Evolving Understandings About Complex Regional Pain Syndrome and its Treatment

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Complex regional pain syndrome (CRPS) is still a puzzling disease. Although pathophysiologic understanding has improved, not every aspect of this challenging neuropathic pain syndrome has been explored. Typical symptoms of CRPS are sensory, motor, and autonomic dysfunctions. In most cases, CRPS occurs after a fracture, limb trauma, or lesion of the peripheral or central nervous system. Sometimes, symptoms develop without any trauma. Recent pathophysiologic concepts basically consider three major mechanisms: enhanced peripheral neurogenic inflammation, dysfunction of the sympathetic nervous system, and structural reorganization in the central nervous system. Moreover, a genetic predisposition may explain increased vulnerability. Treatment usually requires a multidisciplinary approach, including medical and nonmedical therapies. The common therapeutic aim is to maintain or restore normal function of the affected extremity. Beyond highlighting pathophysiologic concepts, this article describes recent therapeutic approaches.

Introduction

The first detailed descriptions of symptoms suggesting complex regional pain syndrome (CRPS) were probably made by Silas Weir Mitchell during the American civil war in 1864 [1]. He observed unusual clinical symptoms in wounded soldiers, consisting of permanent burning pain combined with trophic alterations. In the following decades, this syndrome was called "causalgia" as a combination of the Greek words *kausis* (burning) and *algos* (pain). During World War I, Rene Leriche successfully treated these syndromes by surgical sympathectomy [2]. Then, Livingston [3] proposed a "vicious circle" in 1944. He assumed that the activation of peripheral nociceptors would lead to an excitation of spinal interneurons and of sympathetic efferents. The resulting peripheral vasoconstriction was supposed to induce tissue hypoxia, as the major nociceptive stimulus. In contrast, Doupe et al. [4] postulated a pathologic generation of synapses between nociceptive afferents and sympathetic efferents. Impressed by therapeutic efficacy of sympathetic blocks, Evans [5] created another name in 1946 ("sympathetic reflex dystrophy"), which was also eventually dropped. In the meantime, many other names have been assigned to CRPS. The pathophysiology of CRPS is still controversial today. Therefore, the most recent term for these symptoms is merely descriptive: "complex regional pain syndrome," which was introduced by the International Association for the Study of Pain (IASP) in 1993 [6].

Subtypes, Clinical Signs, and Diagnosis

Diagnostic criteria by the IASP divide CRPS into two subtypes: CRPS-I, which occurs without a clinically apparent nerve lesion, and CRPS-II, with a verified nerve lesion. Many authors characterize different stages of CRPS depending on time from onset. Stage I is characterized mainly by abnormal pain perception and sensory function (hyperalgesia, allodynia), edema, sudomotor, and vasomotor dysfunctions. The dystrophic stage (II) should develop after about 3 to 6 months. It is characterized by aggravation of the symptoms and additionally by alteration of motor functions as well as trophic changes. In the atrophic stage (III), motor and trophic changes are most prominent, with the initial symptoms markedly decreasing [6].

Unfortunately, this classification does not adequately reflect pathophysiologic findings. According to recent pathophysiologic models, a classification into two clinical subtypes (primarily "warm" and primarily "cold" CRPS), which is independent of the prevalence of the aforementioned type I and II, seems rather appropriate. The primarily "warm" type usually develops post-traumatically and presents with increased skin temperature of the affected limb [7], whereas

skin temperature of the affected extremity is markedly decreased from the beginning in primarily "cold" CRPS [8]. This subtype develops often after minimal trauma and sometimes spontaneously [9].

The current IASP diagnostic criteria [10••] are as follows:

1. Continuing pain, which is disproportionate to any inciting event.
2. Patients must report at least one symptom in three of the four following categories: A) hyperalgesia, hyperesthesia; B) skin temperature asymmetry, skin color change or asymmetry; C) sweating asymmetry, edema; and D) decreased range of motion, dystonia, tremor, weakness, trophic changes of hair or nails.
3. Patients must display at least one sign at time of evaluation in two of the four following categories: A) pinprick hyperalgesia, brush-evoked pain, hyperalgesia/allodynia to deep somatic pressure; B) skin temperature asymmetry, skin color change or asymmetry; C) sweating asymmetry, edema; and D) decreased range of motion, dystonia, tremor, weakness, trophic changes of hair or nails.
4. There is no other diagnosis that better explains the signs and symptoms.

