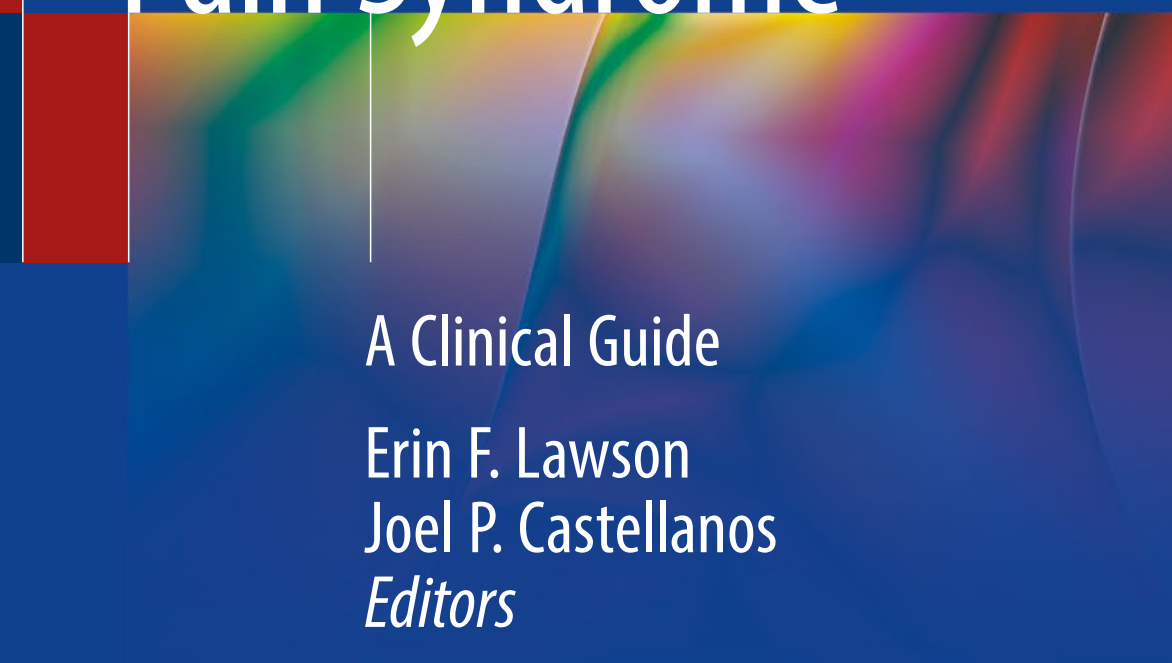
Complex Regional Pain Syndrome



A Clinical Guide

Erin F. Lawson
Joel P. Castellanos
Editors

Springer

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We would like to dedicate this text to the scientists and providers who have worked determinedly for decades in order to develop an understanding of CRPS. The advances in knowledge of the origins and pathophysiology of CRPS have led to tangible gains in patients' lives through ever-improving treatment programs and options.

Preface

Complex regional pain syndrome (CRPS) is a devastating chronic disease of severe pain and dysfunction. While much has changed in our understanding of the disease since the suffering first widely seen on the American Civil War battlefield, treatment remains a vexing challenge. Recent decades have brought several meaningful changes in the approach to diagnostics and new treatments. However, managing CRPS often remains a disheartening venture for healthcare providers who struggle to alleviate pain and disability and for patients who often struggle mightily with everyday activities. This text brings together experts in CRPS to elucidate the current understanding of the disease, approach to diagnosis, and the scope of treatments available. We are happy to share the treatment approaches of these leaders in the field in order to help patients and providers address this unfortunate syndrome.

Lexington, SC, USA — Erin F. Lawson
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Acknowledgments

We acknowledge with gratitude the authors who contributed to this text. We are grateful for their dedicated time and effort during a devastating pandemic and their willingness to share their expertise in order to help patients. We also acknowledge Nishanthini Vetrivel, Developmental Editor for Springer, who guided us during this process. Finally, we thank the CRPS patients who shared their experiences with us; together we delight in their advances and commiserate in their setbacks.

