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Complex Regional Pain Syndrome: Diagnostic Controversies, Psychological Dysfunction, and Emerging Concepts

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Abstract

Complex regional pain syndromes (CRPS) types I and II are neuropathic pain disorders that involve dysfunction of the peripheral and central nervous system. CRPS type I and type II were known formerly as reflex sympathetic dystrophy and causalgia, respectively. Most experts believe that a multidisciplinary approach including pharmacotherapy, physiotherapy, and psychotherapy is warranted. Historically, there has been considerable controversy regarding this disease entity. In particular, the precise mechanism of the sympathetic dysfunction as well as the nature of the psychological dysfunction commonly observed in patients with CRPS has been the subject of considerable debate. Current strides in our understanding of the pathophysiology of this disease have improved treatment options.

Introduction

Complex regional pain syndrome (CRPS) type I and type II, formerly known as reflex sympathetic dystrophy (RSD) and causalgia, respectively, are neuropathic pain disorders likely involving dysfunction of both the peripheral and central nervous system (CNS). The pathophysiology is poorly understood and treatments often are directed at managing the signs and symptoms of disease. A significant number of patients exhibit comorbid psychological dysfunction which has led some clinicians to believe incorrectly that CRPS is entirely a psychiatric disease. Animal research has improved our mechanistic understanding of neuropathic pain and this awareness may facilitate our understanding of CRPS (particularly CRPS type II). Recent clinical investigation has

resulted in an improved understanding of the biological dysfunction observed in patients with CRPS. This review will (1) summarize the historical arguments and controversy surrounding the disease, (2) describe the psychological dysfunction often observed in patients with CRPS, and (3) discuss recent trends in the neurobiological understanding of CRPS.

CRPS Controversy and Misunderstanding

CRPS History

Several authors have questioned the validity of CRPS type I as an actual organically based neurological disease and have doubted the involvement of the sympathetic nervous system in the maintenance of the pain. Many aspects of the disease, including nomenclature, etiopathogenesis, diagnosis, and treatment have generated considerable controversy. As a result, CRPS type I (RSD) has been considered by some experts an expression of somatoform disease and therefore has been designated as pseudoneuropathy of psychogenic origin. A brief discussion of several of these arguments is warranted.

Nomenclature

Causalgia was first described in 1864 as a distinct disease entity by Silas Weir Mitchell who noted extreme pain, autonomic abnormalities, trophic changes, and involuntary movements in Civil War soldiers who suffered from traumatic injury to peripheral nerves. Rene Leriche later postulated in 1916 that the sympathetic nervous system was involved in pain states involving major tissue or nerve injury. The term RSD was coined nearly half a century later in 1946 by J.A. Evans to describe patients who exhibited causalgia-like symptoms but without evidence of major tissue or nerve injury. Several other terms have been used to describe this disease such as minor causalgia, algodystrophy, shoulder-hand syndrome, posttraumatic dystrophy, and Sudeck's atrophy. In general, the disease was given different names based on the personal assumptions, frame of reference, institutional background, or country of origin of the investigators who were describing the disease process.

In 1994, a task force commissioned by the International Association for the Study of Pain (IASP) introduced the present day descriptive terminology to standardize the nomenclature, remove obsolete mechanistic understandings, and improve disease recognition. Until this time, scholars had argued that the term RSD erroneously implied an underlying 'reflexive' mechanism presumably related to aberrant function (ex. hyperactivity) of the sympathetic nervous system that if left untreated would inevitably lead to permanent dystrophic change. Today, most authorities recognize that sympathetic 'overactivity' is not

observed and that sympathetic dysfunction and dystrophic changes occur only in a subset of patients with CRPS. Furthermore, certain therapies specifically aimed at the sympathetic nervous system may be unwarranted [1, 2]. Despite the efforts of the IASP, many clinicians are unfamiliar with modern taxonomy and the majority of contemporary investigators fail to utilize the diagnostic criteria proposed by the IASP [3, 4].

Diagnosis

According to the IASP, the diagnosis of CRPS requires (1) an initiating noxious event or cause of immobilization, (2) continuing pain, allodynia, or hyperalgesia disproportionate to any inciting event, (3) evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity, and (4) the exclusion of a medical condition that would otherwise account for the degree of pain and dysfunction. The presence of an initiating noxious event or cause of immobilization was not required according to the original publication by the IASP in 1994; however, this statement was omitted from the more widely available and Medline-indexed summary statement from the consensus meeting published in 1995 [5]. Importantly, a precipitating inciting event may not be detected in approximately 10% of patients with CRPS [6]. This definition is entirely descriptive and does not imply etiology nor specific pathophysiology. This lack of mechanism-based specificity in the proposed diagnostic criteria has detracted somewhat from its universal acceptance by the scientific community.

