Pathophysiology of Complex Regional Pain Syndrome Type I: Update

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Abstract

Background: Complex regional pain syndrome type I (CRPS I), also known as reflex sympathetic dystrophy (RSD), develops as disabling painful disorder following a trauma or surgery to a limb. We provide a review based on the current literature concerning the epidemiology and pathophysiology of CRPS I. Possible pathophysiological mechanisms of CRPS I are inflammation, sympathetic-afferent coupling and cortical changes.

Methods: A literature search was conducted using, as electronic bibliographic database, Medline from 1980 until today.

Results: CRPS I is a multifactorial disorder with complex aetiology and pathogenesis.

Conclusions: The pathophysiology of CRPS I is complex and may change during its course. CRPS I is more than a peripheral disease because peripheral mechanisms such as neurogenic inflammation and sympathetic-afferent coupling incompletely explain its pathophysiology. CRPS I is a pain disorder involving the somatosensory, the somatomotor and the sympathetic nervous systems. Genetic findings suggest there might be a predisposition to CRPS I and it has been confirmed in multiple studies that psychological factors are not predictors for the development of CRPS I. The complexity and diversity of the mechanisms involved will be liable to the heterogeneity of the clinical presentation and may explain the difficulty in achieving an evidence-based treatment of CRPS I.

Keywords: Complex Regional Pain Syndrome; Reflex Sympathetic Dystrophy; Neurogenic Inflammation; Sympathetic Nervous System; Neuropathic Pain.

Introduction

Complex regional pain syndrome Type I (CRPS I), previously known as reflex sympathetic dystrophy (RSD), is a painful and disabling disorder that can occur in an extremity after a minor trauma or surgery or may develop spontaneously [1-3]. This topical review describes the epidemiology and focuses on updated pathophysiological mechanisms of CRPS I. The purpose of this review is to contribute to the dissemination of knowledge among clinicians of pathophysiological mechanisms since, an increased understanding of the pathogenesis of CRPS I provides the possibility to develop mechanism-based treatments.

Methods

A search for published articles, focusing on epidemiology and pathophysiology, was performed using, as electronic bibliographic database, Medline from 1980 until present. For each pathophysiological mechanism, a separate search was conducted in Medline, using the query ‘complex regional pain syndrome Type I’ combined with one of the following queries: for autonomic nervous system dysfunction was used ‘sympathetic nervous system’ or ‘sympathetically maintained pain’; for inflammation, ‘inflammation’ or ‘neurogenic inflammation’ or ‘neuropeptide’ or ‘hypoxia’; for central sensitization, ‘hypealgesia’ or ‘wind-up’ or ‘NMDA receptor’ or ‘glial cells’; for brain plasticity, ‘cortical reorganization’ or ‘referred sensations’ or ‘hemisensory impairment’; for psychological factors, ‘psychology’ or ‘psychiatric’ or ‘behavior’. With the purpose of overviewing the known risk factors, the query ‘complex regional pain syndrome Type I’ was combined with the following terms: ‘incidence’, ‘prevalence’, ‘genetic factors’. Abstracts were screened manually, and full text papers were considered if the abstract suggested an experimental or observational study focused on the pathogenesis of CRPS I or a review concerning one or more pathogenetic mechanisms or an association between CRPS I and risk factors. Only articles written in English were included.
Historical Background

In 1946, Evans coined the term ‘reflex sympathetic dystrophy’ (RSD) based on the hypothesis that the sympathetic dysfunction was involved in generation and perpetuation of pain [1]. In 1986, Roberts introduced the term ‘sympathetically maintained pain’ (SMP) as a synonym of RSD [1]. However, the traditional concept of the involvement of the sympathetic nervous system has been questioned because many patients do not respond to sympathetic blockade. Also, as pain is maintained by the sympathetic efferent innervation or by circulating catecholamines in only a subset of patients with CRPS I, the term SMP should be restricted to the aspect of pain that is relieved by specific sympatheticolytic procedures. So, the term ‘reflex sympathetic dystrophy’ was abandoned and, in 1993, a Special Consensus Workshop of the International Association for the Study of Pain (IASP) introduced the term ‘CRPS’ to describe this painful period of chronic disturbances, which are also associated with vasomotor and sudomotor changes, with the aim of improving recognition of the disease and facilitating treatment outcome [3]. CRPS is classified as Type I (CRPS I) when it develops after a minor trauma or a small nerve injury and as type II (CRPS II), once known as causalgia, when it follows a demonstrable nerve injury [3].

