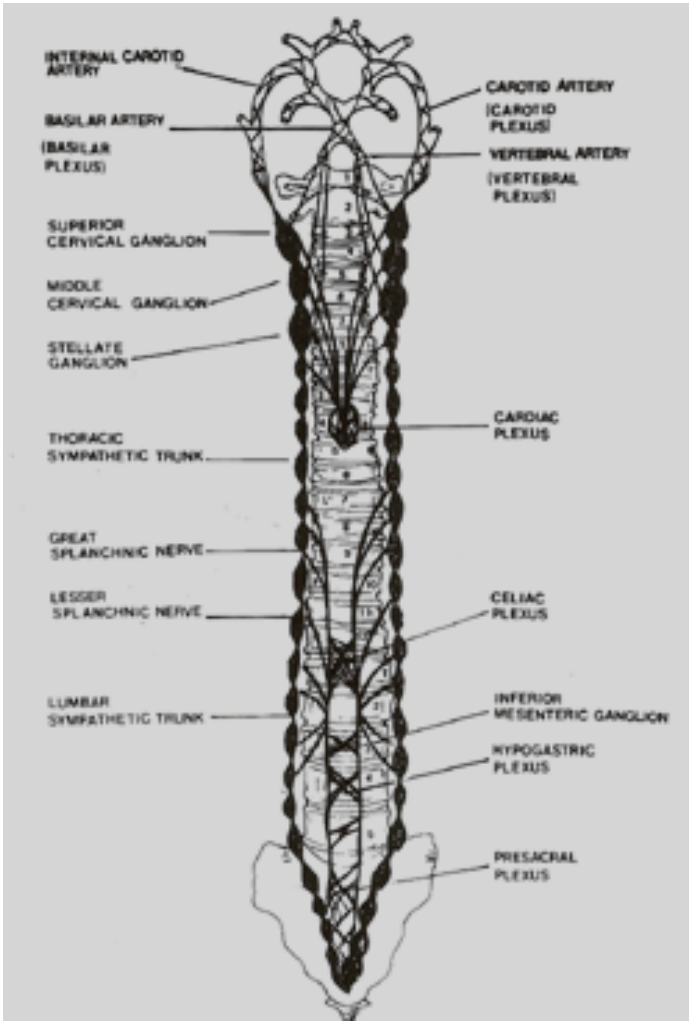


Figure 2. Vertical and midline connections and plexi of sympathetic nervous system. This complex intermingling of SNS fibers renders unilateral sympathectomy ineffective in the long run. The affinity of the sympathetic nervous system to the spine explains the involvement of the SNS in spinal injuries in the form of "neuropathetic pain." "SMP" and in other manifestations such as vascular headaches, vertebral artery insufficiency (dizziness, tinnitus, ataxia, and poor memory, and, extremity or visceral inflammation.

Because of the above complex phenomenon and because of the fact that 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 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 put up with in the course of their treatment. Then the patient is sent to the psychiatrist who tries to shut the patient up with strong tranquilizers, benzodiazepams, Haldol, Valium, Xanax, Halcion, Ativan, Tranxene, etc., with further disastrous results by aggravating CRPS due to inactivity, and due to the stress of strong addicting benzodiazipams affecting the formation of brain's own endobenzodiazepams and endorphines.

The sympathetic system is complex, bilateral, and diffuse. Its job is alerting the mechanism to alert the entire body against stress and its manifestations are complex and multifaceted.

FACTORS IN THE SPREAD OF COMPLEX REGIONAL PAIN SYNDROME (CRPS)

The usual factors facilitating the spread of the disease are surgical procedures, application of ice, and stress of too much activity or inactivity (6). In our study of 824 CRPS patients, the number one aggravator was cryosurgery, followed by surface cryotherapy applied more than two months. The surface cryotherapy less than two months did not show the tendency for spread of CRPS (6,9)(Table 1).

Cryosurgery, similar to radiofrequency surgery, does not limit the freezing damage to a circumscribed nerve. The concentric field of freezing cannot limit itself to a small anatomical target. Damage to the adjacent normal nerves contribute to spread and expansion of the lesion.

Table I. The therapeutic influence of cryotherapy and cryosurgery on the out come of the disease (Stages I-IV).

Characteristics of treatment (% of 284 patients)	Stage I * number of patients	Stage II number of patients	Stage III-IV** number of patients
Cryotherapy Rx>2 Months 236Patients	16 (7%)	92 (39%)	128 (54%) (P<0.001)
Cryotherapy Rx<2 Months 34 Patients	13 (38%)	11 (32%)	10 (30%)
Cryosurgery 14 Patients	0 (0%)	1 (7.15 %)	13 (92.85%) (P<0.001)

(*) Stage I = Dysfunction; Stage II= Dystrophy; Stage III= Atrophy; Stage IV= Autonomic and Immune System Failure.
(**) Depending on the nature of treatment, stage III may reverse to stage I and vice-versa.