Thus, CRPS is diagnosed clinically. Nevertheless, other diseases that could account for symptoms resembling CRPS have to be excluded [11]. For example, a local infection is able to mimic "warm" CRPS (exclusion by routine blood investigation), or an arterial occlusive disease can resemble "cold" CRPS (exclusion either by history or ultrasound examination). In some cases, additional examinations (ie, conventional radiography, three-phase bone scintigraphy, thermography, and assessment of sweating) might be helpful to confirm the clinical impression. However, at present negative findings should not rule out the clinical diagnosis of CRPS. Once CRPS is diagnosed, treatment should start immediately.

The following data on clinical symptoms mainly refer to the results of a prospective examination in our outpatient department [12].

Sensory dysfunctions

Pain represents the most imposing symptom of CRPS. Seventy-five percent of untreated CRPS patients report ongoing pain even when the affected extremity is completely at rest [12]. Pain quality is mostly considered as burning, tearing, or stinging pain and is generally localized in deep tissues (muscles, bones). Spontaneous pain is often persisting, with fluctuating intensity. Less frequently, shooting pain attacks are also reported. In 93% of patients, pain increases during orthostatic regulation, excitement, emotionally stressful situations, or changes of ambient temperature. In many cases, pain is more pronounced at night. Among sensory signs, mechanical hyperalgesia (increased sensation of pain for lightly painful stimuli) or allodynia (pain for light touch) are common findings [13,14]. These represent sensory "plus" signs. Simultaneously, "minus" signs such as hypesthesia or hypalgesia are observed in the same area.

In a thorough neurologic examination, these sensory abnormalities can be found in up to 90% of all CRPS patients. Their distribution is usually glove- or stocking-like and does not adhere to the area of a single nerve.

Autonomic and trophic dysfunctions

One clinical CRPS symptom is the presence of a distally localized edema, which can be found in approximately 80% of patients [7,12]. This can be enhanced by exercise. In about 80% of the patients, differences in skin temperature between the affected and the unaffected side can be detected [12]. A difference of 1° C or more is considered as relevant in most studies. Because skin temperature essentially depends on ambient temperature, acclimatization is necessary. Fifty-five percent of CRPS patients present with altered sweating of the affected limb; hyperhidrosis is more common than hypohidrosis [15]. Initially, skin color often looks rather red, but becomes livid in chronic stages.

Trophic disturbances affect skin, nails, and hair. Hair and nail growth can be increased. In chronic stages, atrophic skin or muscles as well as contractures, which impair motor functions, are prominent.

Motor dysfunctions

Most patients present with a weakness. In acute stages, this might be explained as pain-dependent "guarding" weakness. Moreover, the coexistence of an edema or muscle hypertension in acute stages, and contraction and fibrosis of palmar or plantar aponeuroses in chronic stages, can contribute to motor dysfunctions [12]. A neglect-like phenomenon can be observed in some patients. In these cases, objects can only be handled properly under visual control. It has been shown that this phenomenon does not represent a classic neglect syndrome but rather that patients report a "foreign" feeling of the affected limb [16]. Moreover, the ability to identify the respective finger after touching is markedly diminished [16].

In 50% of patients, a tremor on the affected side can be detected, which has been classified as an enhanced postural tremor [17]. Myoclonic jerks or even focal distal limb dystonia are reported by 30% of patients [18]. These symptoms occur especially in CRPS-II with major nerve lesions [19].

Pathophysiology

Most knowledge of pathology exists for posttraumatic "warm" CRPS because it was most intensively studied. The mechanisms leading to "cold" CRPS are less clear.

Because of the different pathomechanisms, findings from "warm" CRPS can hardly be transferred to "cold" CRPS. Previous attempts to explain CRPS by only one pathophysiologic process have failed. Therefore, by now several pathophysiologic components have been identified, which support rather than exclude each other.

Immune system

The exact role of the immune system in initiating and maintaining CRPS has not been completely elucidated, but it is likely to be involved in peripheral inflammation and interaction with the sympathetic nervous system (SNS). Moreover, alterations in the immune system might indicate a higher vulnerability for developing CRPS. Because of these complex interactions, it is difficult to dissect the role of the immune system. Therefore, its contribution is discussed in the respective context (see following text).

Predisposition

There is clinical and molecular evidence that some patients have a greater susceptibility to develop CRPS. An association to human leukocyte antigen II loci DR 15 and DQ 1 [20], and—in CRPS patients with dystonia—to locus DR 13, has been found [19,21]. In addition, pedigrees of CRPS families have been published [22]. With respect to psychosocial predictors, personality traits such as increased anxiety or somatization were found to predispose to CRPS-like symptoms [23] or definite CRPS [24]. Furthermore, a history of significantly more stressful life events was recorded in CRPS patients in comparison with other chronic pain patients [25].

