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Systemic Complications of Complex Regional Pain Syndrome

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ABSTRACT

Complex Regional Pain Syndrome (CRPS) is a neuropathic pain disorder that is characterized by: (1) severe pain beyond the area of injury; (2) autonomic dysregulation; (3) neuropathic edema; (4) a movement disorder, atrophy and dystrophy. It is most often caused by a fracture, soft-tissue injury or surgical procedure and is divided into Type I, in which no nerve lesion is identified (classic reflex sympathetic dystrophy), and Type II where a specific nerve has been damaged (causalgia). In addition to the peripheral manifestations, there are many internal medical complications whose etiology is often not appreciated. This article will examine how CRPS affects the systems of: cognition; constitutional, cardiac, and respiratory complications; systemic autonomic dysregulation; neurogenic edema; musculoskeletal, endocrine and dermatological manifestations; as well as urological and gastrointestinal function.

Keywords: Complex Regional Pain Syndrome; CRPS; CRPS-1; CRPS-2; Chronic pain; Reflex Sympathetic Dystrophy; RSD

1. Introduction

Complex Regional Pain Syndrome (CRPS) is a neuropathic pain disorder that is characterized by: (1) severe pain beyond the area of injury; (2) autonomic dysregulation; (3) neuropathic edema; (4) a movement disorder, atrophy and dystrophy [1]. It is most often caused by a fracture, soft-tissue injury or surgical procedure and is divided into Type I, in which no nerve lesion is identified (classic reflex sympathetic dystrophy), and Type II where a specific nerve has been damaged (causalgia). Converging evidence suggests that CRPS-I is due to injury and distal degeneration of axons and terminal twigs of A-δ and C fibers [2]. Cluster analysis reveals that the signs and symptoms in the syndrome comprise four distinct groups: (1) abnormalities in pain processing (mechanical and thermal allodynia; hyperalgesia, and hyperpathia); (2) temperature change and erythema, cyanosis or mottling; (3) neurogenic edema and sudomotor dysregulation; (4) a motor syndrome and trophic changes [3-7]. There may be subtypes: (1) a limited syndrome with predominant autonomic dysregulation; (2) a syndrome limited to one extremity that is characterized by neuropathic pain with minimal autonomic dysregulation and neurogenic edema; (3) a severe disorder that has spread from the site or original injury, is long standing and comprises all components of the syndrome [4]. The present diagnostic criterion requires at least one symptom in each of the four factors and one sign in at least two of the four factors [7]. In general, early in the course of the disease patients demonstrate prominent inflammatory signs and symptoms that include neurogenic edema, erythema and an increased temperature of the affected extremity while long standing patients suffer pain spread and an apparent centralization of the process with concomitant severe generalized autonomic motor and trophic changes of skin, nails, bone and muscle [1, 8-11].

The epidemiology of the syndrome is uncertain. Many patients diagnosed with fibromyalgia clearly have CRPS, the pressure points being components of the brachial plexus, the intercostobrachial (ICB) nerve and concomitant L_5-S_1, injury [12, 13]. The most representative population-based study from the Netherlands revealed an incidence of 40.4 females and 11.9 males per 100,000 person-years at risk [14]. The variable incidence reported are due to the cohorts studied, the time period in the course of the disease in which they were studied and the skill of the examiners [15-19].

The purpose of this article is to discuss the systemic medical complications of CRPS. As Janig has pointed out, with time CRPS centralizes to affect somatosensory**,** autonomic and limbic components of the syndrome [20]. The immune component of neuropathic pain is now viewed as pivotal to both in its initiation and maintenance. Many of the features seen peripherally occur in systemic organs.

2. Neuropsychological Deficits Associated with CRPS

Severe neuropathic chronic pain is associated with poor performance on neuropsychological tests that assess working memory, language and executive function [21-23]. Patients whose pain was due to a variety of underlying medical conditions demonstrated decreased information processing speed [24].

Over 500 patients with severe CRPS (met all IASP criteria [25]) underwent a battery of neuropsychological tests that assesses executive systems function, naming/ lexical retrieval, memory and learning prior to treatment with an outpatient ketamine protocol. The assessment method is based on the work of Libon *et al* [26]. Executive system function was measured by the digit span subtest from the Wechsler Adult Intelligence Scale – III (WAIS-III) [27] . The digits backward portion of the test was used to evaluate working memory deficits [28, 29]. Executive function was also evaluated by tests of letter fluency which activate the left dorsolateral prefrontal cortex in both young and older patients [30]. Naming was assessed with the Boston Naming Test [31] and lexical retrieval by a test of semantic fluency [32]. Converging evidence supports category fluency tests as a measure of lexical retrieval and semantic knowledge that activate the left temporal lobe [33, 34]. Memory and learning was evaluated by the California Verbal Learning Test – II [35]. Delayed free recall and delayed recognition discrimination index have been linked to parahippocampal atrophy and the presence of anterograde amnesia [29]. Adjunctive tests administered with the above were the McGill Pain Inventory [36] and the Beck Depression Inventory – II [37]. The patterns of neuropsychological impairment seen in this large cohort of CRPS patients were determined by a statistical cluster algorithm which demonstrated three distinct groups. Approximately 35% of patients had no neuropsychological deficits, group I. The second, group II, 42% of patients had mild dysexecutive deficits. Group III, 22% of patients had cognitive impairment that included poor performance on tests of executive function, naming and memory. Both affected CRPS groups II and III (65%) of patients) had difficulty with repeating numbers backward. This function is thought to demonstrate higher-order mental manipulation that depends on working memory and visual imagery mechanisms [26]. There is also evidence that decreased output on letter fluency and poor performance on a backwards digit span test are correlated with left inferior frontal lobe pathology [34] . CRPS group III patients' memory deficits suggest executive (retrieval) rather than amnesic (encoding) dysfunction. The improvement of this group in the delayed recognition test suggests impairment of frontal memory systems [38]. This detailed evaluation of over 500 patients suggests that a wide network of cortical and subcortical anatomical nodes is involved in the illness and that a dysexecutive syndrome is the primary deficit. A neurocognitive study on nine patients prior to and following a ketamine anesthesia protocol [39] by Koffler demonstrated improvement in brief auditory attention and processing speed [40] . Levels of depression and extent (number of limbs involved) or duration of illness is not a factor in these cognitive changes.