Epidemiology

CRPS I occurs more frequently in females than in males (2.3:1-4:1) [4, 5]. In adults, the upper limbs are more often affected than the lower limbs. CRPS I most commonly affects a single limb. The onset of CRPS I is usually linked to a history of fractures, contusions/ruptures and surgery. In approximately 10% of cases [6], CRPS I develops spontaneously. Data on the incidence of CRPS I are scarce. Sandroni and colleagues [5] were the first to evaluate the incidence of CRPS I in the general population (Olmsted County, USA) and they calculated an incidence rate of 5.46 per 100,000 person-years and a prevalence rate of 20.57 per 100,000. The population-based incidence rate of CRPS I in the Netherlands was 26.2% per 100,000 person-years with a peak incidence at 61-70 years of age [6]. The age-related increasing incidence rate of CRPS I is due to a higher incidence of fracture in older age. Postmenopausal woman appeared to be at the highest risk for the development of CRPS I. In a recent prospective study of 596 patients with fractures [7], 7% of the patients developed CRPS I and none of the patients were free of symptoms at a 1-year follow-up. The lower incidence of the development of CRPS I in the present study might be explained by the use of diagnostic criteria with a higher specificity (0.94). Only few patients develop CRPS I after distal radius fracture. A few genetic studies performed in CRPS I suggested that genetic factors may play a role in the pathophysiology of CRPS I. Early genetic studies revealed associations of CRPS I with class II (HLA-DQ1, HLA-DR15) (MHC) antigens [8, 9] and of CRPS I that progressed towards multifocal or generalized dystonia with HLA-DR13 allele [10]. Two distinct microsatellite loci contribute to the genetic predisposition to CRPS I with multifocal or generalized dystonia with HLA-DR13 allele [10]. Associations of HLA-DQ8 with both CRPS I with and CRPS I without dystonia, and of HLA-B62 only with CRPS I with dystonia, suggest that CRPS I patients with and without dystonia are genetically different [12, 13]. Also CRPS I may show familial occurrence which suggests a genetic predisposition to develop CRPS I [14].

Pathophysiologic Mechanisms of CRPS I

The pathogenesis of CRPS I seems to be multifactorial. The mechanisms contributing to CRPS I differ from patient to patient and, even in the same patient, change over time. There are a number of different mechanisms accepted and documented in the literature [15].

Autonomic Nervous System Dysfunction

The traditional concept of sympathetic dysfunction in CRPS I speculates that the autonomic sympathetic hyperactivity in response to the heightened afferent activity from the damaged area caused pain, increased sweating, trophic changes, and vasocostriction-related coldness [16, 17]. However, the involvement of the sympathetic nervous system in the pathogenesis of CRPS I differs from classic theory [18]. Intraneuronal recordings have not evidenced an increased sympathetic neural discharge to the skin and catecholamines levels in serum are lower in the affected limb than in the unaffected limb [19-23]. The role of the sympathetic nervous system in the development and maintenance of sympathotomology is not an excessive sympathetic outflow to the skin, but rather an increased sensitivity of blood vessels to catecholamines and the development of the adrenergic sensitivity by nociceptive neurons [19]. Nociceptive afferents develop adrenergic responsiveness following nerve trauma or tissue trauma associated with inflammation. This coupling between sympathetic postganglionic neurons and afferent neurons is mediated by α-adrenoceptors [24]. In fact, the expression of α2-adrenoceptors mRNA is up-regulated in DRG neurons following peripheral nerve injury or inflammation in a neuropathic pain model, and the expression of cutaneous α2-AR is increased bilaterally in the dural nerves and keratinocytes of patients with CRPS I [25-27]. Furthermore, the intradermal injection of noradrenaline in patients with CRPS I and SMP on affected limbs caused a dose-dependent increase in pain once the patient had achieved pain relief following a sympathetic ganglion block [28].