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Part I

CRPS Basics

Complex Regional Pain Syndrome: An Introduction

1

Elena S. Haight, Nolan A. Huck, Claire E. Jordan, and Vivianne L. Tawfik

Introduction

Complex regional pain syndrome (CRPS) is a debilitating chronic pain disorder that typically results after minor trauma such as surgery or fracture. The first reports of CRPS-like syndromes date back to the sixteenth century, when Ambroise Pare recorded King Charles's unremitting pain and contractures following blood-letting [81]. Centuries later during the American Civil War, Silas Weir Mitchell described a cohort of patients with gunshot wounds who developed persistent pain distal to their wound and disproportionate to the inciting injury, accompanied by motor and trophic changes [47]. Research and effective clinical therapies evaded clinicians due to profound clinical heterogeneity among patients, with numerous taxonomic changes over time as the medical community explored mechanisms underlying the condition and sought names to fit the pathophysiology. The term *causalgia* applied to the observed persistent pain in response to a peripheral nerve injury [81], while *Sudeck's atrophy* addressed the pain and trophic changes that resulted from neurovascular and osseous changes [46]. The late 1940s sparked yet another evolution in understanding this syndrome, when the American physician James Evans coined the term *reflex sympathetic dystrophy (RSD)* [46]. With this taxonomy, Dr. Evans proposed a contribution of persistent sympathetic nervous stimulation to the mottling, temperature change, and pain that characterized the syndrome, a theory he suggested was confirmed by analgesic efficacy of sympathetic ganglion blockade. Importantly, despite evolving terminology to describe the same clinical syndrome, none ever encompassed the entirety of patients who presented after a trauma with

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unremitting pain, vasomotor, sudomotor, and motor changes. As such, the term *CRPS* was adopted in 1994 [85], moving the medical community away from etiological descriptors to a diagnosis that began to accommodate heterogeneity in clinical presentation, and reflected the lack of concrete pathophysiologic understanding. Two CRPS subtypes were established based on the absence (CRPS type I, previously RSD) or presence (CRPS type II, previously causalgia) of an identifiable nerve injury.

Diagnosis

In its early stages, CRPS can bear close resemblance to acute inflammation, characterized by pain, temperature changes, and erythema of the injured limb. As a result, it is important for physicians to consider the expected trajectory of a patient's injury. For example, in a patient with an uncomplicated distal radius or carpal fracture—a common inciting injury for CRPS [70]—the expected time to complete healing is approximately 6–8 weeks [74]. It would therefore be prudent to consider CRPS in a patient presenting 3 months after injury with persistent pain and signs of inflammation. To distinguish CRPS from acute inflammation, the International Association for the Study of Pain (IASP) established a cluster of hallmarks of CRPS, including sensory, sudomotor, and vasomotor symptoms [85]. Clinically, these criteria were based only on patient-reported symptoms, and they did not include motor criteria, which resulted in reduced diagnostic accuracy and low specificity. This rendered CRPS somewhat of a "garbage bag diagnosis" offered to patients who lacked a clear explanation for persistent pain. This resulted in such heterogeneity among patients with a CRPS diagnosis that clinical research was frequently hindered by confounds [8, 38]. In 2003, a group of scholars convened in Budapest to establish updated diagnostics criteria for CRPS which included signs and symptoms in four categories: sensory, vasomotor, sudomotor, and motor/trophic. Diagnosis with CRPS required one or more patient-reported symptoms in at least three of the four categories, and one or more objective signs on evaluation in at least two of the four categories [41]. These criteria—the "Budapest Criteria" (Table 1.1)—comprise the modern standards for CRPS diagnosis and have been validated as a specific and accurate means of diagnosis [39].

Since the development of the Budapest Criteria, numerous efforts have been made to understand whether subgroups of patients with CRPS exist based on condition severity and/or presentation. One such effort was the development of the CRPS Severity Score (CSS) [40], a tool for quantifying CRPS severity based on the presence of both patient-reported symptoms and physician-observed signs (Table 1.2). Although its use has not been widespread among clinicians treating patients with CRPS, the CSS represents a useful tool for assessing the severity of a patient's condition at a given point in time and for tracking the evolution of a case over time. As would be expected, in initial studies of the CSS, a higher CSS was associated with increased disease burden, higher pain intensity, comorbid mood disorders, and poor physical and social functioning [40]. Incorporating the CSS into

Table 1.1 Budapest criteria for CRPS

Category	Symptom/sign
Sensory	Allodynia Hyperalgesia
Sudomotor	Asymmetric edema Sweating changes Sweating asymmetry
Vasomotor	Temperature asymmetry (>1 °C) Skin color changes Skin color asymmetry
Motor	Decreased range of motion Motor dysfunction (weakness, tremors, dystonia) Trophic changes (hair, nails, skin)
Continuing pain, disproportionate to the inciting event Must have 1 symptom in 3 of 4 categories Must have 1 sign in at least 2 categories at time of evaluation No other diagnosis better explains symptoms and signs	