Functional MRI (fMRI) studies in patients with CRPS-I and II have given insights into cognitive function and activity dependent neuroplasticity in this illness. There is clear alteration of the CRPS hand representation in the primary somatosensory cortex (SI) cortex of the affected versus unaffected side [41-44]. The side opposite the affected hand is decreased or increased [44] in parallel with the degree of mechanical hyperalgesia and pain intensity [41, 42] which reversed with recovery [42] [43]. In a recent study, patients with CRPS estimated their hand size of the affected extremity to be larger when compared to expanded or compressed schematic drawings of hands. The overestimation correlated with disease duration, increased two-point discrimination and neglect score [44]. In addition to tactile and proprioceptive deficits [45], a significant proportion of CRPS patients feel as if their hand is "foreign or strange" [46] or not belonging to their body [47]. Studies with fMRI during electrical stimulation of both index fingers revealed smaller signals in both contralateral SI and secondary somatosensory cortices (SII) that were associated with impaired 2-point discrimination deficits. This suggests that patterns of cortical reorganization in both SI and SII parallel impaired tactile discrimination [48] and pain intensity. In addition to plastic aberrations of the body schema in CRPS patients, increased activation of areas thought to process affective components of pain, the cingulate gyrus and frontal cortices have been demonstrated that may persist after recovery [41, 49]. A recent paper describes the neuropsychological dissociation in which a CRPS patient had preservation of object recognition and naming but was unable to recognize object orientation (agnosia for object orientation) [50]. This

finding may be consistent with a previous fMRI study that demonstrated aberrant activation within the intraparietal sulcus (a multimodal association area) and was associated with motor dysfunction [51]. The impaired spatial orientation demonstrated by this patient suggests posterior parietal dysfunction.

The impaired cognitive function demonstrated by these studies may also be associated with structural brain changes demonstrated in other severe neuropathic pain states and in CRPS patients maybe at least partially reversible [40, 52]. Factors that also have to be considered in the cognitive performance of patients with severe neuropathic CRPS pain are medication, stress, and distraction that detract from working memory [53, 54]. A recent experimental study on resolving postoperative neuroinflammation and cognitive decline suggests a mechanism for the neuropsychological deficits defined in CRPS patients [55]. In C57BL/6J and other species of mice, peripheral surgery was shown to cause disruption of the blood brain barrier (BBB). The proposed mechanism was release of tumor necrosis factor-alpha (TNF-α) that facilitated the migration of macrophages into the hippocampus by activation of nuclear factor kappa B (NF-κB). This signaling pathway induces neuroinflammation, microglial activation and release of proinflammatory cytokines. Activation of the alpha7 nAChR (acetylcholine receptor) prevented the migration of monocyte-derived macrophages into the CNS. Entry of leukocyte like CD4+T cells may be mediated by NF-κB amplification of interleukin-6 (IL-6) that is expressed in cerebral endothelial cells and can lead to increased expression and accumulation of inflammatory cytokines. This endothelial activation and breakdown of the BBB may be initiated by peripheral nerve injury [56].

3. Constitutional Symptoms

CRPS-I and CRPS-II are systematic diseases which can potentially affect any organ system [1, 15]. Almost all severely affected patients (those with more that one extremity involved) have complaints of lethargy, tiredness, or weakness – the etiology of which is multifactorial. Following injury mast cells, macrophages, leukocytes are activated and recruited to the involved area [57]. As the illness progresses proinflammatory cytokines increase in the serum and cerebrospinal fluid (TNF-α and IL-6) while anti-inflammatory cytokines Interleukin-4 (IL-4) and Interleukin-10 (IL-10) decline [57-65]. Inflammatory cytokines act both peripherally at the site of injury and in the CNS at multiple levels in the pain matrix [57]. In patients with long-standing disease the percentage of CD14+ and CD16+ monocyte /macrophage activity (proinflammatory) in the serum increases although the total monocyte count remains normal [66] and anti-inflammatory cytokines such as IL-10 decreases. Further evidence for autoimmune mechanisms in the pathophysiology of the constitutional symptoms noted in CRPS is suggested by the finding that approximately 35% of patients have surface-binding autoantibodies against sympathetic and mesenteric plexus neurons [67, 68].

The body's initial nonspecific immune activation following injury or infection is evident within hours and is called the sickness response. It is initiated by immune system to brain interactions that trigger a cascade of nervous system reactions that include pain facilitation [69].

As noted above, inflammatory cytokines are released from activated immune cells at the site of injury. Interleukin-1 (IL-1), IL-6 and TNF-α activate specialized sensory structures, paraganglia, that synapse with sensory vagal fibers [70-72]. Sickness-induced pain facilitation can be blocked in experimental neuropathic pain models by IL-1 receptor antagonists, TNF-α binding protein or subdiaphragmatic vagotomy [73-77]. The severe fatigue suffered by CRPS patients may result in part from the sickness response circuitry [76]. Other contributing comorbidities are disruptions of sleep architecture, hypothyroidism, secondary hypoadrenalism from a chronic stress response, deconditioning and severe depression.