STAGES OF CRPS

CRPS has been divided into four different stages. Depending on the nature of injury, the stages vary in their duration. In the 22 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 (10). This is in contrast with CRPS in children in whom stages would stagnate, reverse or improve slowly.

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(11). In stage I, the pain is usually sympathetically maintained pain (SMP) in nature (Table II).

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 (Figures 3,4,5). Due to the confusing clinical manifestations, the patient may be accused of factitious self-mutilation and "Münchausen syndrome(12)." All these dystrophic changes may not be present at the same time nor in the same patient(13). Careful history taking is important in this regard.

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 (13-15). At stage II or III it is not at all uncommon for CRPS to spread to other extremities(1,2,11,16). At times, it may become generalized (11). The generalized CRPS is an infrequent late stage complication. 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(1,11,17,18). 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(19-22).

STAGE IV:

(i). Failure of the immune system, reduction of helper T-cell lymphocytes and elevation of killer T-cell lymphocytes.

(ii). Intractable hypertension changes to orthostatic hypotension.

(iii). Intractable generalized edema involving the abdomen, pelvis, lungs, and extremities.

(iv). 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 (23).

(v). High risks of cancer and suicide are increased.

(vi). 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(6,24).

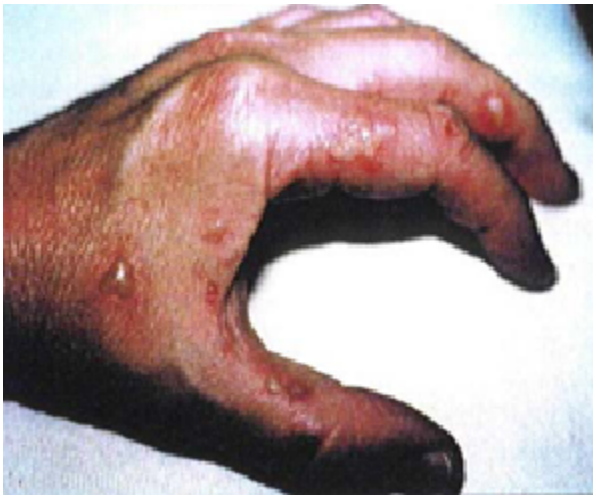


Figure 3. 9/22/96: Venipuncture CRPS II, five months after a blood test, resulted in neuroinflammatory bulbous lesions(10).

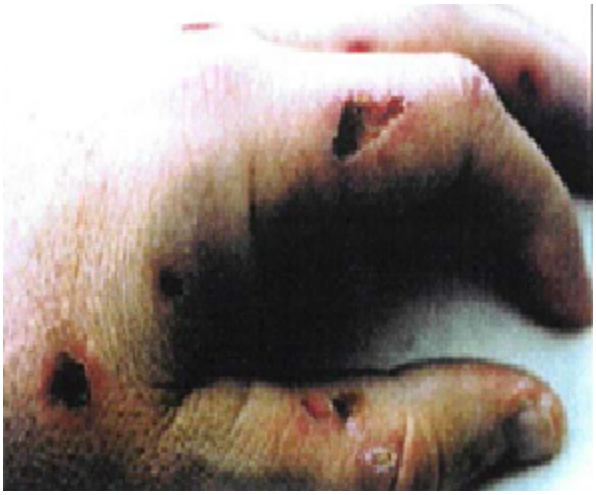


Figure 4. 9/27/96: Lesions became ulcerated(10).

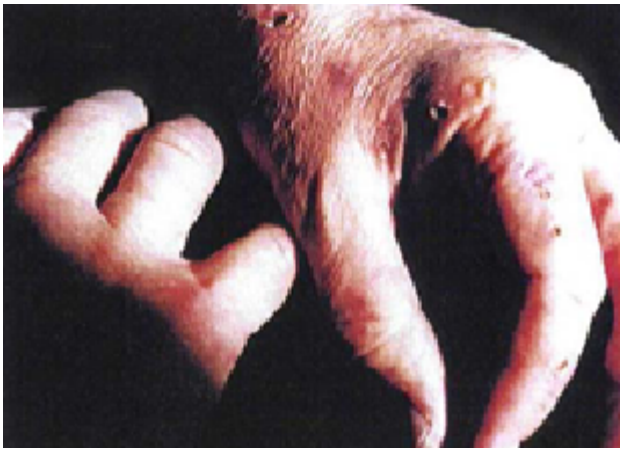


Figure 5. 11/1/96: The lesion healed after treatment with I.V. mannitol and I.V. immunoglobulin treatment(10).

Table II. With passage of time, and types of treatment, CRPS goes through stages with variable time tables and sympathetic responses.