Adapted from: Harden et al. [39]

Table 1.2 CRPS severity score (CSS)

Self-reported symptoms	
Continuing disproportionate pain	
Sensory	Allodynia or hyperalgesia
Sudomotor	Asymmetric edema Sweating asymmetry or changes
Vasomotor	Temperature asymmetry Skin color asymmetry or changes
Motor	Motor dysfunction (weakness, tremors, dystonia) Trophic changes
Signs observed during evaluation	
Sensory	Allodynia Hyperalgesia to pinprick
Sudomotor	Asymmetrical edema Sweating asymmetry or changes
Vasomotor	Temperature asymmetry Skin color asymmetry or changes
Motor	Motor dysfunction (weakness, tremors, dystonia) Trophic changes

Adapted from: Harden et al. [40]

practice may serve as a way to streamline patients into certain treatment regimens, such as physical therapy and pain psychology, and to evaluate the impact of these interventions with a more objective measure than is typically used (e.g., visual analog scale).

As mentioned, traditional nomenclature distinguishes two subtypes of CRPS: CRPS-I, in the absence of a *known* nerve injury, and CRPS-II, which involves an identified nerve injury. Historically, however, there has been limited effort both to identify nerve injuries in patients presenting with CRPS after physical trauma and to offer targeted treatment based on a known nerve injury [71]. That said, identifying a

nerve injury may offer patients considerable benefit, creating alternative focused therapeutic and interventional options. Electrodiagnostic studies (nerve conduction and electromyography) in patients who tolerate it represents one avenue for identifying patients with CRPS-II. Advanced imaging, such as magnetic resonance neurography (MRN) of peripheral nerves [12], may provide an additional diagnostic modality for patients with CRPS and is an area of current active study [52].

Epidemiology

There have been multiple retrospective population-based studies investigating the incidence of CRPS. One study, completed in Olmsted County, Minnesota, USA, by Sandroni et al. [78] found an incidence of 5.5 cases per 100,000 person-years. A retrospective cohort study performed in the Netherlands by de Mos et al. [18] found an incidence of 26.2 cases per 100,000 person-years using a sensitive search algorithm to look for the diagnosis of CRPS in 600,000 electronic health records. Recently, two major epidemiologic studies were completed to estimate an updated incidence of CRPS. One study took advantage of the fact that there is one primary CRPS outpatient clinic serving the city of Erlangen, Germany [72]. Based on the local population size, they calculated an incidence of 13.6 cases per 100,000 person-years. This was suggested to be an underestimate, as CRPS is relatively underdiagnosed due to factors such as limited clinician awareness and the similarity of CRPS to post-injury inflammation. An additional study from the Republic of Korea by Kim et al. [55] found an overall CRPS incidence rate of 29.0 per 100,000 person-years. It is worth noting that this study identified a significantly higher population incidence of CRPS than previous studies, in addition to a more balanced incidence between sexes (1:1.3 male-to-female); however, an advantage of the study is that South Korea has a national health insurance program, so the total number of CRPS diagnoses could be extracted for the entire country between 2011 and 2015. The variable incidence reported in these studies highlights regional variations in the presentation or diagnosis of CRPS. For example, in the latter study [55], in legal disability claims, many clinicians utilized the Persistent Disability and Assessment Guidelines by the American Medical Association rather than the IASP or Budapest criteria. The four epidemiological studies pertaining to CRPS are summarized in Table 1.3.

The incidence of CRPS in adults increases with age until 70 years old [18, 72, 78]; however, in the above-mentioned study [55], the peak incidence of CRPS was found at ages 70–79. Although limited in sample size, a recent study investigating the pediatric incidence of CRPS in Scotland by Abu-Arafeh et al. (2016) found that the age at diagnosis ranged from 5.5 to15.4 years with a mean of 11.9 years. As is true for numerous chronic pain conditions, females are more likely to develop CRPS than males, at a ratio of 2–4:1 [1, 18, 72, 78]. Additionally, female patients are at higher risk of developing severe complications of CRPS including infections, ulcers, chronic edema, or marked movement disorders [91, 94].