4. Cardiac Complications of CRPS

Approximately 2,500 CRPS patients with disease duration of greater than 2 years and at least two-extremity involvement have been evaluated at the Drexel University Pain Clinic. Five hundred had EKG and echocardiogram evaluation prior to sub-anesthetic ketamine treatment. There were no specific EKG abnormalities other than a higher than normal pulse rate ranging from 80-100 beats per minute. The ejection fraction was between 50-65% which did not differ from control male and female controls. Approximately 10% of patients described syncope or presyncope during the course of their illness [78]. Seventy four patients underwent head-up tilt test (HUTT) to evaluate their complaints of syncope and were compared to an age and gender-matched comparator group and to literature standards of control patients that underwent HUTT. The mean duration of CRPS of the tested patients was 6.5 years whose average pain on a Likert numeric scoring system was 7.7 (0 being no pain and 10 being the worst pain imaginable). All patients were extremely ill and had some spread of pain from the original site of injury. Twenty nine patients (39%) had generalized total body CRPS. Eight patients were not

able to complete a HUTT due to pain. Twenty eight (42.4%) CRPS patients out of the sixty six tested had a positive HUTT that could be classified as: (1) 17 (61%) mixed response (heart rate decreased by greater that 10% but does not decrease to less than 40 beats per minute for greater than 10 seconds and the blood pressure fell prior to heart rate; (2) 1 patient (4%) had cardioinhibition without asystole in which blood pressure falls before heart rate; (3) two patients (7.1%) had a cardioinhibitory response with asystole in which the blood pressure fell prior to a decreased heart rate. Three patients (11%) demonstrated a vasodepressor response in which the heart rate does not fall greater than 10% from the maximum rate during tilt. The fall in blood pressure however precipitates syncope [79]. The majority of CRPS patients (23/28; 88%) required nitroglycerine provocation to induce a positive HUTT. There was no correlation between specific pain characteristics (dynamic or static mechanical allodynia, hyperalgesia or hyperpathia) or duration of illness with positive a head-up tilt test although it occurred more frequently in younger patients. CRPS patients were 4.5 times more likely to have a positive HUTT than age and gender-matched control subjects. There was no significant difference in heart rate variability between CRPS patients with or without a positive HUTT. Fifty four percent of our HUTT-positive CRPS patients were less than 40 years of age. Approximately 38% of the CRPS patients that completed the study had at least one prior complaint of presyncope or syncope. CRPS patients with involvement of the lower limbs are more likely to have vasovagal syncope and positive orthostatic HUTT than those with upper extremity or total body disease. Patients with CRPS have an enhanced predisposition to neurocardiogenic syncope during head-up tilt table testing compared to the vasovagal response of historical controls of asymptomatic subjects [80-83]. In children and adolescents with CRPS the tilt test demonstrates orthostatic stability but a higher mean heart rate with tilt than in control subjects [84]. Another recent study of twenty age, sex and body-mass index-matched control subjects demonstrated increased heart rate and decreased heart rate variability in CRPS patients during rest, mental and orthostatic stress. Baroreceptor sensitivity was maintained [85]. During a 60 degree tilt, CRPS patients had a drop in cardiac output and an exaggerated increase in total peripheral resistance. The autonomic changes correlated with disease duration but not pain intensity. The authors concluded that the increased heart rate and decreased heart rate variability was due to a generalized autonomic imbalance and increased their susceptibility to sudden death [85]. Evidence is emerging that measures of reduced heart rate variability may be a prognostic factor for cardiac arrhythmias [86].

Atypical chest pain is a common complaint of patients with CRPS. Most of these patients have suffered a neuropathic ICB nerve traction injury [13]. Atypical chest pain often presents in young women who uncommonly have coronary artery disease (CAD). If CAD is present, they have a 7% higher risk of death than age matched men [87]. Noninvasive cardiac screening tests that include stress EKG are less sensitive in female patients [88]. This often leads to coronary arteriography in these patients where the ICB nerve is generating the chest pain.

Approximately 25% of all coronary angiograms are negative in the general population and no positive studies have been seen in our young patients with sensitized ICB nerves from trauma or CRPS [89]. Most of our patients with chest pain complained of anterior lateral and under the breast pain and received extensive cardiac evaluations that ended with negative catheter studies. The patients themselves did not think that their chest pain was related to their CRPS. The majority of chest pain reported by these patients (n = 35 in the Rasmussen study) [13] was bilateral (66%), radiated to the jaw/ head/ neck (concomitant cervical plexus C2-C4 involvement) [90] and the brachial plexus distributions in the shoulder and arm (46%). The majority of these patients that sought care from their primary care physicians received an EKG (79%) or were diagnosed with chest pain of unknown origin (26%); costochondritis (21%); psychosomatic illness (21%); cardiac disease (16%); Gastroesophageal reflux disease (GERD) (5%); hormonal disorders (11%) and diseases of unknown etiology (26%).