The role of Inflammatory Factors

Especially in the acute phase, the CRPS I affected limb often displays the classic signs of inflammation (redness, heat, swelling) that suggest a local inflammatory process. Classic inflammation is characterized by typical immune cells such as lymphocytes, phagocytes, and mastcells, which secrete pro-inflammatory cytokines [29]. CRPS I patients display significant increases in pro-inflammatory cytokines (TNF-α, IL-1β, IL-2, IL-6) locally, in the blood plasma and in the cerebrospinal fluid. However, these patients manifest reduced systemic levels of anti-inflammatory cytokines (IL-10) when compared to controls [15, 29-34]. Additionally, there is an enhanced migration of injected radiolabeled autologous leukocytes or nonspecific immunoglobulins towards the acute CRPS I affected location [35, 36]. Pro-inflammatory cytokines can excite nociceptors and induce long-term peripheral sensitization and have been shown to increase the release of cytokine-related peptide (CGRP) from primary afferent neurons [32, 37]. It is postulated that the systemic pro-inflammatory observed cytokine profile may be a crucial factor in the pathogenesis of CRPS I [32]. Moreover, the sympathetic-afferent coupling may sensitize the nociceptive primary afferents and lead to the release of neuropeptides (Substance P and CGRP) from peptidergic unmyelinated fibers [24, 38]. Neuropeptides (SP and CGRP) are released from the nerve endings in the skin and consequently...
evoke vasodilation and protein extravasation in the tissue, and the resulting signs (reddening, warming and edema) are called neurogenic inflammation [37]. Neurogenic vasodilation is generally more intensive on the contralateral unaffected limbs in CRPS I patients than healthy subjects [39]. This suggests that facilitated neurogenic inflammation might be one predisposing factor for CRPS I. The importance of neuropeptides for CRPS I pathophysiology is further underlined by the recent finding that CRPS I is associated with ACE-inhibitor therapy [40]. ACE metabolizes the neuropeptides SP and bradykinin to inactive forms, thus ACE inhibitors may lead to higher tissue levels of both neuropeptides. Their use is associated with an increased risk of CRPS I. Furthermore, previous data have demonstrated elevated systemic CGRP and SP levels in patients with acute CRPS I, and that neurogenic inflammation contributes to the clinical manifestation of acute CRPS I [41, 44]. The important contribution of inflammation to CRPS I is underlined by open-label studies on treatments with infliximab (anti-TNF) [45-46] and thalidomide [47]. Additionally, oral prednisone was significantly more effective than the placebo [48]; oral prednisolone resulted in significant improvement in the symptoms and signs of CRPS I following a stroke, when compared to piroxicam [49] and methylprednisolone had anti-edematous effects in a rat CRPS I model [50]. Endothelial dysfunction has been demonstrated in chronic stages of CRPS I. In cold type CRPS I patients, peripheral vasoconstriction could enhance tissue hypoxia and tissue acidosis. The production of free radicals within the ischemic limb may be responsible for the endothelial dysfunction observed in CRPS I patients [51]. Impaired endothelial function in chronic CRPS I plays a major role in the pathogenesis of trophic changes observed in both the superficial and deep tissues. Furthermore, tissue acidosis is followed by sensitization and most likely the activation of nociceptive afferents, which is followed by a spontaneous pain sensation [51].

**Central Sensitization**

The activity of nociceptive afferents will trigger a central sensitization process, which will be responsible for the development of allodynia and hyperalgesia [51]. Central sensitization is a state of CNS neuronal hyperactivity due to increased nociceptive input, particularly at the dorsal horn level of the spinal cord [52]. This process may play a crucial role in the pathogenesis of chronic pain and is the driving factor for CRPS I [53]. Central sensitization results in exaggerated responses to nociceptive stimuli (hyperalgesia) and permits normally nonpainful stimuli, such as light contact on the skin or cold, to become painful (allodynia) [29]. "Windup" refers to the progressive increase in the magnitude of C-fiber evoked responses of dorsal horn neurons produced by repetitive activation of C-fibers [54]. Temporal summation of repeated painful stimuli has been regarded as a psychophysical correlate of windup [55]. CRPS I patients display significantly greater temporal summation of pain in response to repeated mechanical stimuli applied to the affected limb than on the contralateral or other limbs. A marked mechanical hyperalgesia to brief impact stimuli (dynamic mechanical hyperalgesia) and to repetitive impact stimuli (windup) are arguments in favor of the strong central component in CRPS I pathogenesis [56]. N-methyl D-aspartate (NMDA) receptors play a critical role in central sensitization [53, 57, 58].

**The Role of Glia Activation**

Spinal cord glia activation plays a major role in driving exaggerated pain states, including CRPS I [59, 60]. Activated glia drive the creation and maintenance of allodynia and hyperalgesia. On activation, the glia release a number of substances that potentiate pain transmission by neurons [61]. These substances include pro-inflammatory cytokines, nitric oxide, excitatory amino acids, prostaglandins and ATP [59]. Indeed, elevated levels of the pro-inflammatory cytokines interleukin-6 (IL-6) and interleukin-1β (IL-1β), of glial fibrillary acidic protein (GFAP), MCP1, NO metabolites, glutamate and calcium have been found in the cerebrospinal fluid (CSF) of patients afflicted with CRPS I [62].