Table 1.3 Summary of epidemiological studies on CRPS

Comparison of complex regional pain syndrome epidemiological studies							
Reference	Country, years surveyed	Incidence (per 10^5/yr)	Incidence female:male (per 10^5 person yrs)	Prevalence (per 10^5)	Number of cases	Average age of onset (yr)	Most common extremity affected
Sandroni et al. [78]	MN, USA 1989–1999	Type I: 5.46 Type II: 0.82	8.57:2.16[a]	Type I: 20.57 Type II: 4.2	85[c]	46	Upper extremity
De Mos M et al. [18]	The Netherlands, 1996–2005	26.2	40.4:11.9	–	238	52.7	Upper extremity
Kim et al. [55]	Korea, 2011–2015	Type I: 18.2 Type II: 10.8	10.2:8.0	–	74,349	70–79[d]	Lower extremity/ pelvis
Ott and Mihöfner [72]	Nuremberg, Germany, 1993–2014	13.6	71:29[b]	–	1043	50.9	Upper extremity

[a]Incidence only for CRPS I. CRPS = Complex regional pain syndrome
[b]Incidence reported as percentage
[c]Extrapolated data from study
[d]Data reported as highest incidence per decade

With respect to the distribution of affected limbs, three of the four epidemiological studies of CRPS reported that 60% or more of CRPS cases occur in the upper extremity, with the remaining 40% in the lower extremity [18, 72, 78]. In the South Korean study of insurance claims [55], however, they found that the pelvis, thigh, and lower limb were more likely to be affected than the upper limb. One explanation for this discrepancy could be varying diagnostic criteria between studies, as previously mentioned. Finally, resolution rates for CRPS vary depending on length of disease, ranging from 74% in the first year after onset [78] to 36% by 6 years after onset [21]. Understanding the true rate of resolution is limited by heterogeneity of patient presentation, inconsistencies in diagnostic criteria between practices and adherence to a uniform set of criteria even within a single practice, and a lack of consensus on the definition of recovery.

Risk Factors

Certain injuries, such as fracture, sprain, and elective surgery, are associated with a higher risk of developing CRPS, while spontaneous onset is uncommon [18, 25, 95]. Several investigators have studied distal radius fracture as an inciting injury for CRPS. Most recently, Moseley et al. [70] performed a prospective cohort study in 1549 consecutive patients who presented with wrist fracture. Patients were managed nonsurgically, and the initial assessment was completed within 1 week of injury and followed up at 4 months. The incidence of CRPS in this cohort was 3.8% at 4 months,

and a pain score in the first week of 5 or greater was a predictor for the development of CRPS and a suggested "red flag" during patient evaluation.

The management of bone fractures often requires immobilization of the injured limb, and an early report by Schwartzman and McLellan [80] indicated that such immobilization may be a risk factor for CRPS. Interestingly, healthy human volunteers subjected to immobilization displayed mild signs of CRPS, including cold and mechanical hypersensitivity [73, 88]. In addition, perceived cast "tightness" has also been suggested as a risk factor for the development of CRPS [100]. In rodent models of CRPS, immobilization (casting) alone elicits expression of inflammatory mediators and CRPS-like changes, such as allodynia, warmth, and edema of the injured limb [34]. Taken together, these findings all suggest that careful consideration of the need for post-injury immobilization is necessary, particularly for high-risk patients.

Some studies have also assessed the interaction between certain medications and medical conditions and the development of CRPS. In a series of large population-based studies, de Mos et al. [19, 20] found that the use of angiotensin-converting-enzyme (ACE) inhibitors at the time of trauma or a history of migraine or asthma was associated with an increased risk of CRPS. In an additional study, migraine was also a noted risk factor for CRPS [75]. At this time, the pathophysiologic connection between ACE inhibitors, migraine, or asthma and CRPS remains elusive.

It is unclear if psychological factors confer risk for the development of CRPS or whether some patients, once diagnosed with CRPS, develop mood disorders. A large population-based case-control study found that psychological factors were not associated with CRPS onset [19]. Another prospective multicenter study of 600 consecutive patients with a single fracture showed that psychological factors did not predict the development of CRPS [3]. In contrast, there is evidence that patients with CRPS have higher rates of anxiety and depression compared to healthy controls [59]. However, it is unclear whether patients with CRPS are more severely anxious or depressed than patients suffering from other forms of chronic pain [2, 69]. As a result, cause and effect remains to be investigated.