Posttraumatic inflammation

The acute phase of CRPS (eg, the first 3 months) seems to be a disorder of exaggerated neurogenic inflammation. Acute CRPS indeed mimics inflammation, including increased skin temperature, edema, redness, pain, and loss of function. After trauma, these signs and symptoms usually resolve. In CRPS, they may even aggravate. This suggests an insufficient remission of inflammation in CRPS, which may be one of the initial pathogenic factors [9]. The neuropeptide calcitonin gene–related peptide (CGRP) and substance P–mediated plasma protein extravasation were increased [26]. Electrical stimulation of nociceptive afferents induced a more intense neurogenic flare compared with controls, most likely mediated by CGRP. Proinflammatory cytokines are implicated in exaggerated pain states after physical trauma. Patients with CRPS have an imbalance in the cytokine system profiles shifted toward a proinflammatory profile [27•,28]. Cytokines may induce pain and hyperalgesia by direct and indirect mechanisms. Examples for direct mechanisms leading to hyperalgesia are peripheral nociceptors sensitized by proinflammatory cytokines and enhanced spinal nociceptive transmission [29]. Furthermore, tumor necrosis factor (TNF)-α, a prototypic proinflammatory cytokine, increases the production and release of CGRP in in vitro and in vivo models [30], indicating a close link between the neuropeptide and cytokine systems. The concept of a pathophysiologic role of cytokines in CRPS is further supported by reports of successful anti-TNF treatments of CRPS [31].

Sympathetic disturbances and sympathetically maintained pain

The activity in the SNS may be involved in the generation of pain and CRPS symptoms. This assumption is based mainly upon two observations: 1) the pain is spatially correlated with signs of autonomic dysfunction (ie, with abnormalities in blood flow, sweating, and trophic changes); and 2) blocking the sympathetic supply to the affected part relieves pain (sympathetically maintained pain). Today, this concept is supported by human and animal experiments indicating that sympathetic activity and catecholamines can activate primary afferent nociceptors and enhance pain behavior [32,33]. Furthermore, neurophysiologic studies indicate that the activity patterns of efferent sympathetic channels dramatically change in CRPS patients [34]. These findings point to central reorganization of autonomic circuits in the spinal cord or brain. The SNS has a further impact on peripheral inflammation. The SNS influences dendritic cells, in particular Langerhans cells, which are highly prevalent in CRPS tissue [35]. These cells play an important role in the innate immune response. It has been shown that in inflammation (eg, posttraumatic), immune cells downregulate the expression of β_2 receptors and upregulate α_1-receptor expression [36]. α_1 receptors stimulate production and release of proinflammatory cytokines. A recently detected mechanism of sympatho-immune interaction is the occurrence of antisympathetic autoantibodies in CRPS [37,38]. These autoantibodies are directed against surface epitopes and intracellular antigens and thus may be of major clinical importance. They were, however, detected in only 30% of CRPS patients—another hint for a nonhomogeneous CRPS pathophysiology.

Central sensory and motor neuroplasticity

There is accumulating evidence that central nervous system changes significantly contribute to CRPS pathogenesis. With regard to the somatosensory system, a substantial reorganization of the primary somatosensory cortex (S1) of CRPS patients has been found [39]. Using functional imaging techniques, shrinkage of the cortical hand representation contralateral to the CRPS-affected painful arm was detected [40]. In addition, the hand position was shifted toward the lip. Predictors for this cortical reorganization were pain and mechanical hyperalgesia. When treatment was efficacious, S1 reorganization reversed [41]. Cortical reorganization may also be able to explain sensory disturbances, tactile-induced referred sensations, and hemisensory deficits. Furthermore, the motor system is significantly altered. Clinical signs are

muscle weakness, difficulties performing complex movements, tremor, dystonia, and myoclonus. In addition, the neglect-like syndrome may contribute to disuse of the limb [42]. Since these changes are lateralized, they may be related to pain-induced changes in spinal reflex circuits linked to motor neurons. However, during the past years there have been reports of cerebral abnormalities, which might be even more important for motor abnormalities in CRPS patients. Transcranial magnetic stimulation studies revealed a deficiency of inhibitory mechanisms and an increased excitability at the level of the primary motor cortex—on both sides [43]. Understanding neuroplastic changes in CRPS might be prerequisite for new treatment strategies.