**Cortical Reorganization**

This syndrome is considered a disease of the central nervous system (CNS). It is speculated that the sensory, somatomotor and autonomic changes observed in patients with CRPS, in particular those with CRPS I, are the result of an abnormal information processing in the central nervous system and of plastic changes involving the autonomic nervous system, the somatomotor system and the somatosensory system [63]. The persistent activity of nociceptive primary neurons generates plastic changes in the primary somatosensory cortex (SI). Cortical reorganization is not restricted to the lesion of the afferent nervous system, because shifts of cortical somatotopic maps have also been demonstrated in cases of non-amputation-related pain [64]. In a recent study, magnetoencephalography (MEG) was used to assess cortical reorganization in the primary somatosensory cortex (SI), during acute CRPS I. A reduction in the size of the region representing the hand has been found and the cortical area representation of the affected hand has moved to a more lateral and inferior position towards the lower lip. This cortical reorganization appears to be correlated with the amount of CRPS pain and the extent of mechanical hyperalgesia [64]. These SI changes were reversed following successful treatment and recovery from CRPS I [65]. In addition, referred sensations and hemisensory deficits in patients with CRPS I provide further evidence of central sensory reorganization in such patients [66-68]. Furthermore, adaptive cortical changes within the motor system may occur in CRPS I and it has been shown that activation of the posterior parietal cortices, primary motor and supplementary cortices are correlated with the extent of motor dysfunction [69]. Excitability changes in the motor cortex were identified with transcranial magnetic stimulation. A significant reduction of intracortical inhibition was found in both hemispheres [70]. A recent controlled study supports a discrepancy between central motor output and sensory input as underlying mechanism in CRPS I [71]. Mirror therapy is thought to reconcile motor output and sensory feedback [72]. A motor imagery program, consisting of hand laterality recognition followed by imagined movements and then mirror movements, reduced pain and disability in CRPS I patients [73]. The effect of the motor imagery program is not due to sustained attention to the affected limb but is consistent with sequential activation of cortical motor networks [74].

**Psychological Factors**

It has been hypothesized that the presence of a psychiatric disorder, particularly anxiety or depression, and life stressors may predispose one to develop CRPS I. Patients with CRPS I are more anxious and depressed than healthy control individuals, but the popular presumption that anxiety and depression predispose to CRPS I is incorrect [37] as psychological factors and personality traits are not factors that predispose an individual to develop...
CRPS I [2]. In a retrospective study psychological factors were not associated with CRPS I onset [75]. Being observational, this study should be interpreted in the light of its limitations. Prospective studies are required. In a large prospective study of 748 patients with fracture, psychological factors did not predict the development of CRPS I [76] and two recent reviews have not identified any relationship between psychological factors and the development of CRPS I [79, 80]. Negative outcomes of CRPS I are both psychological (e.g. increased depression and anxiety) and psychosocial (e.g. reduced quality of life, impaired occupational function) in nature. Psychological factors such as emotional distress (e.g. anxiety, depression) could potentially exacerbate vasomotor signs of CRPS I (via up-regulated adrenergic receptors) and directly increase pain intensity (via adrenergic receptors sprouting on nociceptive fibers post-injury) [34].