Etiopathogenesis

Patients with CRPS exhibit signs of emotional duress and psychological dysfunction. Consequently, it was tempting for early investigators to conclude that much of the pain and symptomatology was the result of untreated psychiatric disease or caused by exaggerated sympathoarousal secondary to underlying stress. The term RSD helped to maintain this cause and effect link between the sympathetic nervous system and the pain. As a result, many patients underwent therapies designed to mitigate sympathetic nervous system function. Today, there is convincing evidence in animals and humans that nerve injury and tissue inflammation may be associated with aberrant functioning of the sympathetic nervous system [7] (table 1). Despite this link, the pathophysiology of CRPS is incompletely understood and several mechanisms may be operational simultaneously. Furthermore, it is commonly recognized that only a subset of patients with CRPS have sympathetically maintained pain, which is defined as pain that is modulated by sympathetic block or pharmacological antagonism of α-adrenoceptor function.

Table 1. Sympathetic nervous system involvement after nerve injury and inflammation

Animal studies	Sprouting of sympathetic fibers in neuroma and DRG
	Upregulation of adrenoceptors in neuroma and DRG
	Sympathetic fiber migration into denervated skin
	Increase afferent, neuroma, and DRG sensitivity to NE, sympathetic stimulation, and stress; effects are decreased by α-adrenergic antagonists
	Decrease in allodynia or hyperalgesia after chemical or surgical sympathectomy
	NE rekindles pain behavior after sympathectomy
	Increase in pain behaviors with NE injection or during stress
Human studies	Sympathetic sprouting in DRG [29]
	Increase in adrenoceptors in skin [30]
	Topical α_2-adrenoceptor agonists decrease pain in the affected region
	Chemical or surgical sympathectomy decreases pain
	Subcutaneous injection of NE or sympathetic stimulation rekindles pain after sympathectomy
	Increase in reported pain with stress or NE [31]
	Chemically mediated allodynia and hyperalgesia are decreased by adrenergic antagonists and increased by NE [32]
	Increase in pain and hyperalgesia after physiological activation of the sympathetic nervous system [35]

Selected references provided [for further details, see 7].

Psychological Dysfunction

Psychiatric Comorbid Conditions in Chronic Pain

Chronic pain patients frequently have associated comorbid psychiatric disease [8]. When ranked from most frequent to least frequent, the following comorbid conditions likely are associated more with chronic pain patients than with the general population: affective disorders (depression), psychoactive substance use-related disorders, somatoform disorders, and anxiety disorders. Moreover, a significant number of chronic pain patients may have more than one axis I psychiatric comorbidity. Psychiatric comorbidities can have a negative impact on chronic pain and functional status. In addition, there are a group of conditions commonly observed in chronic pain patients that are not necessarily psychiatric in nature, which in addition do not satisfy formal Diagnostic and Statistical Manual (DSM) criteria. These observations include such things as pain behaviors, sleep disturbance, somatization, nonorganic physical findings,

and impaired functional status out of proportion to physician expectations based on objective findings [8]. The prognostic implications of these conditions is unknown.

Psychiatric Disease in CRPS

Patients with CRPS commonly suffer from psychological dysfunction. In fact, patients with CRPS experience a significant amount of depression, anxiety, and phobia. However, attempts to establish a unique 'CRPS personality' have been unsuccessful. In general, early studies lacked validity due to various flaws in methodological design. For example, studies failed to examine premorbid personality data, study investigators used heterogenous definitions of psychiatric terminology, and psychometric instruments had not been 'normed' on pain populations [9]. Nevertheless, reported prevalence of psychiatric disorders in patients with CRPS ranges from 18 to 64% [10]. Psychological examination using the Structured Clinical Interview (SCID) of the DSM-IV demonstrates a high frequency of affective disorder (46%), anxiety disorder (27%), and substance abuse disorder (14%) in patients with CRPS [11]. However, the prevalence of psychiatric disorders in patients with CRPS may not be much different from chronic pain patients in general. For example, the prevalence of major depression (1.5–54.5%), anxiety disorders (7–62.5%), and substance abuse disorders (3.2–18.9%) in chronic pain patients is reported in similar rates as CRPS patients [8]. Finally, Bruehl and Carlson [10] reviewed data strictly from studies which used the Minnesota Multiphasic Personality Inventory (MMPI) and concluded that patients with CRPS, like patients with chronic pain in general, are somatically preoccupied, depressed, and use repression as a psychological defense mechanism.