Psychosocial dysfunction

CRPS, like any other chronic medical syndrome (in particular chronic pain syndrome), is most appropriately conceptualized with the biopsychosocial model. Psychosocial factors contribute directly by affecting neuroendocrine pathways (which affect inflammation, autonomic dysregulation, and neuroplasticity) and indirectly by affecting health behavior, coping strategies, and treatment adherence [44,45]. With respect to CRPS, it has been shown that these patients have psychologic distress, which might influence the course of the disease [46•]. Whereas specificity of psychiatric comorbidity is controversial, the "neglect-like" syndrome of body image disorder was found to be more specific for CRPS [42]. This specificity of the body image disturbance is also supported by the effectiveness of cognitive-behavioral interventions such as motor imagery and mirror therapy [47]. Furthermore, there are suggestions that psychosocial factors such as stressful life events [25] or increased and premorbid anxiety predispose for CRPS symptoms [23].

Concepts for Treatment

Controlled studies about therapy of CRPS are rare. Therefore, results from other neuropathic pain syndromes are often adopted. In general, successful therapy of CRPS requires a multidisciplinary concept and should be controlled by an experienced therapist [48]. Treatment of CRPS not only focuses on pain relief but also on regaining of normal function and is therefore based on the combination of nonmedical and medical strategies.

Nonmedical therapies

Physiotherapy is one essential part in the treatment of CRPS even though only few controlled studies have been performed [49]. Exercises should be initiated as early as possible in order to avoid loss of function. Physiotherapy also aims to reduce secondary musculoskeletal pain. However, physiotherapy should be below pain level in order to avoid worsening of symptoms.

Meanwhile, the efficacy of mirror therapy has been impressively demonstrated. In acute stages, the use of mirror images of the unaffected extremity while moving is very effective [50]. A graded motor learning concept is required in chronic cases [47], which contains a limb recognition task, then imagination of movements, and then use of the aforementioned mirror therapy.

Medical therapies

Anti-inflammatory treatment (glucocorticoids, TNF-α antagonists)

Because the induction of cytokine expression and neurogenic inflammation seems to reflect the most important mechanism in "warm" acute CRPS, an anti-inflammatory treatment seems reasonable. The positive effect of steroids has been demonstrated in one small controlled study [51]. Our dose scheme consists of 100 mg methylprednisolone, tapered down by 25 mg every 4 days. There have been several promising case reports on the use of TNF-α receptor antibodies [31,52], but their efficacy now has to be demonstrated in randomized controlled trials.

Oxygen radical scavengers

Dimethyl-sulfoxide, 50% in fatty cream base, has been effective to relieve CRPS symptoms and pain [53], especially in "warm" CRPS. Oral N-acetyl-cysteine seems more promising in "cold" CRPS [54].

Blocking of osteoclast activity

The positive effects of bisphosphonates on pain, edema, and motor function have been demonstrated in controlled randomized studies [55,56]. Studies on calcitonin were ambiguous [57–59].

Symptomatic treatment of neuropathic pain

Only very few data exist on neuropathic treatment in patients with CRPS. One study reported positive effects of the antiepileptic gabapentin [60]. The use of other antiepileptic drugs, antidepressants, and opioids refers to the evidence gained in treatment of neuropathic pain in general, and therefore is not discussed further in this article (for treatment of neuropathic pain we refer to a recent review by Dworkin et al. [61]).

Symptomatic treatment of dystonia

Oral antispastic drugs have not been positively tested for treatment of dystonia in CRPS. Moreover, botulinum toxin had only low effects compared with the efficacy in primary dystonia [62]. In a small series of seven CRPS patients, intrathecal application of antispastic baclofen relieved pain and reduced dysfunction associated with dystonia [63].

Invasive therapies

Sympathetic blocks

Stellate ganglion blocks (for upper extremities), and respectively, lumbar sympathetic blocks (for lower extremities), represent another therapeutic option [64]. After successful test blocks, indicated by a pain reduction of at least 50%, a series of sympathetic blocks over 5 weeks (twice a week)

should follow. Unfortunately, there is no reliable test to predict if a patient benefits from sympathetic blocks. In controlled studies, peripheral guanethidine blocks were not effective [65].

Spinal cord stimulation

Spinal cord stimulation relieves pain even in chronic stages after unsuccessful medical treatment [66] but does not improve function of the affected extremity. It should only be used after failure of other therapeutic options.

Conclusions

Knowledge about pathophysiology and therapy of CRPS has increased in the past years. Recent concepts consider three main aspects in the development of CRPS symptoms, which are crucial for the development of CRPS and widely support each other. After diagnosis, treatment should be initiated as early as possible and requires a multidisciplinary approach. Therefore, physicians should be sensitized for typical symptoms of CRPS. Treatment includes medical and nonmedical therapies, with the aim of keeping or maintaining a normal function of the affected limb. However, further randomized controlled trials are necessary to enhance evidence-based treatment of CRPS.

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Disclosures

No potential conflicts of interest relevant to this article were reported.

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