In the CRPS patients, only 40% described their pain or burning while most (60%) felt it as deep or aching. Approximately 65% of CRPS patients could elicit the chest pain by elevating their arm and stretching the brachial plexus that in turn would cause traction on the ICB nerve. It has been demonstrated experimentally that nerve injury over time induces pain markers on somatic mechanical afferent nerves which then activate dorsal horn pain transmission neurons [91]. The anatomy of the nerve explains its radiations and how discharge in its territory can easily be confused with coronary artery pain. It arises from the second intercostal nerve (T2) with variable contributions from T3 and T4 nerve roots [92, 93]. The ICB nerve innervates the axilla, medial and anterior arm as well as contributing to the innervation with the posterior antebrachial cutaneous nerve. It innervates the anterior chest wall by connections to the long thoracic nerve [92, 93] and on occasion innervates the pectoralis minor and major muscles [93]. In thirty percent of patients the ICB nerve is connected to the brachial plexus from the medial cord [94]. T2 is the primary root of the ICB nerve and connects to the brachial

plexus 100% of the time, either via the ICB nerve (80%) or from direct intrathoracic connections in 20% of patients [95]. The nerve is very frequently injured during breast surgery [96-98] which may also cause CRPS.

5. Respiratory System

In the longitudinal study of 270 consecutive patients with moderate to severe CRPS, shortness of breath was reported in 42 (15.5%) [1]. Evaluation of these patients revealed subsegmental atelectasis on chest x-ray in 33%, low lung volume in 16.7% and only one patient (.5%) had evidence of chronic obstructive lung disease (COPD). One patient had mild congestive heart failure. Hilar adenopathy and small pleural effusions were noted in three patients. Nine of the 42 patients underwent formal pulmonary function tests. Five had restrictive lung disease and two had mild restrictive lung disease. One patient had normal studies.

In addition to these non-specific pulmonary abnormalities, many patients complain of not being able to take a deep breath. Dystonia of the chest wall muscles is common in severe long-standing patients but no epidemiological studies have been done that would determine its incidence and prevalence. Dystonia is a major component of the movement disorder of CRPS [99-102]. That it can affect chest wall muscles causing restrictive lung disease has only recently been recognized [103]. In general, the presence of dystonia in CRPS patients is associated with a younger age and longer duration of disease [101]. The onset of dystonia is variable but may precede other manifestations of the disease [99]. Another cause of chest wall discomfort that prevents patients from normal inspiration is irritation of the ICB nerve that often innervates pectoral and intercostal muscles [13]. Involvement of this nerve is most often confused with cardiac pain if it occurs on the left side and gall bladder disease if it is in the right chest wall.

6. Systemic Manifestations of Autonomic Dysregulation in CRPS

Failure of a compensatory reflex-induced increase in heart rate when blood pressure falls is a manifestation of autonomic dysregulation which has both peripheral and CNS components [20]. The affected extremities of CRPS patients are most often warm early in the course of the illness and then become cold which suggests a change in activity of the vasoconstrictor neurons in the spinal inter mediolateral column [104]. Clinical studies utilizing whole body warming and cooling combined with respiratory stimuli were utilized to evaluated CRPS patients who suffered various durations of the illness [105, 106]. Those patients with less than four months of disease had a warm extremity and higher skin perfusion values than the unaffected extremity. Norepinepherine concentration from the affected extremity was decreased [106]. In those patients with mean disease duration of 15 months had either a warmer or cooler affected extremity that depended on variable sympathetic activity. Patients with cold affected extremities had disease duration of a mean of 28 months and also demonstrated low norepinephrine concentrations in the venous effluent from the affected extremity [106]. In a significant portion of long standing patients sympathetic vasoconstriction returns to normal although the affected extremity is cold [106]. It has been postulated that early in the illness there is central nervous system efferent autonomic dysregulation while over time there may be increased density or sensitivity of blood vessel noradrenergic receptors to circulating norepinephrine from the adrenal gland [107-110]. Earlier studies utilizing laser Doppler fluxemetery found that the normal reduction of skin blood flow from activation of the sympathetic efferents by a Valsalva maneuver or cold presser test was absent in CRPS patients. Sympathetic innervation of arterioles is the major innervation that controls blood flow to capillaries in the extremities. Vasomotion, the normal sympathetically mediated spontaneous wave-like fluctuations in veins are also reduced or absent in CRPS patients [110]. These earlier studies are supported by another study that demonstrated sympathetically induced vasoconstriction is reduced in early CRPS patients which returns to normal over time [106, 111, 112]. That sympathetic dysfunction maybe an early component of any post-traumatic neuropathy was suggested by a thermographic study of 200 injuries suffered by 1000 recruits during basic training [113]. Immobilization of an injured limb may also induce temperature changes in an injured extremity and maybe a risk factor for the subsequent development of CRPS [114, 115]. Sudomotor dysfunction is common in CRPS patients both early and late in the course of illness. It usually manifests as an increased resting sweat output of the affected extremity [116]. Sweat glands normally respond to cholinergic stimulation but an adrenergic sweat response may occur in CRPS – affected limbs following iontophoresis of an alpha-adrenergic agonist [117]. This suggests that in CRPS there is activation of systems that are not normally under adrenergic control.

Anatomical connections of the sympathetic nervous system innervation to afferent nociceptors occur after experimental axotomy [118, 119]. In the dorsal root ganglion (DRG) sympathetic fibers from blood vessels sprout and form baskets around mechanoreceptors and innervate thinly myelinated fibers. This is in response to upregulation of p75 receptors that guide sympathetic fibers and lymphocyte inhibitory factor (LIF) that in-

duces sympathetic nerve sprouting. There are other potential mechanisms for the coupling of sympathetic efferents to nociceptive afferents that occur at the site of injury [119]. Mechanosensitive sensory afferents and nociceptive fibers express adrenoreceptors that may be upregulated and activated following nerve injury. An increased density of α -1 adrenergic receptors occurs in the hyperalgesic skin of CRPS-I patients [119, 120]. The involvement of the sympathetic nervous system in CRPS is further demonstrated by: (1) the response of early CRPS patients to sympatholysis; (2) the demonstration of acute antibodies to sympathetic ganglia; (3) denervation hypersensitivity of vascular smooth muscle (due to loss or dysfunction of vasomotor neurons in the intermediolateral column); (4) sensitization of mechanoreceptors from the adrenal release of epinephrine; (5) immune sympathetic system interaction [67, 121-123].