Discussion

Complex regional pain syndrome Type I is a chronic painful disorder that usually develops after a trauma to a limb, without an obvious peripheral nerve damage. Fractures, contusions, distortions and elective surgery are the most common triggers. In a large prospective study of 596 patients with fracture the incidence rate of the diagnosis of CRPS I based on the Harden and Bruehl criteria was 7.0% [7]. In 10% of cases, CRPS I develops spontaneously [77]. CRPS I is a “complex” disorder in terms of its pathophysiology, diagnosis and treatment. The CRPS I has a multifactorial pathogenesis that can not be explained with a single mechanism, such as peripheral inflammation or sympathetic-afferent coupling [34]. The complexity and diversity of the mechanisms involved will be liable to the heterogeneity of the clinical presentation and may explain the difficulty of achieving an evidence-based treatment of CRPS I [78]. Enhanced understanding of the pathophysiology of CRPS I increases the possibility to develop mechanism-based treatments [34]. The main question is why do some people develop CRPS I and other people, with similar traumas do not? [81]. Genetic factors have been hypothesized to increase susceptibility to CRPS I in some individuals and a few genetic studies suggest that possible susceptibility genes reside in the Human Leukocyte Antigen (HLA) complex on the short arm of chromosome 6 [8, 9, 11]. Indeed it is now over forty years since the first associations between particular HLA antigens and disease susceptibility were described [82, 83]. An increased genetic predisposition could explain why some patients develop the syndrome without an eliciting event. There is an open debate whether the CRPS I can be considered a neuropathic pain syndrome in the light of recent definition of neuropathic pain [84, 85]. Although CRPS I is defined by the absence of major nerve lesion, Oaklander et al. [86] demonstrated a focal small-fiber axonal degeneration in the CRPS-affected skin sites. Albrecht et al. [87] reported decreased C-fiber and Aδ-fiber density in the affected limbs of CRPS I patients compared with nonpainful control sites on the same extremity and compared with healthy controls. Both studies indicate that CRPS I can be associated with pathological peripheral changes of the afferent innervation of the skin and, thus, support the hypothesis that CRPS I is a neuropathic condition, and that small-fiber axonal damage is involved in pathogenesis. In addition, several sensory phenomena of CRPS I patients are very similar to those present in other neuropathic pain disorders (e.g. postherpetic neuralgia or painful diabetic neuropathy). There is convincing evidence for facilitated neurogenic inflammation [41, 89], endothelial dysfunction [51], pathological sympathetic-afferent coupling [89-91] and cortical changes [63]. The coupling between sympathetic postganglionic neurons and primary afferent neurons is the underlying mechanism of SMP. It is likely to be located within the skin as predicted by the pain-enhancing effect of intracutaneous norepinephrine injections [28]. This coupling may occur not only in the skin but also in deep somatic tissues, such as bone, muscles, or joints which are especially painful in some patients with CRPS I. Besides the direct coupling mediated by adrenoceptors, it may also occur indirectly, via the vascular bed or the immune system [38]. The decrease of sympathetic outflow to the affected limb leads to an increase of skin blood flow in arteriovenous anastomoses and to impairment of nutritive blood flow [21, 92]. This means that there is skin hypoxia and acidosis [92]. The emerging protons are powerful algesic substances and cause pain in ‘acute’ CRPS I. Research in the last decade has focused on two mechanisms: posttraumatic inflammation in acute CRPS I and cortical reorganization mainly later. Increasing evidence indicates that CRPS I is the result of an exaggerated regional inflammatory response to injury or surgical procedure and that inflammatory processes are involved in the pathogenesis of early CRPS I [33, 44]. Clinical trials have shown that free radical scavengers can reduce signs and symptoms of CRPS I, indirectly suggesting that free radicals and increased oxidative stress are involved in the pathogenesis of CRPS I [93-95]. Recently other studies have indicated a role of the immune system in CRPS I [96, 97]. The hypothesis that an autoimmune mechanism could be involved in the pathogenesis of CRPS I has been suggested by the following findings: IgG antibodies transferred from a patient with CRPS I to a group of mice (passive transfer) have induced a significant depression of rearing behavior [98]; moreover, treatment with intravenous immunoglobulin reduces pain in patients with CRPS I [99]. Recently, reorganization of somatotopic maps within the primary somatosensory cortex has been shown in CRPS I patients, using functional neuroimaging techniques [64, 65, 100-102]. In CRPS I and other neuropathic syndromes, cortical reorganization correlates with the amount of pain [65, 102, 103]. CRPS I patients also show reorganization of central motor circuits [69, 104]. Cortical reorganization may be reversed by a successful treatment [64, 67, 102]. The present results suggest that, when pain persists, reorganization in the brain may actually contribute to chronic pain which may significantly alter central tactile and motor processing in CRPS I patients [103, 105]. Based on all these findings, mirror therapy and graded motor imagery have been proposed at restoring the integrity of neural processing in the sensory-motor cortex in individuals with CRPS I [73, 106, 107]. In fact, the mismatch between motor intention and sensory feedback of the moving limb may generate pain in CRPS I and neurorehabilitative strategies have proved to be effective also in pain reduction [100, 106, 108, 109].

Summary

CRPS I is a complication occurring in an extremity, mostly following a minor injury or surgery. Acute CRPS I is considered a peripheral disorder, but chronic CRPS I is now widely established to be a central nervous system disease [110]. Persistent nociceptive CNS inputs, due to peripheral mechanisms such as neurogenic or classic inflammation, induce plastic changes in central network of tactile perception and motor control. Disruption of body-related representations promotes pain perception, being at least cause and not only consequence of chronic pain in patients with CRPS I [100, 111].