There have been several case reports describing familial clusters of early onset CRPS, suggesting a potential genetic predisposition [22, 23, 44]. Certain alleles of the human leukocyte antigen (HLA) system have been described as a susceptibility factor for CRPS, first in 1994 by Mailis and Wade [66]. Further studies supported an association between different CRPS phenotypes, such as dystonia-predominant, and specific HLA loci, such as HLA-B62 and HLA-DQ8 [24, 54, 89, 92]; however, consensus has not been reached on the predictive value of these genetic factors. A study published in 2016 by Janicki et al. [48] investigating 83% of all of the common single nucleotide polymorphisms between CRPS patients and controls did not identify a significant difference between the two groups. While whole genome-wide expression profiles can develop a picture of genetic predisposition to CRPS, more studies are needed to determine if specific genetic alterations are causative in the development of CRPS.

One further highly controversial area is post-vaccination CRPS. Following media reports in Japan alleging an association between HPV vaccination and CRPS,

the country temporarily suspended the national HPV vaccination recommendation (R. Wilson, P. Paterson and H. Larson A Report of the CSIS Global Health Policy Centre, Cent Strateg Int Stud (2014) http://csis.org/publication/hpv-vaccination-japan). Given the gravity of such a sweeping move to the health of young women, the risk of CRPS after receiving the HPV 16/18 vaccine was further explored in a study by Huygen et al. [45]. After independent analysis of all possible HPV vaccine-associated cases of CRPS and comparison to the expected background rate of girls in this age group developing CRPS, they concluded that there was insufficient evidence to suggest an association between CRPS and HPV 16/18 vaccination. A follow-up study conducted by Weinbaum and Cano [97] used the US primary reports in the Vaccine Adverse Event Reporting System to explore how US-reported data compared to the study by Huygen et al. For a 10-year period from 2006 to 2015, they found that 0.07% of "vaccine-associated CRPS" reports satisfied diagnostic criteria for CRPS; however, these were correlative data. It has been suggested that cases of CRPS-like conditions may have been due to minor tissue trauma from the vaccine injection, as seen in other rare cases [31, 77]. A review from the European Medicines Agency (EMA) concluded, however, that the evidence is insufficient to establish a causal link of HPV vaccination to CRPS [49].

Pathophysiology

Much of the complexity inherent in CRPS is the result of heterogeneous pathophysiology, with multiple mechanisms underlying a single patient's condition and underlying mechanisms likely varying between patients. In recent years, considerable advances have been made in understanding the myriad pathophysiologic drivers of CRPS, although clinical efforts to establish targeted interventions have lagged behind (Fig. 1.1).

Sympathetically Maintained Pain

Much of the early literature surrounding CRPS was based on the premise of sympathetically maintained pain (SMP), and it was this theory of sympathetic hyperactivity that generated the term RSD. By definition, patients with CRPS have physical changes on the affected limb that appear autonomically mediated (temperature change, erythema, trophic disturbances). As a result, early interventions for patients with CRPS included sympathetic ganglion blockade, which provided analgesia for a significant proportion of patients with CRPS-I [10] and was long considered of diagnostic value in patients suspected of having CRPS. In conflict with this theory of sympathetic hyperactivation, studies demonstrated decreased concentrations of neuropeptide Y [27] and norepinephrine [28] in plasma of the ipsilateral (injured) limb. Instead of tonic sympathetic activation, researchers posited that patients' pain resulted from abnormal responses to sympathetic stimuli or alterations in adrenergic receptor expression [42]. With continued study, however, patients were identified