The autonomic manifestations of CPRS are frequently misdiagnosed as Raynaud's phenomena (particularly if the affected extremity is minimally painful), fibromyalgia and vascular insufficiency. This occurs in the setting of a cold blue extremity, with mottling and livedo reticularis and neurogenic edema. The erythematous warm extremity is often thought to be infected.

7. Inflammation/ Neurogenic Edema

In a longitudinal study of over 600 patients with CRPS of at least one year's duration, 75% were positive for neurogenic edema. In those with long standing disease, 90% were positive. The swelling correlated with disease duration and may be generalized and massive [1]. There is often sustained diuresis at the initiation of ketamine therapy. The average weight loss of moderate to severely affected CRPS patients when the edema is mobilized is between 10 and 12 pounds. Diuretics are often administered for the edema and are ineffective. Frequently affected body parts are concomitantly erythematous as well as swollen. If these signs are present in a painful lower extremity, patients are misdiagnosed as suffering from thrombophlebitis. There are often severe dystrophic skin, nail and integument changes in the affected lower extremities that in association with erythema and increased temperature suggest infection.

At the site of injury an "inflammatory soup" develops. It originates from the blood or inflammatory cells that include: inflammatory cytokines (IL-1, IL-6 and TNF-α, prostaglandins (PGE2), serotonin (5-hydroxy- tryptamine), brandykinin, epinephrine, lipoxygenase, neurotrophic factors (nerve growth factor (NGF), brain derived neurotrophic factor (BDNF)), neurotrophin-3 (NT-3) and nucleotide transmitters such as adenosine [124, 125]. This microenvironment blurs the distinction between inflammatory or purely neuropathic pain in CRPS. The effect of these cytokines, neutrophilic factors, small molecules and enzymes is to directly activate the terminal membranes of C and A-δ nociceptors or to decrease their firing threshold. This effect is mediated by activation of phosphokinase A (PKA) and phosphokinase C (PKC) which phosphorylate tetrodotoxin (TTX) resistant sensory neurons and specific sodium channels [126]. In addition, cytokines TNF-α, Interleukin-1 beta (IL-1β) and IL-6 release calcitonin gene related peptide into the skin. Retrogradely transported NGF has also been shown to regulate gene expression (new receptors and proteins) and biosynthesis in neonatal rat sensory neurons [127, 128]. The activation of these C and A-δ terminal twigs induces an axon reflex that releases the vasoactive neuropeptides substance-P, calcitonin gene related peptide (CGRP) and neurokinin A which causes vasodilation and protein extravasation. The associated neurogenic inflammation causes erythema, increased temperature and edema [129]. The majority of the neurogenic inflammation, edema and augmented flare response in CRPS patients are caused by substance-P and CGRP [130-134]. Substance-P has also been demonstrated to stimulate skin keratinocytes to express cytokines in the affected extremities of CRPS patients [135, 136]. Further evidence for the involvement of inflammatory cytokines in neuroinflammation and edema in the affected extremities of CRPS patients is: (1) increased concentration of TNF-α and IL-6 in skin blister fluid from fracture sites in the CRPS affected limb [58, 59]; (2) serum concentrations of soluble TNF receptors and TNF-α receptors, IL-1 and interleukin-8 (IL-8) are elevated in early CRPS (mean of 3 months) while the anti-inflammatory cytokines IL-4, IL-10 and transforming growth factor beta-1 (TGFβ-1) are decreased [62, 131]. A contrary study found that blister fluid and serum cytokine concentrations were not linked to disease duration or clinical signs other than mechanical hyperalgesia [62, 137, 138]. An aberrant inflammatory response to tissue injury inducing erythema, warmth and neurogenic edema appears to be an important aspect of CRPS. In addition to pain relief, these inflammatory changes respond dramatically to N-Methyl-D-aspartate (NMDA) blockade by ketamine protocols [139]. The erythema and neurogenic edema seen on both early and long standing CRPS patients is often mistaken for thrombophlebitis or infection when it occurs in the lower extremities. Unfortunately, the grossly edematous and poorly perfused lower extremities often do get infected.

8. Musculoskeletal System

The musculoskeletal system is profoundly affected in almost all patients with CRPS. Weakness was reported in approximately 70% of patients in a longitudinal study [1]. In addition to weakness, patients suffer atrophy in muscles that maybe normally exercised. This is apparent particularly in intrinsic hand and foot muscles as well as the gastrocnemius muscles. Occasionally a specific component of muscle will be atrophied in a muscle that does not appear to be involved with the illness. Evaluation of muscle from the amputated limbs of 14 severe end-stage CRPS patients revealed fatty degeneration, Type I and II fiber atrophy and evidence of degeneration with reinnervation. There was no difference in the pathology between arm or legs and no correlation with duration of illness [140]. Under hypoxic conditions elevated levels of reactive oxygen species are produced which act as second messengers that activate hypoxia inducible factors (HIPs) that help to maintain ATP levels [141]. Magnetic resonance spectroscopy has demonstrated that muscle in CRPS patients is hypoxic [142] which causes failure to maintain a normal redox state and that in turn will increase reactive oxygen species (ROS) production and cell injury [143]. Mitochondrial dysfunction has been demonstrated in severe late stage patients in limbs prior to amputation [144]. Biochemical analysis suggests that decreased activity of mitochondrial succinate dehydrogenase (complex II) is causative of mitochondrial energy production failure and free radical production [145]. ROS cause carbonylation of mitochondrial proteins which signifies oxidative damage [146]. These observations of oxidative damage in muscle support previous observations of free radical damage as a pathologic mechanism in CRPS [147, 148] [149]. Eight children with mitochondrial disease and probable CRPS have been described which also lends further support to a role of dysfunctional mitochondria as a possible mechanism of the muscle dysfunction that occurs in CRPS patients [150].