There has been historical debate whether chronic pain or psychiatric illness is the primary process. The reciprocal relationship between pain and psychological dysfunction in patients with CRPS is evident from a recent study of daily diaries which demonstrated that yesterday's depressed mood contributed to today's increased pain and that yesterday's pain also contributed to today's depression, anxiety, and anger [12]. Several literature reviews have examined whether psychological dysfunction was the cause or effect of CRPS [9, 10, 13]. In general, the majority of historical studies suffered from flaws in methodology such as lack of consistent and homogenous diagnostic groups, lack of control groups and significant statistical tests, lack of objective measures of psychological disease, poorly defined behavioral criteria, and incorrect use of psychiatric or psychological terminology [13]. As a result, Lynch [13] concluded there is no valid evidence that certain personality traits or psychological factors predispose one to the development of CRPS. Similarly, due to the methodological weakness of the literature, Bruehl and Carlson [10] concluded

there is insufficient data to draw meaningful conclusions whether or not preexisting psychological factors predispose to the development of CRPS.

In summary, most authors have concluded that comorbid psychological disease in patients with CRPS is a consequence of the chronic pain rather than its cause [9, 13]. Furthermore, there is no evidence that individuals with certain personality types are predisposed to developing CRPS. Finally, there are no consistent psychological differences between CRPS and non-CRPS pain patients [14–22] (table 2).

Factitious Disorder

The overall prevalence of factitious disorder in chronic pain patients is between 0.14 and 2% [8]. Patients with conversion disorder and factitious illness may have similar clinical presentation to patients with CRPS. In fact, certain sensory signs (ex. nonanatomical and expansive areas of hypoesthesia or hyperalgesia with normal peripheral sensory nerve conduction or somatosensory evoked potentials) or features (ex. normalization of hypoesthesia by nerve blocks) identified in patients with CRPS type I likely are psychogenic in origin. Moreover, neurophysiological investigation suggests that certain positive motor signs (dystonia, tremors, spasms, irregular jerks) identified in patients with CRPS type I are in fact psychogenic in origin and represent pseudoneurological illness [23].

Strain and Distress in Caregivers

Caregivers of patients with CRPS experience significant levels of strain and susceptibility to depression measured by the Caregiver Strain Index (CSI) and General Health Questionnaire-12 (GHQ-12), respectively [24]. Caregiver health can have a significant impact on recipient care. Thus, physicians should not only implement psychosocial interventions directed at patients but also at caregivers of patients with CRPS.

Other Issues (Legal, Disability)

Allen et al. [25] recently performed a retrospective chart review of the epidemiology of CRPS. They reported that 54% of patients had a worker compensation claim and that 17% had a lawsuit related to the CRPS. The effect of litigation on pain severity and clinical outcomes for patients with CRPS is unknown.

Neglect-Like Symptoms

Patients with CRPS often display signs of motor dysfunction that appear to be related to voluntary guarding in order to avoid exacerbation of pain.

Table 2. Psychological comparisons of CRPS and chronic pain patients

Study	Comparison group	Psychological measure(s)	Conclusion
Haddox et al., 1988 [14]	Painful radiculopathy	STAI, DPQ, McGill Pain Questionnaire	No differences
Zuchinni et al., 1989 [15]	Nerve lesion	MMPI	No differences
DeGood et al., 1993 [16]	Chronic low back pain	SCL-90R	Less distress but higher pain-related disability and pain scores in CRPS
Nelson and Novy, 1996 [17]	Myofascial pain syndrome	MMPI	Less pyschological dysfunction, less pain medication, more employment disruption, and more worker's compensation in CRPS
Bruehl et al., 1996 [18]	Chronic low back pain and chronic limb pain	McGill Pain Questionnaire, CSQ, BSI	More emotional distress, positive pain coping behavior, and somatization in CRPS
Ciccone et al., 1997 [19]	Chronic low back pain and chronic radiculopathy	BDI, CSAQ, SIP	No differences except greater disability days in CRPS and low back pain
Geertzen et al., 1998 [20]	Hand pathology	SCL-90, STAI	More depression in female patients and more anxiety in male patients with CRPS
Monti et al., 1998 [21]	Chronic low back pain	SCID, SCID II	No differences
Van der Laan et al., 1999 [22]	CRPS with dystonia and chronic Rehab population	SCL-90R	No differences except more insomnia and less somatization in CRPS-dystonia group

STAI = State-Trait Anxiety Inventory; DPQ = Dartmount Pain Questionnaire; SCL-90R = System Checklist-90 Revised; CSQ = Coping Strategies Questionnaire; BSI = Brief System Inventory; BDI = Beck Depression Inventory; CSAQ = Cognitive-Somatic Anxiety Questionnaire; SIP = Sickness Impact Profile.