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

STAGING CAN BE MISLEADING

Dogmatic reliance on staging is somewhat artificial in nature. Each patient follows a different course. In children and teenagers, the prognosis is excellent and stages need not develop with passage of time due to the fact that their rich cerebral growth hormone, sex hormone and endorphin formation prevent deterioration(25-29). The same logic applies to pregnant women. With early treatment, the disease is frozen at stage one. Even patients suffering from stages II or III revert to stage I with proper treatments. The reverse is true: unnecessary surgery, as an stressor can cause rapid regression from stage I to III, as well as spreading the disease to other extremities (6).

SURGERY

Elective surgery for presumptive conditions such as carpal tunnel, tarsal tunnel, and thoracic outlet syndrome (TOS)- in spite of normal nerve conduction studies - only adds a new source of neuropathic pain at the surgical scar. According to Cherington, et al , there is a tendency for unnecessary TOS surgery, elective surgery is the strongest predictor ($P<0.001$) of poor treatment outcome(30).

According to Rowbotham, "amputation is not to be recommend as pain therapy(31)." All 11 patients in our series of 824 CRPS patients who underwent amputation showed marked deterioration post-op. The surgical stump was the source of multiple neuromas with sever CRPS II type of intractable pain. Amputation should be avoided by all means due to its side effects of aggravation of pain and tendency for spread of CRPS (6).

Twenty-two of 824 CRPS patients, had undergone surgical sympathectomy with temporary partial relief of 6 days to 38 weeks in 9 patients: up to 54 weeks in 10 patients: and no relief in 3(6). Chemical sympathectomy was done (prior to referral to our medical center) on 13 patients with temporary relief of 3 days to 29 weeks in 4 patients, no relief in 5, and rapid deterioration of CRPS in 4 patients (6). Surgical, radiofrequency and chemical or (neurolytic), sympathectomies, have been applied in treatment of CRPS since 1916(32,33). Sympathectomy may provide temporary pain relief, but after a few weeks to months it loses its effect(5,34). The success has been limited to the series that have had short-term patient follow-ups of a few months after surgery. Sympathectomy and application of neurolytic agents should be limited to patients with life expectancies measured in weeks or months - e.g., cancer and end stage advanced occlusive vascular disease patients(5). On the other hand, CRPS patients usually have 3 to 5 decades of life expectancy ahead of them(5). They should not be exposed to aggravation of pain due to sympathectomy. The sympathectomized patients developed post operative spread of CRPS in 12 of our 35 patients (37%). This high incidence of spread is in contrast to the 18% incidence in the rest of 824 cases(6).

Surgical procedures in neuropathic pain patients, in general, are sources of stress and produce characteristic neuro-endocrine and metabolic responses, local inflammation, and can cause disturbance of immune system function.

The body responds in the opposite direction to surgery for somatic versus neuropathic pain. An acute appendicitis or cholecystitis responds quite nicely to surgery. On the other hand, surgery in the area of the extremity involved with neuropathic pain has the potential of aggravating the condition. Tissue damage from the surgical procedures results in the local release of inflammatory neurokines. This biochemical and cellular chain of events leads to up-regulation of the immune system and nervous system activation by releasing Substance P, histamine, serotonin, CGRP, bradykinin, prostaglandins, and other agents. This leads to a local vasodilation response in the area of the surgical scar, increased capillary permeability, and sensitization of the peripheral afferent nerve fibers resulting in allodynia and hyperpathia. Surgery can cause suppression of immune function aggravating the manifestations of neuropathic pain. Post-operatively, there is a tendency for dysfunction of the lymphocytic role in immune regulation. This is manifested by a decrease in number of T-cell lymphocytes and the function of the T-cell lymphocytes. The disturbance and suppression of the immune system due to surgery enhances the malignant tumor growth and metastasis . Surgery "results in a perturbation of nervous, endocrine and immune system as well as their interregulatory mechanisms leading to compromised immunity." This disturbance of immunity may manifest itself in skin ulcerations noted in 2 of 11 amputees referred to our clinic during a five year period from 1990-1995. A similar case of an amputee with skin ulcers has been recently reported .

INTERNAL ORGAN INVOLVEMENT

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.

Laparoscopy may reveal congestion and inflammation of the ovaries, uterus or small bowel.

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.

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.

The use of nerve blocks and more importantly physical therapy can help improve the skin circulation and reduce the deep circulation calming down the inflammatory affect of CRPS over the internal organs. As mentioned above, alpha I blockers are quite affective in treatment of this condition.

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 anticonvulsants (Tegretol or Neurontin).

The use of catheters adjacent to the sympathetic chain such as in the lumbar sympathetic chain can help prevent repeated needle infection from sympathetic nerve blocks. However, because of the congestion of the internal organs the catheter may irritate the sympathetic nerve branches causing constriction of the blood vessels to the spinal cord with temporary paraplegia. As soon as the weakness of extremities develops, the catheter should be removed. Not heeding to this ominous sign can result in paralysis of the lower extremities and incontinence.

CONCLUSION

The main reason for 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.

In treating CRPS, even if the opposite extremity looks normal, the treatment should be given to both extremities because of this principle of bilateral innervation.

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