Bone and joint pain are suffered by a majority of CRPS patients. X-rays of the affected extremities demonstrate bone lakes (intracortical excavation) associated with periarticular, trabecular and periosteal demineralization and bone resorption [151]. These changes are thought to be the result of osteoclastic activation possibly from nociceptor release of substance P [152]. During bone resorption, activated osteoclasts reduce pH enough to depolarize pain afferents which densely innervate bone [151]. Magnetic resonance imaging often reveals bone marrow edema and triple phase bone scans demonstrate pooling in the late phase [151, 153] in 30 to 50% of patients. Pathologic fractures are very common in CRPS-I patients. A frequent fracture occurs in the 5th metatarsal bone. Most patients suffer fractures during their usual activities or with minimal trauma. Experimental evidence demonstrates that bone formation and maintenance are critically dependent on an intact small fiber innervation which is dysfunctional in CRPS-I patients [2] [154-156]. These fractures are difficult to heal which may also be a reflection of dysfunction of bone innervation.

9. Endocrine System

All patients with moderate to severe CRPS experience stress due to pain itself and the disruption of work, personal relationships and activities of daily living. In a longitudinal study of 270 patients, 69% described severe tiredness and unusual fatigue. Disproportionate unexplained fatigue may be due to congestive heart failure, hepatic and renal failure, decreased systemic oxygenation (anemia or COPD), endocrine dysfunction (hypothyroidism, adrenal insufficiency), depression or inflammatory cytokine mediated illness (malignancy, human immunodeficiency, HIV, Epstein-Barr and other viral infections) and medications including narcotics. Twenty six patients with severe fatigue and total body CRPS underwent evaluation of their hypothalamic pituitary axis. Twenty three were females and 3 were males whose median age was 44 years (mean 43 years, range 20 to 64 years). No patient had anemia, congestive heart failure, COPD, renal or hepatic failure, HIV, malignancy or recent infection. No patient had active major depression or had a history of recent steroid use. Low baseline cortisol levels were noted in ten of the twenty six patients – one of whom had a low TSH level. The adrenocorticotrophic hormone (ACTH) stimulation test was administered to patients with low baseline cortisol levels. All ten patients with low cortisol levels responded with a significant increase in serum cortisol within one hour. This implies normal adrenal gland function but an impaired hypothalamo-pituitary-adrenal [157] axis demonstrating tertiary adrenal insufficiency. In this ongoing study [158] approximately 38% of severe CRPS patients have a low serum cortisol level.

Experimental studies have demonstrated that systemic corticosterone suppressed the late phase of the formalin test which implies a role in control of central sensitization [159, 160] or inhibition of inflammatory mediators [161]. Further support that glucocorticoids mediate central effects in neuropathic pain is derived from models in which the development and maintenance of mechanical hyperalgesia and allodynia following nerve injury is decreased following systemic administration of betamethasone [162]. Glucocorticoids may decrease pain

by several mechanisms: (1) suppression of intracellular cascades mediated by phospholipase A_2 [163]; (2) decreasing ectopic discharge from experimental neuromas; (3) blocking neurotransmission in C fibers [164, 165]; (4) decreasing microglial activation [166]. Approximately 40% of CRPS patients have low cortisol levels which can be a component of their sustained pain.

Approximately one third of moderate to severe CRPS patients suffer hypothyroidism [1]. The effect of this deficit is not known other than that noted in Sudek's atrophy. Hyperparathyroid function and bone metabolism has not been reported.

The role of the HPA in chronic stress is well documented. [167, 168]. The above data that demonstrates low cortisol levels in a significant portion of CRPS patients with normal adrenal function after cosyntropin stimulation supports failure of the HPA axis in the illness.

A great percentage of patients with severe CRPS are treated with large doses of strong opiods. A recent study has demonstrated pituitary dysfunction in all of its axes with hypofunction of: (1) the hypothalamic- pituitary-gonadal axis; (2) hyperfunction of the HPA axis; (3) higher prolactin levels. Cessation of narcotics can reverse the endocrine dysfunction [169].

10. Dermatologic Manifestations of CRPS

In a longitudinal study of the natural history of CRPS 71% of patients reported skin color changes within 5 years that increased to 81% after 15 years. This was usually a combination of erythema, mottling, livedo reticularis and cyanosis [1]. Swelling was noted in 75% of patients by the first year and in 90% of patients after 15 years [1]. A peculiar finding noted in several patients was the "ligature sign" - as if the patient had tied a ligature around the edematous extremity that persisted even as edema decreased during treatment. Approximately 20 % of patients report a slightly raised morbilliform rash. The most common lesion seen is a well circumscribed 1-3 mm punched out ulcer-like lesion that is preceded by a pruritic skin lesion resembling an insect bite. Within 2 to 3 days, the center of the lesion is excavated and its circumference is raised. The pruritis ends at this stage. The lesion heals with an atrophic thin center and clearly erythematous margins. In an early publication, two of nine patients suffered recurrent bullae in their chronically edematous legs [170] . Ultrastructural evaluation of biopsy material from a bullous lesion in one patient revealed abnormalities in basement membrane and anchoring fibrils. In some areas the basement membrane did not contain any anchoring fibrils and segments of basement membrane revealed decreased electron density and focal disruption. Two patients demonstrated lesions similar to pigmented purpura. These patients had the acute onset of marked erythema in their chronically edematous leg. Biopsy revealed lymphocytes and histiocytes surrounding blood vessels with extravasted erythrocytes that most closely resembled Schamberg's disease [171]. After approximately two years, the skin of the affected extremity becomes atrophic, smooth and often dry. Brittleness, ridging and thinning of the nails occurs concomitantly. Verrucous changes often seen in patients with venous stasis do occur in addition to cellulitis and ulceration. A subset of these patients slough large areas of skin. Patients with bullae and evidence of disruption of collagenous anchoring fibrils had normal dermoepidermal immunofluorescence. The bullous eruption seen in these patients is similar to that described in diabetic patients with neuropathy [172-174].