However, recent evidence suggests that motor dysfunction may be related to neglect-like symptoms (i.e. cognitive neglect, motor neglect) in a subset of patients with CRPS [26]. Of note, self-reported motor dysfunction is the second most commonly reported group of symptoms after sensory dysfunction in patients with CRPS [27].

Quality of Life

A pilot study demonstrated substantial interference with quality of life measured by modified Brief Pain Inventory (mBPI) as well as significant sleep disturbance in patients with CRPS [27].

Stressful Life Events

Stressful life events were more common in patients with CRPS than in a control group of patients with hand pathology measured by the Social Readjustment Rating Scale (SRRS) [20]. However, these authors concluded that there was no direct causal relationship between these stressful life events or any underlying psychological dysfunction (measured by SCL-90) and the onset of CRPS. In a retrospective study, Geertzen et al. [28] concluded that stressful life events and psychological dysfunction, measured by the SRRS and RAND 36-item Health Survey (RAND-36), respectively, already existed at the time of diagnosis of CRPS and did not result from CRPS.

Recent Trends

Sympathetic Nervous System

Classical teaching suggested that the sympathetic nervous system was the cause of pain or maintained the pain in patients with CRPS. Although authors recognized that certain patients with CRPS displayed signs of sympathetic nervous system dysfunction, many were reluctant to concede that pain was caused by the aberrant functioning of the sympathetic nervous system. Contemporary understanding suggests that the sympathetic nervous system not only may be dysfunctional but also that it can modulate the pain experience in patients with CRPS. In addition, the dysfunction of the sympathetic nervous system may be both peripheral and central in origin which may account for the complex and widespread symptomatology observed in patients with CRPS. A brief review of pertinent studies is warranted.

Sympathetic Nervous System and Pain

In animals, there is overwhelming evidence that nerve injury and inflammation can result in functional coupling between the sympathetic efferent and primary sensory afferent neurons within the peripheral nervous system [7]. The site of this aberrant sympathetic-sensory coupling involves the dorsal root ganglia (DRG), the area of injury itself (i.e. neuroma site), or within the tissue innervated by the injured nerve.

Several of these correlates exist in humans and these findings have been summarized in recent reviews [7]. For example, peripheral nerve injury results

in sympathetic sprouting and functional coupling between sympathetic efferent and primary sensory afferent neurons in the DRG [29]. An increase of α_1-adrenoceptors has been observed in the hyperalgesic skin of patients with CRPS type I [30]. Patients with CRPS type I have decreased sympathetic outflow but increased α-adrenergic responsiveness in the affected limbs suggesting adrenergic supersensitivity. This supersensitivity is reversed when CRPS symptoms resolve. Pharmacological or surgical sympathectomy can decrease pain in patients with CRPS and patients with neuropathic pain report increased pain during stress or after intradermal injection of a physiological dose of norepinephrine (NE) [31]. In addition, injection of NE can rekindle pain and mechanical hyperalgesia in patients who have had a previous sympathetic block. Finally, inflammatory pain and hyperalgesia produced by topical capsaicin is decreased by α_1-adrenoceptor antagonists and increased by NE [32].

Despite this evidence, systematic reviews have failed to demonstrate the efficacy of therapies designed to inhibit sympathetic function and question their utility [1, 2]. In fact, some investigators have challenged the validity of pharmacological tests to establish the diagnosis of sympathetically maintained pain. The interpretation of results from diagnostic and prognostic nerve blocks for chronic pain can be challenging even for clinicians with considerable expertise [33].

Recent studies have examined the effect of the natural stimulation of the subject's own sympathetic nervous system on spontaneous pain and hyperalgesia rather than the effect of pharmacological treatment such as sympathetic block or injection of NE. Sympathetic arousal increased pain and vasoconstriction in the affected extremity of patients with CRPS types I and II [34]. Also, sympathetic activation increased spontaneous pain and spatial distribution of mechanical hyperalgesia in patients with CRPS type I who have sympathetically maintained pain [35]. These two investigations were the first to demonstrate that physiological activation of the sympathetic nervous system can modulate the pain experience in humans through endogenous release of NE from sympathetic nerve endings. These findings provide evidence in support of the concept of sympathetically maintained pain, or pain as the result of sympathetic efferent activity.