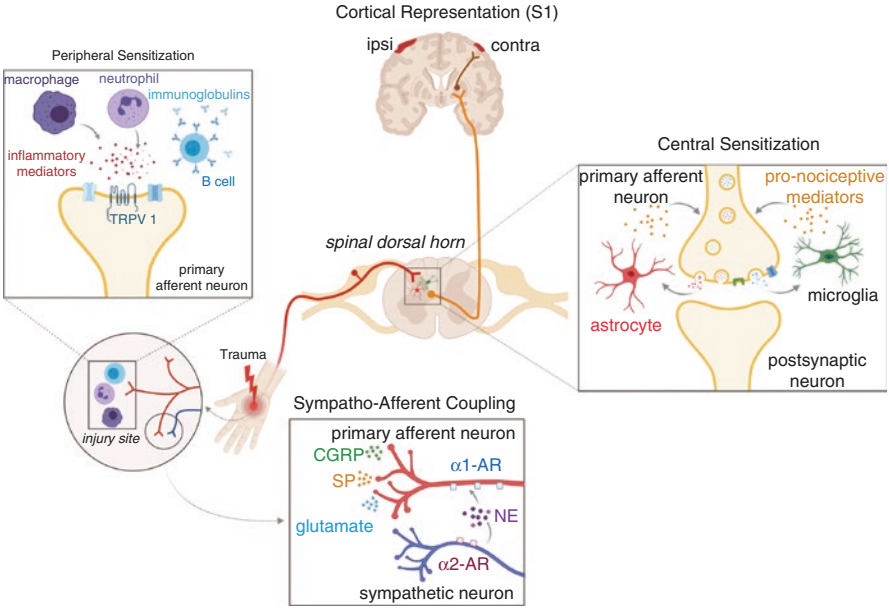

Fig. 1.1 Proposed pathophysiological mechanisms of complex regional pain syndrome (CRPS). Injury to a limb results in peripheral sensitization. Immune cells, such as macrophages and neutrophils, home to the site of injury and release inflammatory mediators that lead to the sensitization of pro-nociceptive channels (TRPV1 channel) on primary afferent neurons. B cells at the injury site release immunoglobulins that may target autoantigens and contribute to CRPS-related autoimmunity. Sympatho-afferent coupling may occur due to the expression of α1-AR on primary afferent neurons. Norepinephrine (NE) released by neighboring sympathetic neurons binds to the α1-AR, causing increased release of calcitonin gene-related peptide (CGRP), substance P (SP), and glutamate from primary afferent neurons. In the spinal cord dorsal horn, local neuroimmune cells such as astrocytes and microglia are activated by pro-nociceptive substances released from central terminals of sensitized primary afferent neurons and contribute to central sensitization by releasing pro-nociceptive mediators themselves. In the somatosensory cortex (S1), cortical representation of the affected limb decreases on the contralateral side contributing to hemi-neglect phenomena in these patients. S1: somatosensory cortex 1, ipsi: ipsilateral, contra: contralateral, NE: norepinephrine, CGRP: calcitonin gene-related peptide, SP: substance P, α1-AR: alpha-1 adrenergic receptor, α2-AR: alpha-2 adrenergic receptor, TRPV1: transient receptor potential cation channel subfamily V member 1

who did not respond to sympathetic blockade, or whose response declined with increasing disease chronicity [37, 84]. Thus, sympathetic aberrancy explained only one component of CRPS in a subset of patients.

Peripheral Sensitization

The onset of inflammation and pain following injury results from the release of inflammatory mediators including cytokines such as interleukins and tumor necrosis

factor-α (TNF-α), nerve growth factor (NGF), bradykinin, ATP, and prostaglandin E_2 (PGE_2) from immune cells [11]. With increased circulating levels of these mediators, mitogen-activated protein kinase (MAPK) pathways become activated, resulting in increased sensitivity of pro-nociceptive channels on primary afferent neurons [53], such as the TRP channels TRPV1-TRPV4, which are believed to mediate the burning sensation in persistent neuropathic pain [13, 17, 51].

Central Sensitization

Central sensitization has been offered as one explanation underlying the persistent pain observed in patients with CRPS and has been confirmed through functional magnetic resonance imaging (fMRI) studies in patients with chronic CRPS [64]. Past literature has emphasized the importance of early diagnosis of CRPS due to the increased challenge of achieving symptom remission in patients with chronic CRPS. The refractory nature of chronic CRPS may be partly explained by preclinical studies demonstrating a transition from peripheral inflammation in the acute stages of CRPS to central inflammation in chronic CRPS mediated in part by microglia [16] and astrocytes [86], which release pro-nociceptive mediators to create a state of persistent inflammation. The development of central sensitization likely results in part from peripheral sensitization, with increased neurotransmitter release (substance P, CGRP, BDNF, glutamate) from primary afferents at their central terminals, leading to chronic neuronal hyperactivity in the CNS [50, 98, 99].