There has been extensive pathologic study of the amputated limbs of 8 CRPS patients which revealed severe muscle atrophy and severely thickened capillaries as well as ultrastructural quantification of C fiber degeneration [149]. Two further anatomical studies of skin from amputated CRPS-I limbs revealed loss of endothelial integrity, blood vessel hypertrophy and reduced epidermal sweat gland and vascular small nerve fiber innervation. Altered neuropeptide profiles were noted in surviving small nociceptive fiber afferents that innervated hair follicles, superficial arterioles and sweat glands [175, 176]. However, a recent study of much less severely affected patients found alterations of small fiber skin innervation in only 20% of CRPS-I patients. There were no patient signs or symptoms or stage of disease that predicted epidermal nerve density [177, 178]. In this study there was no consistent reduction in sweat gland nerve fiber density. An abnormal dense small-fiber innervation around hair follicles has also been described in CRPS-I patients [175].

The trophic effects of CRPS-I are noted in skin, muscle, bone (Sudek's atrophy) and joints. The skin and integument atrophy is often particularly apparent in interphalangeal joints of the hand and the dorsum of the foot and lower leg in conjunction with brawny edema. The nails become thickened, ridged, grow too rapidly and split. Early in the course of the illness when it is often sympathetically maintained, hair becomes thicker, curly and grows more rapidly. As the disease progresses it is lost [114]. Experimental axotomy of cutaneous nerves decreases keratinocyte mitosis and results in epidermal thinning and hair loss [179, 180].

The distal extremities and particularly the finger tips are pivotal for thermo-regulation affected by arteriovenous shunts [2]. The sympathetic innervation of these arterioles normally tonically constricts their smooth muscle

which occludes the arteriovenous shunt (AVS). During the progression of CRPS-I there maybe nervi vasulorum degeneration (small fibers) which would allow blood to bypass nutritive capillaries and thus cause hypoxia of the perfused tissue (loss of skin, connective tissue and muscle). This mechanism has been suggested as a cause of the atrophy seen in the muscles of CRPS patients [2, 142].

Sweating abnormalities are seen in approximately 30 % of patients. In a large study of well characterized CRPS-I patients, 22% had increased resting sweat output, 7% decreased and in 71% it was normal [181] . Patients are often unaware of sweating abnormalities which fluctuate with emotional state and environmental stimuli. Denervated sweat glands that do not respond to neurologic stimuli may respond to circulating norepinephrine although their usual ligand is acetylcholine [117].

The Gardner Diamond syndrome is common in CRPS patients. Patients experience spontaneous bruising which often occurs months following an initial trauma [182]. The bruising occurs in areas that were not injured. The suggested mechanism is an autoimmune reaction against a component of the patient's erythrocytes. Coagulation parameters are normal and skin biopsy reveals nonspecific changes. Possible antigens that elicit this autoimmune response are thought to be phosphatidyl serine – a phosphoglyceride of the red blood cell membrane [183-185]. Occasionally, deep muscle tissue is the site of erythrocyte extravasation. As noted earlier, the inflammatory response resulting in neurogenic edema may be a mechanism for red blood extravasation in CRPS [186, 187].

11. Urological System

Urological symptoms and signs are seen in approximately 25% of CRPS patients [1]. In a study of 20 consecutive CRPS patients who were referred to an academic urology service, the main complaints were frequency, urgency or urinary incontinence. The mean age of these patients was 43 $\pm$ 10 years and the duration of urological symptom was almost 5 years [188]. No patient had voiding problems prior to the onset of CRPS. Endoscopic evaluation of these patients was normal as was cytology. Renal ultrasound cleared upper tract pathology such as hydronephrosis, nephrolithisasis or tumor. Detrusor hyperreflexia was found in 8 patients, detrusor areflexia in 8 patients and sensory urgency in 3. Detrusor hyperreflexia with detrusor external sphincter dysnergia was documented in 1 patient. Four of the patients (women) had stress incontinence. The mean cystometric bladder capacity was 417 $\pm$ 182 ml. Complex regional pain has been diagnosed in the penis one year following transurethral prostatectomy [189]. Pelvic and perineal pain is also seen in CRPS patients particularly if both lower extremities are affected [114, 190].

12. Gastrointestinal System

In the prospective study of 270 patients who were evaluated prior to ketamine infusion [1], constipation was reported most frequently (113 patients, 41%). Common other symptoms were nausea (63 patients, 23.3%), vomiting (31patients, 11.5%), complaints of intermittent diarrhea (18.5%) and indigestion (18.5%). Irritable bowel syndrome was diagnosed in 46 patients (17%) since onset of CRPS.