Sympathetic Nervous System Dysfunction

In the acute stage of CRPS type I, there is complete functional loss of cutaneous sympathetic vasoconstrictor activity as well as decreased venous plasma levels of NE (presumably secondary to decreased postganglionic release from sympathetic terminals) confined to the affected extremity [36]. This autonomic impairment may recover within weeks and likely reflects dysfunction within the CNS. During chronic CRPS, sympathetic vasoconstrictor neurons are still inhibited, but adrenoceptor supersensitivity in vascular tissue results in ongoing

vasoconstriction and subsequent cold skin. These vascular abnormalities are dynamic and more pronounced when examined over the entire range of the thermoregulatory cycle [37].

Patients with acute CRPS type I also demonstrate α-adrenergic supersensitivity of sudomotor nerves that is reversible with disease progression [38]. Unilateral disturbances in sudomotor function determined by quantitative sudomotor axon reflex test (QSART) and thermoregulatory sweat test (TST) also have been reported in patients with chronic CRPS [39].

Sensory Dysfunction

Sensory disturbances are common in patients with CRPS types I and II and predominantly consist of hyperalgesia, allodynia, and spontaneous pain [6]. Quantitative sensory testing (QST) demonstrates an increase in warm perception thresholds and a decrease of cold pain thresholds in patients with CRPS types I and II [40]. Sensory impairments frequently extend beyond the affected area and may involve quadratic or hemilateral regions of the body [41].

Motor Dysfunction

Motor disturbances are prevalent in patients with CRPS types I and II [6] and are independent of sensory and autonomic complaints [40]. The most frequently described motor disturbance is loss of function of the affected extremity. Detailed neurological examination may detect objective evidence of isolated motor weakness, muscle atrophy, tremor, dystonia, or ataxia. Furthermore, electrodiagnostic tests such as electromyography and nerve conduction velocity can be used to document muscle and large fiber abnormalities, respectively. Decrease in active range of motion can be assessed by goniometer. Similarly, muscle power can be assessed by measuring grip force strength or by manual muscle testing. More complex motor tasks can be measured by kinematic analysis. A recent study has demonstrated neurophysiological evidence of impairment of central sensorimotor integration in patients with CRPS type I [42]. These motor deficits may be secondary to abnormal integration of visual and sensory inputs to the parietal cortex [43].

CNS Dysfunction

Evidence suggests that certain autonomic, motor, and sensory disturbances in patients with CRPS are caused by dysfunction within the CNS whereas certain aspects of the pain itself may be related to aberrant peripheral mechanisms. Potential peripheral and central mechanisms are described elsewhere [7, 44]. Occasionally, dysfunction of the sensory, motor, or autonomic nervous system may involve bilateral structures after unilateral nerve or tissue injury [45]. In addition, several investigators have described CNS abnormalities by fMRI,

MRS, or SPECT. Recent investigation suggests that patients with CRPS may develop functional or structural cortical reorganization and change in central representation of sensory maps. However, it is unclear whether these abnormalities are a result of the chronic pain or whether they represent specific regions of primary dysfunction within the CNS.

Treatment Algorithm for CRPS

The therapeutic strategy for patients with CRPS involves the concurrent utilization of pharmaco-, physio-, and psychotherapy. However, randomized controlled trials (RCTs) investigating the impact of psychological interventions on homogenous groups of patients with neuropathic pain, including patients with CRPS, have not been undertaken [46]. Nevertheless, principles derived from operant and cognitive behavior theory are useful to treat chronic pain patients in general and these strategies should be used for patients with CRPS. The goal of pharmacological therapy is to reduce pain in order to facilitate functional restoration. In general, medications that are effective for the treatment of neuropathic pain are used for patients with CRPS. The goal of physical therapy is to improve functional status. In general, desensitization and physical rehabilitation cannot proceed without adequate pain control. Most authorities believe that active participation in physical therapy is instrumental for improvement in patients with CRPS. To date, only the short-term efficacy of physical therapy has been demonstrated by an RCT specifically for patients with CRPS [47]. Recent RCTs have demonstrated the efficacy of spinal cord stimulation for the treatment of pain and intrathecal baclofen for the treatment of dystonia in patients with CRPS. The use of these interventional techniques should be considered in the treatment algorithm when other therapies have failed. A summary of current therapeutic strategies for CRPS has been published [48].

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