Acute-Warm-Peripheral CRPS Versus Chronic-Cold-Central CRPS

The pathophysiologic mechanisms underlying disease duration-associated subtypes of CRPS have largely been studied in preclinical models, with efforts to translate findings achieving limited success. The warm, edematous, erythematous phenotype that characterizes CRPS is more associated with a shorter duration of disease (<1 year), whereas with increasing chronicity, patients are more likely to have a cold, atrophic, blue limb [9]. These findings have been replicated in a clinically relevant, validated rodent model of CRPS, which involves distal tibial fracture followed by 3 weeks of cast immobilization [5]. At the time of cast removal, the rodent's injured limb is warm, edematous, and erythematous [96]. Around 5 weeks post-fracture, peripheral signs of inflammation dissipate, but pain-like behaviors persist. Inflammatory mediators track this transition, with increased peripheral inflammatory cytokines observed during the acute phase returning to normal as central inflammatory cytokines become elevated in the chronic phase [30]. These findings suggest that peripheral inflammation mediates the signs observed in acute CRPS while central inflammation mediates the continued pain associated with chronic CRPS. Efforts to attenuate central inflammation, mediated by microglia and astrocytes, have thus far been mainly conducted in preclinical models [62]. Several currently approved drugs may work in part through glial modulation including

ketamine, which acts on many CNS cell types; low-dose naltrexone, which may antagonize the microglial receptor toll-like receptor 4 (TLR4) [83]; and hydroxychloroquine, which reduces pain in a subset of patients with chronic CRPS and attenuates microglial activation in a mouse model of CRPS [36]. There are likely superior pharmacologic ways to optimize glial modulation for patients with CRPS, and the development of glial-specific pharmacotherapies is an important area for future investigation [35]. That said, preclinical studies showing analgesic efficacy of the centrally acting anesthetic agent ketamine only in the chronic phase of CRPS support the notion that chronic CRPS is centrally mediated [86]. To this point, the mechanisms mediating the transition from acute to chronic CRPS have not been well elucidated, although studies suggest intricate interactions between the nervous and immune systems are a factor [16].

Oxidative Stress

There is a body of evidence suggesting CRPS-I may reflect an ischemic process in the setting of physical injury. Clinically, patients with CRPS have decreased hemoglobin oxygenation in the skin of their affected limb [56], in addition to increased lactate [6]. These findings combined with histologic examination of muscle tissue in CRPS-affected limbs demonstrating lipofuscin accumulation, fiber atrophy, and thickened basement membrane [90] suggest oxidative stress to the affected limb. Moreover, preclinical studies have demonstrated that a model of ischemia and reperfusion wherein a tourniquet is applied to the hindlimb of an anesthetized rodent for 3 hours, then removed to allow reperfusion, is sufficient to induce a chronic neuropathic-like pain state with spreading to other limbs [15], a phenomenon commonly seen in patients with CRPS.

Autoimmunity

Perhaps the most rapidly growing area of CRPS research seeks to understand autoimmune mechanisms in CRPS [14]. Autoimmunity is a maladaptive response of the adaptive immune system, characterized by autoantibody-mediated disease. In preclinical studies, researchers found that depleting CD20+ B cells prior to injury attenuated the signs of CRPS [61], suggesting a contribution of autoimmunity. Interestingly, recent research also shows that the transfer of IgG from patients with CRPS to uninjured mice is sufficient for the establishment of hyperalgesia, edema, and motor impairment in mice [33, 87] and that this may occur in an IL-1B-mediated fashion [43]. Finally, autoimmunity is supported by studies showing autoantibodies against β_2 adrenergic and muscarinic type 2 receptors in some patients with CRPS [7, 57, 58]. Despite these promising data elucidating autoimmune contributions to CRPS, interventions such as intravenous immunoglobulin (IVIg) infusions have not been more effective than placebo at controlling pain for patients with moderate-to-severe CRPS of 1–5 years duration [32].

Central Nervous System Alterations

Brain imaging has long contributed to CRPS research, showing cortical changes that are the target of common physical therapy interventions such as graded motor imagery and mirror box therapy. Patients with CRPS commonly have disruption in the cortical map of their CRPS limb, the extent of which is directly proportional to the severity of pain they report [29, 65, 76]. Patients describe altered perception of the size of their limb and its location in space, feel extreme hostility or disgust toward their affected limb, or lack the ability to create a mental image of their limb [60]. Still others may report pain in their affected limb upon being stimulated with light touch or pinprick at another unaffected site [68]. These changes resemble neglect syndromes seen in other neurologic disorders, and they commonly persist into the chronic stage of CRPS, resolving only if the patient's pain is resolved [65]. Additionally, fMRI studies of patients with CRPS demonstrated enlargement of the contralateral compared to the ipsilateral motor cortex and reduction in size of the contralateral compared to ipsilateral somatosensory cortex [63]. Such findings underscore the need for patients to engage their affected limb to prevent fear-avoidance cycles of limb disuse and subsequent pain exacerbation.