Dysphagia was frequently noted (47 patients, 17.4%) and has been thoroughly evaluated in over 20 patients. Patients typically describe a feeling of food being stuck in their throat. All patients were evaluated by an ENT and swallowing specialist. They underwent a comprehensive head and neck examination that included fiber-optic nasopharyngoscopy. The patients' swallowing function was evaluated with water, thickened juice (nectar, honey) and solids (cottage cheese). The swallowing parameters assessed were: (1) bolus formation; (2) initiation; (3) delay; (4) residual; (5) clearance; (6) spasm; (7) GERD. All patients had difficulty with bolus formation and control. They were slow to initiate swallow and had a significant delay with the bolus which collected at the valleculae for a prolonged period of time. Deglutition demonstrated poor clearance from the hypopharynx with multiple involuntary swallows. Laryngeal penetration and frank aspiration did not occur. The dysphagia experienced by these patients appears to be multifactorial. Inability to initiate movement of pharyngeal musculature causes poor bolus formation with consequent segmentation. Patients also appear to have diminished sensation of the bolus that leads to pooling within the vallecula, a delayed swallow and significant residual within the piriform sinus and poor pharyngeal clearance. GERD is common in the CRPS population (73%). As noted, stress of many types is noted in these patients [191] and multiple medications may contribute to GERD specifically and dysphagia generally.

Gastroparesis is a major problem in almost all long-standing patients that have suffered more than 5 years with CRPS. In general, these patients have multi-limb disease; the lower extremities are affected to a greater extent than the upper and urological symptoms are concomitant. The most frequent complaint is early satiety and bloating. Severe constipation, diarrhea and irritable bowel symptomatology are present in 90% of these patients.

Pain from CRPS involvement on the right side is frequently mistaken for gall bladder disease leading to operation [13]. Although the pain emanates from the axilla and radiates to the anterior chest wall, lateral chest wall (gall bladder region) and may also be felt at the tip of the scapula, its most troubling feature maybe epigastric pain. This is most often diagnosed as GERD. Approximately 5% of our severe patients have had their gall bladder removed for pain caused by the ICB nerve on the right side.

Central sensitization syndrome (CSS), a pathophysiologic component of CRPS, is thought to be important in irritable bowel syndrome (IBS) and functional dyspepsia [192]. A closely related syndrome, fibromyalgia (FB), has been related to the metabolic syndrome in women [193]. FB is also associated with functional bowel disorders and cyclic vomiting syndrome (CVS) [194]. In a study of 18 adult patients with CVS, it was demonstrated that the strongest associations were FB and CRPS [195].

A recent study identified 8 children in seven families who suffered CRPS-I and also had additional gastrointestinal (GI) dysmotility and cyclic vomiting. All 7 children met the Nijmegen (2002) diagnostic criteria for mitochondrial disease and 6 of the 7 probands had probable maternal inheritance [150]. GI disorders are common in CRPS and detailed physiologic studies are in progress.

There is accumulating evidence that thinly myelinated A-δ and unmyelinated C fibers are involved in the somatic manifestations of CRPS [2]. They may also involve internal organs such as the GI tract. Early evidence suggests gastroparesis is a component of the clinical manifestations of early satiety, bloating, nausea and vomiting reported by approximately 5 % of patients [1].

Nociceptive C and A-δ axons innervate blood vessels and their neuroeffector secretions can marginalize immunocytes into the intestinal wall. Lymphocyte, monocytes, and mast cells thus recruited may trigger a neuro-immune cycle of inflammation and vasogenic edema of the intestinal wall similar to their somatic effects [2]. Small fiber involvement and resulting gastroparesis are well documented in diabetics who have small fiber neuropathy [196]. Circulating systemic inflammatory cytokines have also been demonstrated to cause gut edema [197].

13. Conclusion

Almost all organ systems are involved during the course of CRPS. Major progress has been accomplished in understanding its mechanisms as regard to pain [187, 198] but little is known about its plieotropic effects on internal organs which are frequently very perplexing to those that care for these patients.

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Abbreviation List

Complex Regional Pain Syndrome (CRPS)
intercostobrachial (ICB)
Wechsler Adult Intelligence Scale – III (WAIS-III)
functional MRI (fMRI)
primary somatosensory cortex (SI)
secondary somatosensory cortices (SII)
blood brain barrier (BBB)
tumor necrosis factor-alpha (TNF-α)
nuclear factor kappa B (NF-κB)
nAChR (acetylcholine receptor)
interleukin-6 (IL-6)
interleukin-10 (IL-10)
interleukin-1 (IL-1)
head-up tilt test (HUTT)
coronary artery disease (CAD)
Gastroesophageal reflux disease (GERD)
second intercostal nerve (T2)
chronic obstructive lung disease (COPD)
dorsal root ganglion (DRG)
lymphocyte inhibitory factor (LIF)
prostaglandins (PGE2)
neurotrophic factors (nerve growth factor (NGF)
brain derived neurotrophic factor (BDNF)
neurotrophin-3 (NT-3)
phosphokinase A (PKA)
phosphokinase C (PKC)
tetrodotoxin (TTX)
interleukin-1 beta (IL-1β)
calcitonin gene related peptide (CGRP)
interleukin-8 (IL-8)
transforming growth factor beta-1 (TGFβ-1)
N-Methyl-D-aspartate (NMDA)
hypoxia inducible factors (HIPs)
reactive oxygen species (ROS)
adrenocorticotrophic hormone (ACTH)
arteriovenous shunt (AVS)
central sensitization syndrome (CSS)
irritable bowel syndrome (IBS)
fibromyalgia (FB)
cyclic vomiting syndrome (CVS)
gastrointestinal (GI)