Psychological Mechanisms

As described above, patients with CRPS are more likely to have psychiatric comorbidities, namely depression and anxiety [59]. It is possible that psychiatric conditions such as depression and anxiety contribute to the pathophysiology of CRPS by enhancing CNS catecholamine release and activating sympathetic nerves. Providing adequate psychological services to patients with CRPS, then, is critically important in light of the contribution of sympathetic activation to CRPS, particularly in the acute stage.

Natural History

Acute Versus Chronic

It is generally accepted among clinicians that CRPS treated early is significantly more likely to resolve, or be managed well, than CRPS that is first treated in its chronic stage. For this reason, early evaluation is critical for patients suspected of having CRPS. Studies have shown that CRPS is most commonly diagnosed within approximately 3 months of the expected time to resolution of the inciting injury [4]. Interestingly, the patients in this study ($n = 596$) had developed CRPS after a fracture and were more likely to be diagnosed at 3 months after cast removal instead of at the time of cast removal. This, in conjunction with cast immobilization being an independent risk factor for CRPS [73], suggests that the most likely time to develop CRPS is within 3 months of an inciting trauma.

While monitoring the natural history of CRPS following diagnosis has proven challenging, some research has been conducted on this matter, including a 1998 study wherein patients with a CRPS diagnosis were monitored for a year after their diagnosis without treatment [101]. In this study, 26 of the 30 patients experienced resolution of their symptoms by the end of the study period. Just 3 of the 30 patients withdrew from the study to receive treatment. It is important to note that this study was conducted prior to implementation of the Budapest criteria, so the findings of this study may not reflect the natural course of CRPS we would observe with stricter diagnostic criteria. One additional study conducted with the IASP diagnostic criteria (pain, vasomotor, and sudomotor changes; excludes the motor changes of the Budapest criteria) suggests a similarly high rate of resolution (74%) of acute CRPS-I. This is in contrast to chronic CRPS-I, which had a 30% resolution rate in a study of 102 patients. Sixteen percent of these patients had progressive deterioration, while 54% continued to experience stable pain and CRPS-like vasomotor, sudomotor, and motor changes [79]. Understanding the natural history of CRPS in coming years will likely depend on widespread adoption of registries to track patients with CRPS, such as the CRPS-UK Registry, which was established in the United Kingdom in 2008 and has more than 600 patients enrolled as of March 2020 [82].

CRPS Spread

Non-dermatomal spreading of CRPS is a feared complication of CRPS, most common in patients with a young age of CRPS onset and those reporting a more significant impact of their CRPS [93]. CRPS spread was evaluated among 185 patients with a CRPS diagnosis; 89 patients had CRPS in multiple limbs, with 49% spreading to the contralateral limb, 30% spreading ipsilaterally, and 14% spreading diagonally [93]. Trauma to the region of spread was reported in 37% of patients with contralateral spread, 44% of patients with ipsilateral spread, and 91% of patients with diagonal spread. The risk of spread following trauma was higher in patients with more limbs affected. Proposed pathophysiologic mechanisms for spread include peripheral hyperexcitability causing hyperexcitability in the brainstem and higher brain regions, in addition to impaired pain modulation [26], and compromised response by the CNS to neurogenic inflammation [67].

Conclusions

CRPS is an enigmatic condition that typically develops after minor injury such as surgery or fracture, with a 3–4:1 female-to-male predominance. Our understanding of CRPS has evolved significantly since it was first described in the sixteenth century, creating more specific diagnostic criteria and targeted research. Distinct stages characterize CRPS—an acute stage mediated by peripheral factors such as sympathetic dysregulation and circulating pro-inflammatory mediators, and a

chronic stage mediated by central mechanisms such as CNS glial activation and central sensitization. Clinical experience suggests that the acute stage of the disorder is more likely to achieve remission or successful management, which creates a challenge for clinicians given that CRPS has myriad presentations and underlying pathophysiologic mechanisms, both of which contribute to the delayed diagnosis and treatment that is common for patients with CRPS. Moving forward, we expect that our growing understanding of the mechanisms underlying CRPS will enable more targeted, successful management of the disorder.

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